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Investigation of the Deprotonative Generation and Borylation of Diamine-Ligated α-Lithiated Carbamates and Benzoates by in Situ IR spectroscopy

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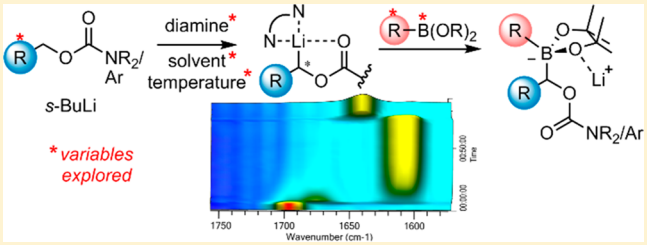
Supporting Information

ABSTRACT: Diamine-mediated α-deprotonation of *O*-alkyl carbamates or benzoates with alkyllithium reagents, trapping of the carbanion with organoboron compounds, and 1,2-metalate rearrangement of the resulting boronate complex are the primary steps by which organoboron compounds can be stereoselectively homologated. Although the final step can be easily monitored by ^{11}B NMR spectroscopy, the first two steps, which are typically carried out at cryogenic temperatures, are less well understood owing to the requirement for specialized analytical techniques. Investigation of these steps by in situ IR spectroscopy has provided invaluable data for optimizing the homologation reactions of organoboron compounds. Although the deprotonation of benzoates in noncoordinating solvents is faster than that in ethereal solvents, the deprotonation of carbamates shows the opposite trend, a difference that has its origin in the propensity of carbamates to form inactive parasitic complexes with the diamine-ligated alkyllithium reagent. Borylation of bulky diamine-ligated lithiated species in toluene is extremely slow, owing to the requirement for initial complexation of the oxygen atoms of the diol ligand on boron with the lithium ion prior to boron−lithium exchange. However, ethereal solvent, or very small amounts of THF, facilitate precomplexation through initial displacement of the bulky diamines coordinated to the lithium ion. Comparison of the carbonyl stretching frequencies of boronates derived from pinacol boronic esters with those derived from trialkylboranes suggests that the displaced lithium ion is residing on the pinacol oxygen atoms and the benzoate/carbamate carbonyl group, respectively, explaining, at least in part, the faster 1,2-metalate rearrangements of boronates derived from the trialkylboranes.



1. INTRODUCTION

The stereoselective homologation of boronic esters with lithium carbenoids derived from Hoppe-type carbamates[1] and Beak-type triisopropylbenzoates[2] has emerged as a powerful carbon−carbon bond-forming transformation.[3] The process involves three main steps (Scheme 1): step 1, the sparteine-mediated enantioselective deprotonation (lithiation) of a primary carbamate or benzoate with *s*-BuLi in an ethereal solvent (typically, Et_2O, *tert*-butylmethyl ether (TBME), or cyclopentylmethyl ether (CPME)) at low temperature (−78 °C); step 2, the boron−lithium exchange (borylation) of the resulting sparteine-ligated lithium carbenoid through the addition of a boronic ester, a step that is also carried out at low temperature owing to the level of chemical and configurational stability of the carbenoid;[4] step 3, 1,2-metalate rearrangement of the resulting boronate, a process that typically takes place above −20 °C for benzoates and at more elevated temperatures (40 °C) for carbamates.[5] The process can be repeated multiple times with the same or a different carbenoid reagent, allowing carbon chains to be grown one carbon at a time with complete control over substituent identity and configuration.[3a−c] The bringing together of new partners (the carbenoid precursor and the boronic ester), especially those presenting steric hindrance, often demands significant optimization of reaction conditions, such as reaction time, solvent, temperature, and whether to use carbamates or benzoates.[6] The last step of the process is easily monitored by ^{11}B NMR spectroscopy as the process operates at ambient temperatures and the four-coordinate boronate and three-coordinate boronic ester resonate at very distinct regions (~6 ppm and ~30 ppm, respectively). This facility has allowed novel insight that has led to the routine use of magnesium salts and solvent switches (Et_2O to $CHCl_3$) to promote this step when slow migrating groups are encountered.[6b] However, monitoring and troubleshooting the first two steps is more challenging owing to the processes being carried out at cryogenic temperatures and the added complication that the boron−lithium exchange can be reversible at temperature regimes where the 1,2-metalate rearrangement occurs.[6e,7] However, indirect probing of these

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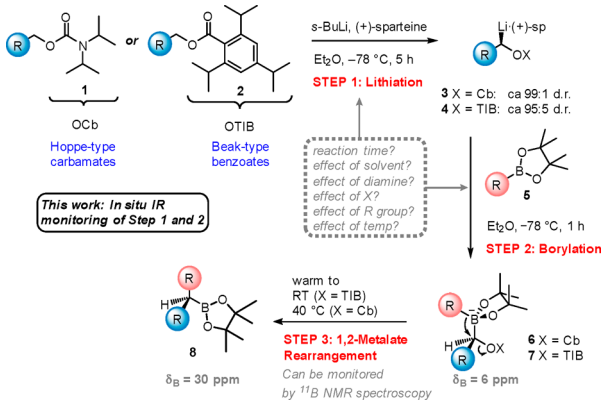
Scheme 1. Stereoselective Homologation of Boronic Esters



processes through deuterium quenching and the addition of other electrophiles (allyl bromide) at judicious points in the process has proven useful.[7] With the aim of gaining more insight into the lithiation and borylation steps, we decided to investigate the process through in situ IR spectroscopy.[8] The variation of solvent, diamine, temperature, as well as the organic group on the organoboron and the carbenoid precursor has revealed surprising trends and interesting effects that shed light on the elementary events that characterize each step.

2. RESULTS AND DISCUSSION

2.1. Initial Comparison of Carbamates and Benzoates. Solutions of ethyl carbamate **1a** and ethyl benzoate **2a** in Et_2O (0.3 M) at −78 °C show a strong $\nu_{C=O}$ band at ∼1697 and 1730 cm^{-1}, respectively, the lower value for the carbamate being consistent with significant contribution from the imidate resonance form, thus engendering a more basic oxygen atom (Figure 1). Treatment of these solutions with (+)-sparteine (1.2 equiv) followed by *s*-BuLi (1.2 equiv, 1.3 M in cyclohexane) leads to the disappearance of the above signals with the appearance of new signals at lower wavenumbers, ∼1616 and 1633 cm^{-1}, which are consistent with the dipole-stabilized α-lithiated carbamate **3a** and benzoate **4a**, respectively, the lithium ion being bound to the bidentate diamine, the carbenoid carbon atom, and the oxygen atom of the carbonyl group. For the carbamate, an intermediate signal, ∼20 cm^{-1} lower than that of the substrate (1678 cm^{-1}), quickly appears and then disappears; this signal presumably represents one or a collection of complexes in which a lithium ion binds to the carbonyl oxygen atom of the carbamate.[9] The stoichiometry of this complex and whether the complexes are intermediates on the pathway to lithiated species (prelithiation complexes) or mostly the products of a parasitic equilibrium was unclear. Monitoring of the benzoate did not show any evidence of a similar complex. The benzoate **2a** undergoes much more rapid lithiation compared to the carbamate **1a**. We find it convenient to report the rate of deprotonation as approximate half-lives ($t_{1/2}$)—the amount of time it takes for half of what will be the full amount of the α-lithiated species to be formed. The alternative method, reporting the amount of time it takes for half of the substrate to be consumed, is more challenging owing to the confounding effects of the initially formed complexes and changes in concentration during the addition of the organolithium reagent. Note: The use of the term half-life here does not apply any certainty on the molecularity (or pseudomolecularity) of the transformation. Ethyl benzoate **2a** undergoes deprotonation ca. four times faster than the carbamate **1a** ($t_{1/2}$ = 8 and 30 min, respectively), despite the similar pK_a values.[10] However, this trend contrasts with results recently published on the amine-free *n*-BuLi deprotonation of benzylic carbamates and benzoates in THF/hexane solvent mixtures. Garcia-Rio and

