

