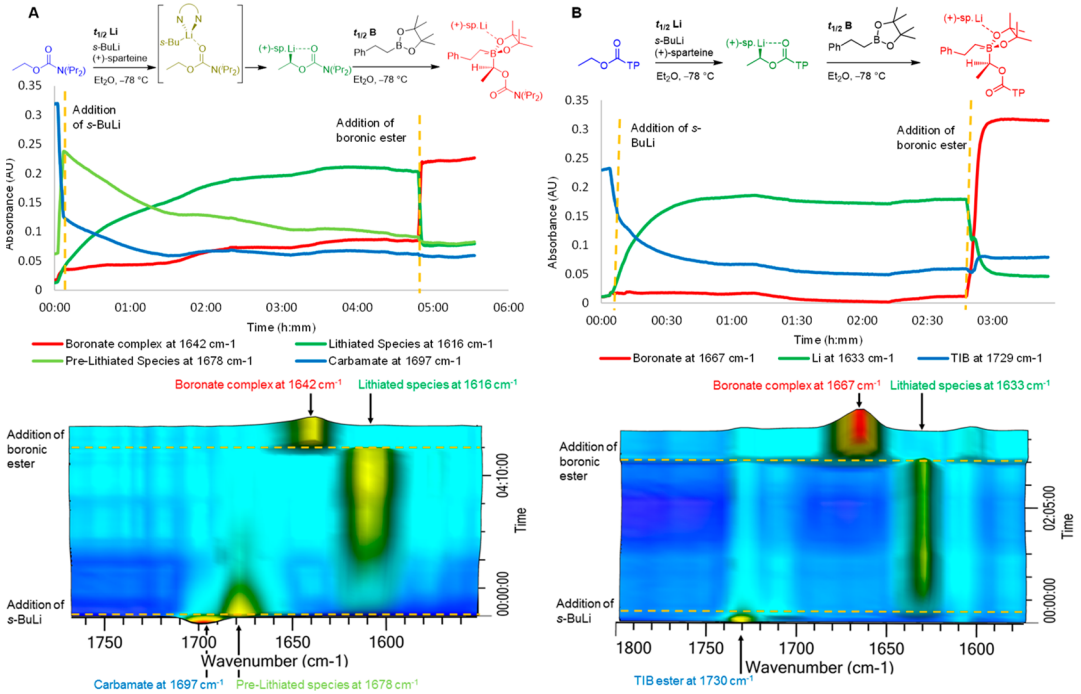


Figure 1. 2D and 3D plots of absorbance versus time for species involved in the lithiation and borylation of ethyl carbamate (A) and ethyl benzoate (B). TP = 2,4,6-triisopropylphenyl.

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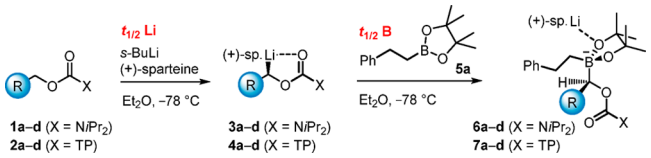
co-workers have shown that benzylic carbamates undergo deprotonation much more rapidly than the corresponding benzoates;[11] this result points toward the involvement of a prelithiation complex, the formation of such an intermediate being both more facile for the carbamate owing to the higher basicity of the carbonyl oxygen atom and rate determining when the deprotonation event is relatively facile, such as, for example, deprotonation at a benzylic position. Upon nearly complete formation of the α-lithiated carbamate and benzoate, the addition of a 1.0 M solution of phenethyl boronic acid pinacol ester in Et_2O leads to rapid conversion of the lithiated species into the corresponding boronate, indicated by the rapid drop in intensity of the bands at 1616 and 1633 cm^{-1} with concomitant appearance and increase in intensity of bands at 1642 and 1667 cm^{-1}, respectively. For the α-lithiated carbamate, the conversion into boronate was almost complete by the time the last drop of boronic ester solution was added (<15 s); for the α-lithiated benzoate, boronate formation was complete in just under 2 min. Warming to 35 °C and room temperature for the reaction mixtures of carbamate and benzoate, respectively, allows for 1,2-metalate rearrangement, giving the one-carbon homologated boronic ester. Upon oxidative workup (aq NaOH/aq. H_2O_2), the corresponding alcohol was isolated in 98:2 and 95:5 er, values that are fully consistent with the levels of enantioselectivity that are normally imposed by sparteine on the deprotonation of carbamates[1] and benzoates,[2] respectively.

2.2. Effect of Steric Hindrance at the β Position. We investigated the effect of steric hindrance on both the rate of deprotonation and the subsequent borylation by sequentially adding a methyl group to the β carbon atom of the ethyl carbamate and benzoate derivatives (Table 1). The $t_{1/2}$ for the sparteine-mediated deprotonation of the ethyl, propyl, and isobutyl carbamate (**1a–c**) was 30 (as given above), 33, and 81 min, respectively; neopentyl carbamate **1d** did not undergo deprotonation at an appreciable rate at −78 °C. The corresponding values for the benzoates **2a–d** were 8, 16, 31, and 94 min, respectively, with the neopentyl substrate undergoing very slow but steady deprotonation at −78 °C. The similar rate for the deprotonation of the ethyl and propyl carbamate (entries 1 and 3, respectively) contrasting with a doubling in $t_{1/2}$ in going from the ethyl to the propyl benzoate, suggests both the absence of an inductive effect of increased substitution on the acidity of the pertinent methylene group and also perhaps the greater proximity of the benzoate's triisopropylphenyl group—lying orthogonal to the carbonyl group—to the β carbon atom, compared to that of the carbamate's diisopropylamino group. The switching-on of sensitivity of deprotonation of the carbamate to steric hindrance upon moving to the isobutyl substrate (entry 5) might reflect its inability to avoid a conformation that imparts significant steric hindrance near the β carbon atom and the sparteine-ligated organolithium reagent during deprotonation. The subsequent borylation appears to be much more sensitive to steric hindrance. Although borylation of the carbamate was rapid across the series (<15 s, <15 s, 3 min; the neopentyl substrate was not lithiated at −78 °C), the rate of borylation of the lithiated benzoate dropped steeply with each addition of a methyl group (2, 8, 35, 296 min). That borylation of an organolithium could be so slow at −78 °C was a surprise, thus giving us cause to reassess our standard protocols for borylation. Additionally, we also investigated the isobutyl derivative of another popular type of carbamate, the Cby group

Table 1. Effect of Steric Hindrance at the β Position[a]



	R/X/Substrate	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)	Yield (%)[b]	e.r.[c]
1	Me/N*i*Pr$_2$/**1a**	30	<15 s	44	98:2
2	Me/TP/**2a**	8	2	45	95:5
3	Et/N*i*Pr$_2$/**1b**	33	<15 s	60	98:2
4	Et/TP/**2b**	16	8	77	97:3
5	*i*Pr/N*i*Pr$_2$/**1c**	81	3	67	98:2
6	*i*Pr/TP/**2c**	31	35	66	97:3
7		145	3	28	98:2
8	*t*Bu/N*i*Pr$_2$/**1d**	-[d]	-	-	-
9	*t*Bu/TP/**2d**	94	296	21	99:1

[a]Conditions: **1**/**2** (0.66 mmol), (+)-sparteine (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 M in cyclohexane), Et_2O, −78 °C; then phenethyl boronic ester (0.79 mmol), Et_2O, −78 °C; warming to rt (X = TP) or 40 °C (X = N*i*Pr$_2$); NaOH/H_2O_2, THF/H_2O. [b]Yield of alcohol as isolated by column chromatography following oxidation of the homologated boronic ester, structures of which are located in the SI. [c]Determined through HPLC analysis of the alcohol product by using a chiral stationary phase. [d]No reaction.

(2,2,4,4-tetramethyl-1,3-oxazolidin-3-yl), which gives slightly higher er than the standard carbamate.[12] Interestingly, it undergoes deprotonation approximately 2-fold slower than the diisopropyl carbamate ($t_{1/2}$: 145 versus 81 min; entry 7). Although the *N*,*O*-acetal moiety of the Cby group would be expected to acidify the pertinent methylene, while engendering a less basic carbonyl group, it seems that the rate of deprotonation is more strongly impacted by the geminal pairs of methyl groups, which, owing to the ring structure, are locked pointing toward the carbonyl group, thus being more sterically imposing than those of the more flexible isopropyl groups in the Cb substrate. The Cby substrate also exhibited a prelithiation complex.

2.3. Effect of a Proximal Aromatic Group. For methodology development in this area, our group normally uses the phenylpropyl carbamate and benzoate as model substrates because lithiation appears to be facile. Indeed, the carbamate and benzoate derivative of this substrate (**1e** and **2e**) undergoes much more rapid deprotonation than the corresponding *n*-propyl parent derivative (Cb: $t_{1/2}$ 5 min versus 33 min; TIB: $t_{1/2}$ 1 min versus 16 min). This rate enhancement could be due to a through-bond inductive withdrawal of electron density or due to a through-space effect, such as a cation−π interaction between the aromatic ring and a lithium ion.[13] Beak and co-workers observed that *N*-Boc-4-phenylpiperidines underwent much more rapid lithiation at the 2 position compared to the unsubstituted piperidines;[14] this

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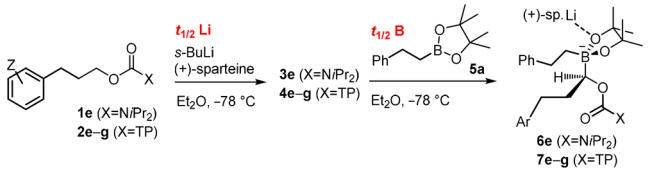
result would suggest that the rate enhancement is due to an inductive effect, as the equatorially positioned phenyl group would not be able to assist in a through-space interaction. We decided to investigate the phenylpropyl benzoate (**2e**), together with the 4-methoxy and 3,5-bis(trifluoromethyl) substituted derivatives (**2f**, **2g**) (Table 2). The 4-methoxyphenyl derivative underwent deprotonation at a slightly lower rate than the phenyl derivative ($t_{1/2}$ 2 min versus 1 min), while the 3,5-bis(trifluoromethyl)phenyl derivative underwent deprotonation at a noticeably higher rate, with conversion being complete by the time the solution of *s*-BuLi was added ($t_{1/2}$ < 15 s). The rate of borylation dropped in the order phenyl ($t_{1/2}$ 3 min) > 4-methoxyphenyl ($t_{1/2}$ 5 min) > 3,5-bis(trifluoromethyl)phenyl ($t_{1/2}$ 12 min). These results suggest that increased inductive withdrawal leads to faster lithiation and slower borylation, as one would expect. However, the lithiated *n*-propyl benzoate, **2b**, undergoes borylation with a $t_{1/2}$ value of 8 min, placing it in the middle of the above series, and not at the beginning, suggesting that the pendent phenyl group promotes borylation through a through-space effect (see section 2.4 for further discussion). The treatment of a 1:1 mixture of sparteine-ligated lithiated *n*-propyl benzoate and phenylpropyl benzoate with phenethyl boronic ester gave a 1:1.9 ratio of homologated boronic esters, respectively, thus being consistent with the above half-lives.

2.4. Effect of Solvent. Diamine-promoted lithiation reactions for subsequent borylation are primarily conducted in Et_2O;[3g] TBME is sometimes used when using very lipophilic substrates[3c] and CPME engenders higher yields when lithiating secondary alkyl benzoates.[15] Notably, the use of THF in sparteine-mediated enantioselective deprotonation leads to products of low ee values, presumably due to nondiamine-ligated alkyllithium monomers and higher aggregates that are competent at deprotonation;[16] interestingly, the use of THF/TMEDA for the stereospecific deprotonation of secondary alkyl benzoates leads to poor yields compared to Et_2O and TBME, indicating other deleterious attributes.[15] Toluene is another common solvent for the deprotonation of carbamates and benzoates[16b] but has not been adequately explored for lithiation/borylation sequences. Using the *n*-propyl benzoate as a test substrate, the relative rates of sparteine-mediated lithiation were determined in Et_2O, TBME, and toluene, with the $t_{1/2}$ values being 16, 26, and 9 min, respectively (Table 3, entries 4–6). The corresponding values for the *n*-propyl carbamate were 33, 43, and 66 min, respectively (Table 3, entries 1–3). That toluene is a very good solvent for lithiating benzoates and a very poor solvent for lithiating carbamates was also apparent with the ethyl (see the Supporting Information) and the isobutyl carbamates/benzoates (Table 3, entries 7–11). The solvent trends are difficult to rationalize with a high level of confidence. Presumably, a high rate of lithiation will be promoted by a suitably high concentration of both monomeric sparteine-ligated *s*-BuLi and substrate so that they can come together to form a complex that is competent for subsequent intracomplex proton transfer. The concentration of both species will be dictated by the stability of other nonproductive complexes. Previous work with *i*PrLi has shown that a major species in ethereal solvents is the heterosolvated dimer of the alkyllithium (Figure 2, **9**: the sparteine ligating one lithium ion and up to two solvent molecules ligating the other lithium ion).[17] This species will presumably need to fragment to monomeric forms (Figure 2, **12**) to allow for productive complexation. The use of poorly coordinating toluene as a solvent will promote the formation of homosolvated dimer **11** (both lithium ions ligated by a bidentate diamine),[18] which, in the case of sparteine, will be relatively labile, thus promoting a relatively high concentration of monomeric sparteine-ligated *s*-BuLi **12**. For the triisopropyl benzoate, complexation with the three-coordinate monomer (to give **13**) will lead directly to lithiation; this hypothesis is supported by the higher rate of lithiation of benzoates in toluene compared to reactions in Et_2O. However, the lithiation of carbamates shows the opposite trend: the reactions are slower in toluene. This different solvent trend could be explained by carbamates being more likely to form stable unproductive heterosolvated dimers (e.g., **10**: sparteine ligating one lithium and one or two molecules of carbamate bound to the other lithium ion), owing to their smaller size and more electron-rich carbonyl oxygen atom, thus engendering a low concentration of both

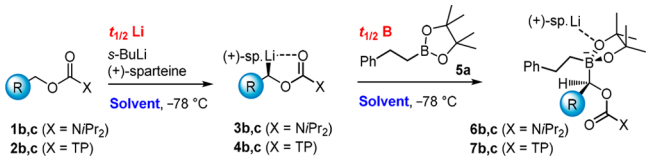
Table 2. Effect of a Proximal Aromatic Group[a]



entry	Z/X/substrate	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)	yield[b] (%)
1	H/N*i*Pr$_2$/**1e**	5	<15 s	58
2	H/TP/**2e**	1	4	67
3	4-OMe/TP/**2f**	2	5	58
4	3,5-(CF$_3$)$_2$/TP/**2g**	<15 s	12	77

[a]Conditions: **1**/**2** (0.66 mmol), (+)-sparteine (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 M in cyclohexane), Et_2O, −78 °C; then phenethyl boronic ester **5a** (0.79 mmol), Et_2O, −78 °C; warming to 40 °C/rt; $NaOH/H_2O_2$, THF/H_2O. [b]Yield of alcohol as isolated by column chromatography following oxidation of the homologated boronic ester.

Table 3. Effect of Solvent[a]



entry	R/X/substrate	solvent	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)
1	Et/N*i*Pr$_2$/**1b**	Et_2O	33	<15 s
2	Et/N*i*Pr$_2$/**1b**	TBME	43	<15 s
3	Et/N*i*Pr$_2$/**1b**	toluene	66	42
4	Et/TP/**2b**	Et_2O	16	8
5	Et/TP/**2b**	TBME	26	13
6	Et/TP/**2b**	toluene	9	501
7	*i*Pr/N*i*Pr$_2$/**1c**	Et_2O	145	3.5
8	*i*Pr/N*i*Pr$_2$/**1c**	toluene	195	>50
9	*i*Pr/TP/**2c**	Et_2O	31	35
10	*i*Pr/TP/**2c**	TBME	52	45
11	*i*Pr/TP/**2c**	toluene	15	NR[b]

[a]Conditions: **1**/**2** (0.66 mmol), (+)-sparteine (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 m in cyclohexane), solvent, −78 °C; then phenethyl boronic ester (0.79 mmol), solvent, −78 °C; warming to rt (X = TP) or 40 °C (X = N*i*Pr$_2$); $NaOH/H_2O_2$, THF/H_2O. [b]The rate of borylation was extremely low.

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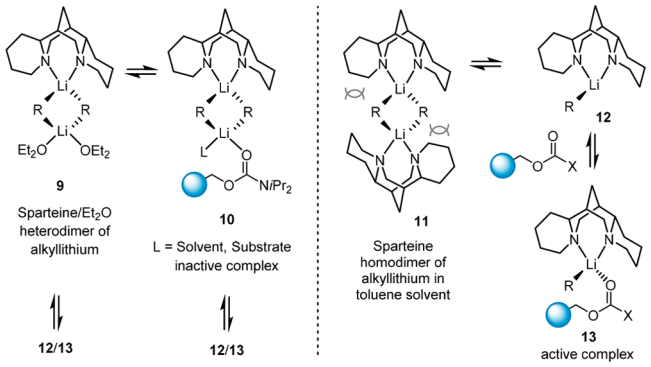
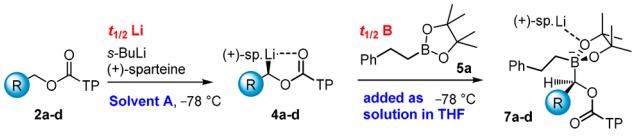


Figure 2. Possible alkyllithium/sparteine/substrate equilibria.

monomeric sparteine-ligated alkyllithium and carbamate. This hypothesis is supported by the high concentrations of lithium-complexed carbamates in toluene (their presence being indicated by the rapid appearance of an IR band of lower frequency relative to free carbamate upon addition of the organolithium reagent), which, in line with data to be presented below, appear to be parasitic intermediates for lithiation. Explaining the lower rate of lithiation in TBME, compared to the reaction in Et_2O, requires much more speculation but might be a consequence of the dynamics centering around the heterosolvated dimer (akin to **9**), including how many solvent molecules (one or two) bind to one of the lithium ions and how this coordination number effects the rate of fragmentation to monomeric form.

The effect of solvent on the rate of borylation was both striking and surprising (Table 3). Although the borylation of lithiated carbamates was always faster than the corresponding benzoates in all solvents, thus in line with the above results (section 2.1), the use of toluene solvent engendered extremely low rates of borylation for benzoates; even the relatively unhindered ethyl substrate underwent borylation with a half-life of approximately 165 min (see Table 4). The borylation of carbamates was also slower in toluene solvent (ethyl carbamate: $t_{1/2}$ ether <15 s, $t_{1/2}$ toluene 42 min) but still relatively fast compared to the benzoates (ethyl benzoate: $t_{1/2}$ ether 8 min, $t_{1/2}$ toluene 501 min). That there was a solvent effect at all was surprising and gave us cause to consider the finer details of borylation. In an earlier comparison of the stereospecificity of the borylation of secondary benzylic

Table 4. Effect of THF on the Rate of Borylation[a]



entry	R	solvent A	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)	$t_{1/2}$ B (min)[b]
1	Me/**2a**	toluene	7	<15 s	165
2	Et/**2b**	toluene	9	2	501
3	*i*Pr/**2c**	toluene	15	11	NR[c]
4	*t*Bu/**2d**	Et_2O	78	15	296

[a]Conditions: **2** (0.66 mmol), (+)-sparteine (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 M in cyclohexane), Solvent, − 78 °C; then phenethyl boronic ester (0.79 mmol, Solvent, − 78 °C; warming to RT; NaOH/H_2O_2, THF/H_2O. [b]The rate of borylation when boronic ester **5a** was added as a solution in solvent A. [c]The rate of borylation was extremely low.

carbamates with boronic esters and boranes, the retentive boron−lithium exchange for boronic esters versus an invertive exchange for trialkyl boranes strongly suggested that one of the oxygen atoms of the diol ligand on boronic esters coordinate to the lithium ion of the lithiated carbonyl compound prior to boron−lithium exchange.[19] This precomplexation could happen through initial dissociation of the carbonyl oxygen atom of the carbamate/benzoate, giving a three-coordinate lithium ion (the ligands being bidentate sparteine and the α carbon atom of the carbonyl substrate) that has an empty site for coordination for the boronic ester (Figure 3; **14** → **15** → **16** → **17**). Dissociation of the carbonyl oxygen atom from the lithium ion should also lead to a more reactive carbon−lithium bond and a more flexible intermediate for boron−lithium exchange. The solvent effect unveiled here suggests that dissociation of the sparteine ligand, either fully or partially (monodentate diamine), and replacement with smaller solvent molecules may be required for either coordination of the boronic ester, subsequent boron−lithium exchange, or both, with both steric as well as electronic effects at play (Figure 3; **14** → **18** → **19**/**20** → **21** →**17**). Such a mechanism may be operating in parallel to one where sparteine remains coordinated in a bidentate fashion to the lithium ion, a pathway that may be more efficient in the case of carbamates. Because we had identified toluene as a good solvent for the lithiation of benzoates, we tested the use of additives for promoting borylation in the hope of identifying a viable toluene-based process for the lithiation−borylation of benzoates. Addition of 0.6 equiv (based on substrate) of THF to a toluene solution of sparteine-ligated lithiated propyl benzoate and phenethyl boronic ester led to a marked increase in the rate of borylation (Figure 4). The addition of the boronic ester as a solution in THF (1 M) led to very rapid borylation ($t_{1/2}$ = 2 min; Table 4). Moreover, the enantioselectivity of the process remained high (~95:5 e.r.). The effect of adding the boronic ester as a solution in THF had a similarly dramatic effect on the rate of borylation of the lithiated isobutyl benzoate (essentially undetectable borylation

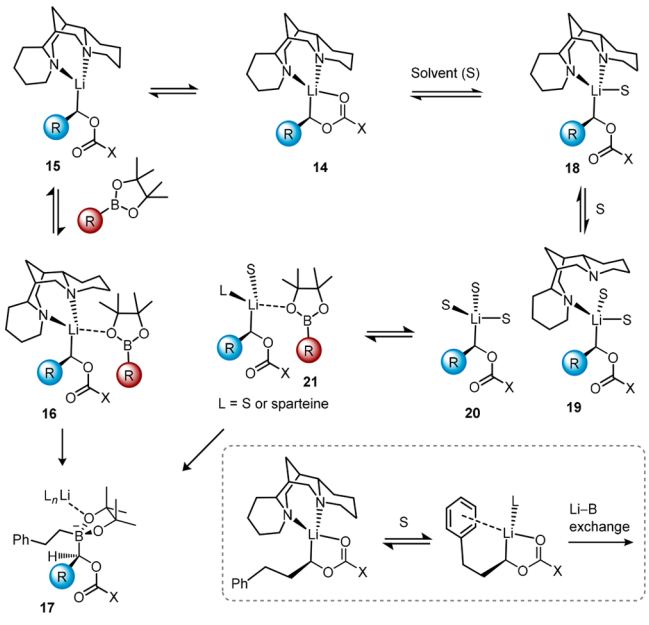


Figure 3. Potential mechanisms for solvent-mediated boron−lithium exchange.

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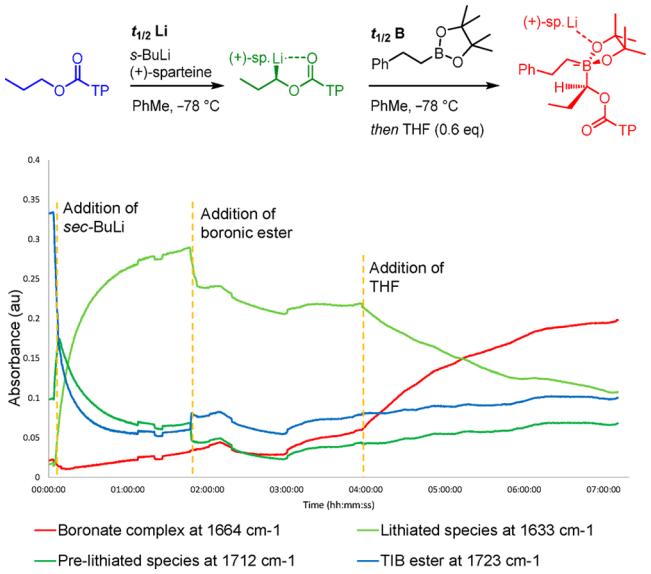
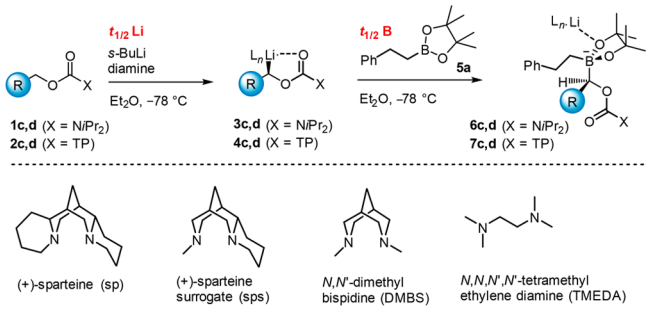


Figure 4. 2D plot of absorbance versus time for the lithiation and borylation of propyl benzoate in toluene solvent, with the addition of THF to promote borylation.

versus a $t_{1/2}$ of 11 min). As documented above, the borylation of the very sterically hindered neopentyl benzoate in Et_2O solvent was very slow ($t_{1/2}$ of ∼296 min). When phenethyl boronic ester was added as a solution in THF, borylation was much more rapid ($t_{1/2}$ of 15 min), indicating that the addition of boronic esters as solutions in THF should form part of most lithiation−borylation protocols. In accordance with the above analysis on the solvent effect on borylation, THF efficiently displaces sparteine as a ligand on lithium, leading to faster borylation. This result also sheds light on the intriguing promotion of borylation in the presence of a pendent electron-rich aromatic ring (section 2.3). It seems reasonable that the pendant phenyl group can displace the sparteine ligand and act as a weak intramolecular ligand on lithium, thus providing a more accessible environment for the boronic ester.[13]

2.5. Effect of Diamine. The reactions described above involved the use of sparteine as the diamine promoter. Owing to the interesting effect of solvent on the rate of lithiation and borylation, we were keen to investigate and compare other diamine ligands. We were particularly interested in the use of the sparteine surrogate (Table 5), a less-sterically hindered derivative of sparteine; this diamine was initially prepared and investigated by the O'Brien laboratory as a surrogate for (+)-sparteine, which at the time was extremely scarce and expensive.[20] Relative to sparteine, the use of the (+)-sparteine surrogate in the deprotonation of isobutyl carbamate led to an approximate 5-fold increase in the rate ($t_{1/2}$ of 15 versus 81 min). Moreover, the enantioselectivity of the process remained high (∼95:5 er). Indeed, our research group observed a similar and highly enabling enhancement in rate for the α-lithiation of a benzoate intermediate in the total synthesis of (−)-stemaphylline.[6b] Similarly, the research group of O'Brien has observed rate enhancements in the lithiation of *N*-Boc piperidines[9b] and pyrrolidines,[21] thus providing further evidence to support the continued investigation of sparteine surrogate (and the development of routes to the (−)-sparteine surrogate),[22] despite the improvement in the availability of (+)-sparteine.[23] Interestingly, the use of the sparteine surrogate leads to faster lithiation compared to that mediated by

Table 5. Effect of Diamine[a]



entry	R/X/substrate	diamine	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)
1	*i*Pr/N*i*Pr$_2$/**1c**	(+)-sp	81	3
2	*i*Pr/N*i*Pr$_2$/**1c**	(+)-sps	15	5
3	*i*Pr/N*i*Pr$_2$/**1c**	TMEDA	42	<15 s
4	*i*Pr/TP/**2c**	(+)-sp	31	35
5	*i*Pr/TP/**2c**	(+)-sps	3	*b*
6	*i*Pr/TP/**2c**	TMEDA	17	<15 s
7	*i*Pr/TP/**2c**	DMBS	1	15
8[c]	*i*Pr/TP/**2c**	DMBS	1	8
9[c]	*i*Pr/TP/**2c**	(+)-sp	52	45
10[c]	*i*Pr/TP/**2c**	(+)-sps	2	111
11	*t*Bu/TP/**2d**	(+)-sp	78	150 (15)[d]
12	*t*Bu/TP/**2d**	(+)-sps	5	*e* (−)[d,e]

[a]Conditions: **1/2** (0.66 mmol), diamine (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 M in cyclohexane), Et_2O, − 78 °C; then phenethyl boronic ester (0.79 mmol), Et_2O, −78 °C; warming to rt (X = TP) or 40 °C (X = N*i*Pr$_2$); NaOH/H_2O_2, THF/H_2O. [b]Precipitation of lithiated benzoate confounded measurement of the rate of borylation, which was very slow; see the results of the reaction carried out in TBME (entries 3) [c]The lithiation−borylation process was carried out in TBME solvent. [d]Boronic ester added as a solution in THF. [e]The rate of borylation was undetectably low.

TMEDA ($t_{1/2}$ of 15 versus 42 min). This comparison contrasts with that observed by O'Brien where *N*-Boc-pyrrolidine is lithiated fastest by using TMEDA.[21] A similar trend was observed for the lithiation of isobutyl benzoate, with the $t_{1/2}$ values for sparteine, TMEDA, and sparteine surrogate being 31, 17, and 3 min, respectively.

The surrogate's reduced steric hindrance (compared to sparteine) and increased rigidity (compared to TMEDA) probably contributes to its effectiveness. Furthermore, the more basic nitrogen atoms within the sparteine scaffold compared to those of TMEDA (three bonds versus two bonds between the electronegative nitrogen atoms) probably enhance the basicity of *s*-BuLi.[24] As mentioned above, sparteine forms a heterodimer with *i*PrLi (a model for *s*-BuLi) in diethyl ether, with sparteine complexed to one lithium ion and solvent molecules on the other lithium ion;[17] O'Brien has shown that the smaller size of the surrogate engenders the homodimer (a diamine ligand on both lithium ions) being the major species in diethyl ether (see Figure 2).[25] Therefore, the kinetics and thermodynamics of the pre-equilibria involving substrate are also likely to be important. That two different types of substrates (O'Brien's *N*-Boc piperidines/pyrrolidines[9b,21] and the *n*-alkyl carbamates/benzoates) show different trends in diamine-mediated deprotonation give credence to the importance of these equilibria. Owing to the contrasteric result of the comparison between TMEDA and sparteine surrogate, we decided to prepare and investigate *N*,*N*′-dimethylbispidine, the least sterically hindered diamine for the sparteine scaffold

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(Table 5).[26] As expected, it was the most effective diamine for lithiation of isobutyl benzoate **2c** ($t_{1/2}$ of 3 versus 1 min for the sparteine surrogate and *N*,*N*′-dimethylbispidine, respectively). For both lithiated benzoates and carbamates, the TMEDA ligand leads to the highest rates of borylation (Table 5). Interestingly, the sparteine surrogate leads to the lowest rates of borylation. The effectiveness of TMEDA is consistent with its relatively small size and high flexibility—boron−lithium exchange might be sufficiently facile without exchange of TMEDA for solvent, and if not, exchange should be very rapid. Initially surprised by the low rate of borylation with sparteine surrogate, we tested the use of THF as a substoichiometric additive and as a vehicle for the introduction of the boronic ester. The low rate of borylation was unperturbed, suggesting that the sparteine surrogate cannot be displaced by THF solvent. This hypothesis is supported by the work of O'Brien: whereas sparteine-mediated deprotonations α to the nitrogen atom of carbamates in THF followed by electrophilic trapping leads to almost exclusive formation of the racemate, that mediated by the sparteine surrogate leads to product with high ee values; only the sparteine surrogate can out-compete THF for the generation of active alkyllithium aggregates/monomers.[25] O'Brien also observed that sparteine-surrogate-ligated α-lithiated piperazines could not be displaced by TMEDA, unlike the corresponding sparteine-ligated species.[27] Borylation of *N*,*N*′-dimethylbispidine-ligated lithiated benzoates in Et_2O was faster than that of sparteine and sparteine surrogate, with the $t_{1/2}$ values of 15 (8 min in TBME), 35 (45 min in TBME), and 111 min (TBME), respectively. Presumably, boron−lithium exchange is relatively facile with the less sterically hindered *N*,*N*′-dimethylbispidine ligand still bound to the lithium ion. Therefore, this result further reinforces the notion that borylation occurs through two mechanisms—direct borylation of the tricoordinate diamine-ligated lithium ion (the carbonyl group being in a dissociated state and the carbon−oxygen single bond being *anti* to the carbon−lithium bond) and borylation of the solvent-displaced derivative, the latter being important with bulky yet labile diamine ligands. Interestingly, the borylation of *N*,*N*′-dimethylbispidine-ligated lithiated species in TBME is faster than that in Et_2O (8 versus 15 min); sparteine-ligated species show the opposite trend. The need to displace the diamine ligand is no longer great for the borylation of the sterically accessible *N*,*N*′-dimethylbispidine-ligated lithiated species, so that instead the less-donating TBME solvent, which previously was poor at displacing the diamine from the diamine-ligated lithiated species, leads to the empty p orbital of the boron atom being more available for engagement in boron−lithium exchange.

2.6. Effect of the Organoboron Partner. Considering the evidence supporting initial coordination of the boronic ester to the lithium ion of the α-lithiated species prior to boron−lithium exchange, we decided to investigate the use of trialkylborane electrophiles. Trialkylboranes are more Lewis acidic than boronic esters but do not contain Lewis basic sites that can coordinate to the lithium ion. We investigated the borylation of benzoates rather than carbamates because the former borylate at a much lower rate, thus allowing differences to be more easily observed. Upon treatment of a sparteine-ligated α-lithiated 3-phenylpropylbenzoate (1636 cm^{-1}) with tributylborane (1 M in Et_2O) at −78 °C, we observed the appearance of a new signal at slightly lower wavenumber (1630 cm^{-1}). At a lower rate, we observed disappearance of the new signal at 1630 cm^{-1} and appearance of a new broader signal at lower wavenumber (1592 cm^{-1}), which corresponds to the lithiated benzoate anion ($TPCO_2Li$), the byproduct of 1,2-metalate rearrangement. The intermediate species indicated at 1630 cm^{-1} is believed to be the tetraalkylboronate; the very low wavenumber of the carbonyl group compared to that of boronates derived from boronic esters (~1665 cm^{-1}) suggests that the lithium ion is coordinating to the carbonyl oxygen atom (in pinacol boronates, the lithium ion presumably coordinates to one of the oxygen atoms of the pinacol ligand). That the 1,2-metalate rearrangement of tetraalkylboronates already occurs at −78 °C (the corresponding pinacol boronates requires temperatures of at least −20 °C)[3c] might be partially due to the positioning of the lithium ion. The alcohol product isolated after oxidation of the homologated organoboron showed that the level and sense of enantioenrichment was similar to the reaction with the boronic ester, thus confirming that the trialkylborane also undergoes stereoretentive boron−lithium exchange. To compare the rates of borylation of boranes and pinacol boronic esters, we used the lithiated isobutyl benzoate as a substrate owing to its low rate of borylation relative to the rate of addition of boronic ester to the lithiated species, as per our normal protocol. The borylation of this substrate with tributylborane exhibited features that were similar to that of the borylation of the phenylpropyl benzoate, although the IR band of the carbonyl group associated with the boronate and lithiated species was now coincident (see Figure 5). Rapid addition of a 1:1 mixture of tributylborane (1.2 equiv) and phenethyl boronic ester (1.2 equiv) in Et_2O (1 M) to a TBME solution of sparteine-ligated lithiated isobutyl benzoate **4c**, allowing the resulting solution to evolve for 4 h at −78 °C followed by warming to room temperature and subsequent oxidative workup, gave a 2:1 mixture of alcohols derived from homologation of the boronic ester and the trialkylborane, respectively (Scheme 2). This result shows that despite boronic esters being less Lewis acidic than trialkylboranes, they exhibit similar rates of boron−lithium exchange owing to the ability of the oxygen atoms of the diol ligand to coordinate to the lithium ion. Borate esters, $B(OR)_3$, which are less Lewis acidic than boronic esters, were investigated to determine whether the presence of an additional Lewis basic oxygen site would lead to more rapid

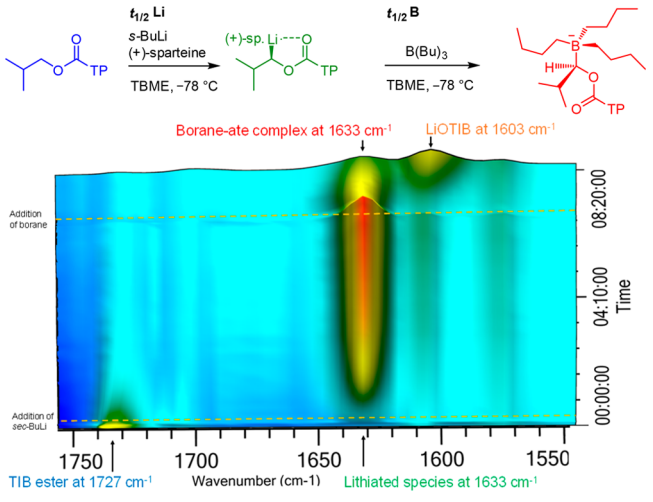

Figure 5. 3D in situ IR spectroscopy trace of the lithiation of isobutyl TIB ester and trapping with tributylborane showing 1,2-migration at −78 °C.

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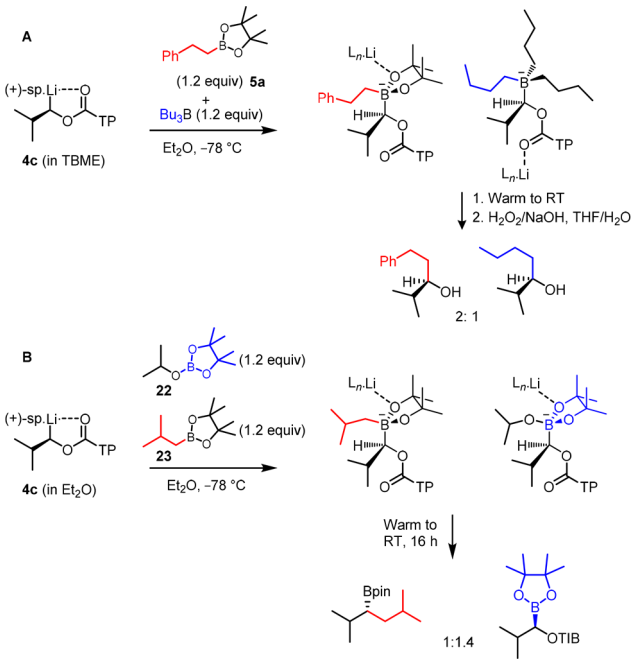
Scheme 2. (A) Comparison of the Rate of Borylation of Boronic Esters and Trialkylboranes[a]. (B) Comparison of the Rate of Borylation of Boronic Esters and Borate Esters[b]



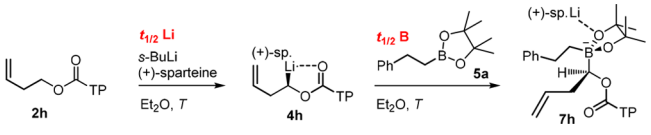
[a]Ratio derived after isolation. [b]Ratio derived by crude ^{1}H NMR.

lithium−boron exchange. In line with the above results, the addition of a 1:1 mixture of isopropoxy borate ester **22** ($t_{1/2}$ B = 36 min) and the isosteric isobutyl boronic acid pinacol ester **23** ($t_{1/2}$ B > 50 min) in Et_2O to the sparteine-ligated lithiated isobutyl benzoate **4c** ultimately led to a 1:1.4 ratio of products, in favor of the borate ester derived product. These results provide reinforcing evidence in support of the importance of lithium−oxygen coordination prior to lithium−boron exchange.

2.7. Effect of Temperature. We decided to investigate the effect of temperature on lithiation and borylation (Table 6). Because we were particularly interested in ascertaining whether the enantioselectivity of the process could be increased by lowering the temperature of lithiation, we chose 3-butenyl benzoate **2h** as a substrate, which undergoes sparteine-mediated deprotonation and borylation at −78 °C to give product with relatively moderate er levels (93:7). Dropping the temperature to −95 °C led to a slight increase in enantioselectivity (er 95:05); conducting the reaction at the higher temperature of −65 °C led to a slight decrease in enantioselectivity. Overall, the rate of lithiation doubles for every 10 °C increase in temperature. The rate of borylation was much more sensitive to temperature, with $t_{1/2}$ values of ∼1, 12, and 363 min at −65, −78, and −95 °C.

2.8. Effect of Concentration. We investigated the effect of reaction mixture concentration on the rate of lithiation while maintaining the relative stoichiometry of reactants at 1:1. Although for ethyl benzoate, the approximate rate of lithiation increased proportionally with reaction mixture concentration in accordance with a reaction that was almost second order—a log/log plot of rate versus concentration fitted a straight line of slope 1.82 (R^2 = 0.987)—that for ethyl carbamate suggested a fractional reaction order between 1 and 2 (slope = 1.22, R^2 = 0.996). We also investigated the lithiation of carbamates and benzoates under pseudo-first-order conditions because Beak and co-workers had studied the sparteine-mediated α-lithiation of *N*-aryl Boc carbamates of allyl amines and *N*-Boc-pyrrolidines under these conditions.[28] To a large excess of *s*-BuLi/sparteine (28 equiv, 0.69 M) in Et_2O/cyclohexane (∼1:1) at −78 °C was added ethyl carbamate. Interestingly, the carbamate did not undergo lithiation under these conditions; instead, the IR signal of the carbonyl group of the carbamate was shifted to a frequency that has been attributed above to a prelithiation complex. The same behavior was observed for the propyl and isobutyl carbamate, although the corresponding prelithiation complexes formed more slowly. This result is further evidence to support the parasitic nature of these "prelithiation complexes" observed in lithiation reactions of the type of carbamates studied herein. We believe that all of the carbamate substrate is quickly sequestered through ligand exchange with the sparteine/solvent-ligated heterodimer of *s*-BuLi, which is present in a large excess under Beak's pseudo-first-order conditions, thus leading to very low concentrations of both free carbamate and three-coordinate sparteine-ligated *s*-BuLi, which we believe need to come together to form an active complex (Figure 6). This hypothesis is consistent with the low rate of lithiation of carbamates in toluene solvent and the apparent fractional overall reaction order just above 1, as measured for reactions under normal preparative conditions. Underlining the diverging behavior of carbamates and

Table 6. Effect of Temperature[a]



entry	T (°C)	$t_{1/2}$ Li (min)	$t_{1/2}$ B (min)	yield (%)[b]	er[c]
1	−65	2	1	69	92:8
2	−78	4	12	78	93:7
3	−95	18	363	68	95:5

[a]Conditions: **2h** (0.66 mmol), (+)-sp (0.79 mmol), *s*-BuLi (0.79 mmol, 1.3 M in cyclohexane), Et_2O, T; then phenethyl boronic ester (0.79 mmol), Et_2O, T; warming to rt; $NaOH/H_2O_2$, THF/H_2O. [b]Yield of alcohol as isolated by column chromatography following oxidation of the homologated boronic ester. [c]Determined through HPLC analysis of the alcohol product by using a chiral stationary phase.

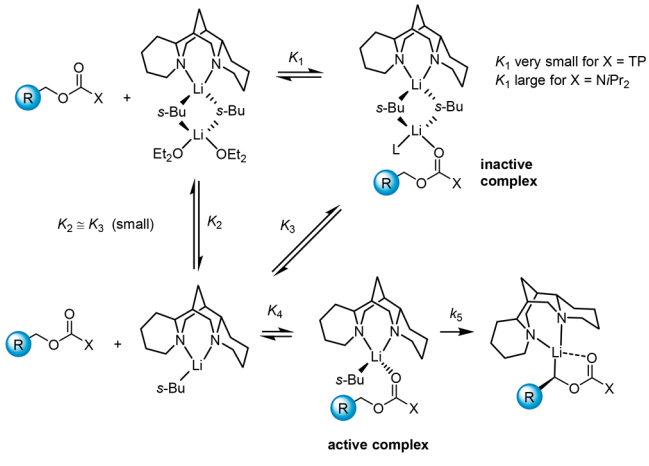


Figure 6. Proposed parasitic equilibria in lithiation reactions.

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benzoates, ethyl benzoate, which does not form observable prelithiation complexes, underwent smooth lithiation under these pseudo-first-order conditions.

3. SUMMARY AND CONCLUSIONS

We have investigated the deprotonative generation and borylation of diamine-ligated lithiated benzoates and carbamates by using in situ IR analysis. The results give rise to the following conclusions, which will be valuable for the troubleshooting and further development of homologation reactions of organoboron compounds by using lithiated carbamates and benzoates:

(1) The diamine/*s*-BuLi-mediated deprotonation of benzoates is approximately two to three times more rapid than that of the corresponding carbamates. This difference appears to be due to the involvement of parasitic complexes involving the organolithium reagent, the diamine, and the carbamate. IR signals of the carbonyl group in such complexes are observed at slightly lower wavenumbers than those of uncomplexed carbamate. That the use of very high concentrations of sparteine/*s*-BuLi relative to carbamate gives rise to quantitative formation of such IR-observable complexes and no observable deprotonation at −78 °C strongly supports this hypothesis. The less basic carbonyl group and more sterically hindered nature of benzoates preclude or keep the concentration of such complexes at very low levels.

(2) Increased steric hindrance at the β carbon atom of carbamates and benzoates leads to slower lithiation and borylation, the significant buttressing ability of the triisopropylphenyl group of benzoates engendering them more sensitive to the change.

(3) The borylation of diamine-ligated lithiated carbamates is considerably more rapid than that of the corresponding benzoates. This difference appears to be steric in origin.

(4) The replacement of ethereal solvents with the poorly coordinating solvent, toluene, leads to faster lithiation of benzoates but slower lithiation of carbamates. The latter effect appears to be due to the increased concentration of parasitic complexes of carbamates in toluene, whereas the former effect is presumably due to a higher concentration of the monomeric diamine-ligated organolithium in toluene.

(5) For both carbamates and benzoates, the borylation of the sparteine-ligated lithiated species is promoted by coordinating solvents (Et_2O) or additives (THF); borylation in toluene solvent in the absence of additives can be undetectably slow. The replacement of the diamine ligand for solvent molecules on the lithium ion allows easy access for the boronic ester to coordinate to the lithium ion through an oxygen atom of the diol ligand, an interaction that appears to precede boron−lithium exchange. This effect appears to be crucial for the borylation involving sterically hindered substrates or diamine ligands. For small or flexible diamine ligands (TMEDA and *N*,*N*′-dimethylbispidine), the primary mechanism of boron−lithium exchange might involve dissociation of the carbonyl group from the lithium ion rather than diamine−solvent exchange. However, the rate of borylation of sparteine-surrogate-ligated lithiated species cannot be increased through the addition of coordinating additives owing to its strong binding to the lithium ion.

(6) The rate of diamine/*s*-BuLi-promoted lithiation of benzoates and carbamates increases in the series *N*,*N*′-dimethylbispidine > sparteine surrogate > TMEDA > sparteine. The nature of the diamine (steric hindrance, basicity, and flexibility) presumably affects both the equilibria involving active and parasitic complexes and the rate constant for the deprotonation event. The rate of borylation increases in the contrasteric series TMEDA > *N*,*N*′-dimethylbispidine > sparteine > sparteine surrogate, suggesting the parallel operation of at least two mechanisms: one where boron−lithium exchange is preceded by exchange of the diamine ligand on the lithium ion for solvent/additive molecules and the other where the exchange is preceded by dissociation of the carbonyl group from the lithium ion (the diamine ligand remaining on the lithium ion). The promotion of borylation through the displacement of diamine ligands also appears to be the origin of the unusually rapid borylation of substrates containing pendant aryl groups, which can intramolecularly displace the diamine ligand through a cation−π interaction.

(7) Although trialkylboranes are more Lewis acidic than boronic esters, these families of organoboron compounds undergo boron−lithium exchange at very similar rates. The poorer Lewis acidity of boronic esters appears to be mitigated by their ability to form a complex with the organolithium, through interaction of an oxygen atom of the diol ligand with the lithium ion, prior to boron−lithium exchange. The unusually low carbonyl stretching frequency of boronate complexes derived from α-lithiated benzoates and trialkylboranes, compared to that of complexes derived from boronic esters, suggests that the lithium ion resides on the carbonyl oxygen atom; for complexes derived from boronic esters, the lithium ion is believed to reside on the oxygen atom of the diol ligand. The ability of boronates derived from trialkylboranes to undergo 1,2-metalate rearrangement even at temperatures as low as −78 °C is believed to be in part due to the positioning of the lithium ion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06871.

Reaction setup and experimental procedures. Full in situ IR data and traces (PDF)

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Notes

The authors declare no competing financial interest.

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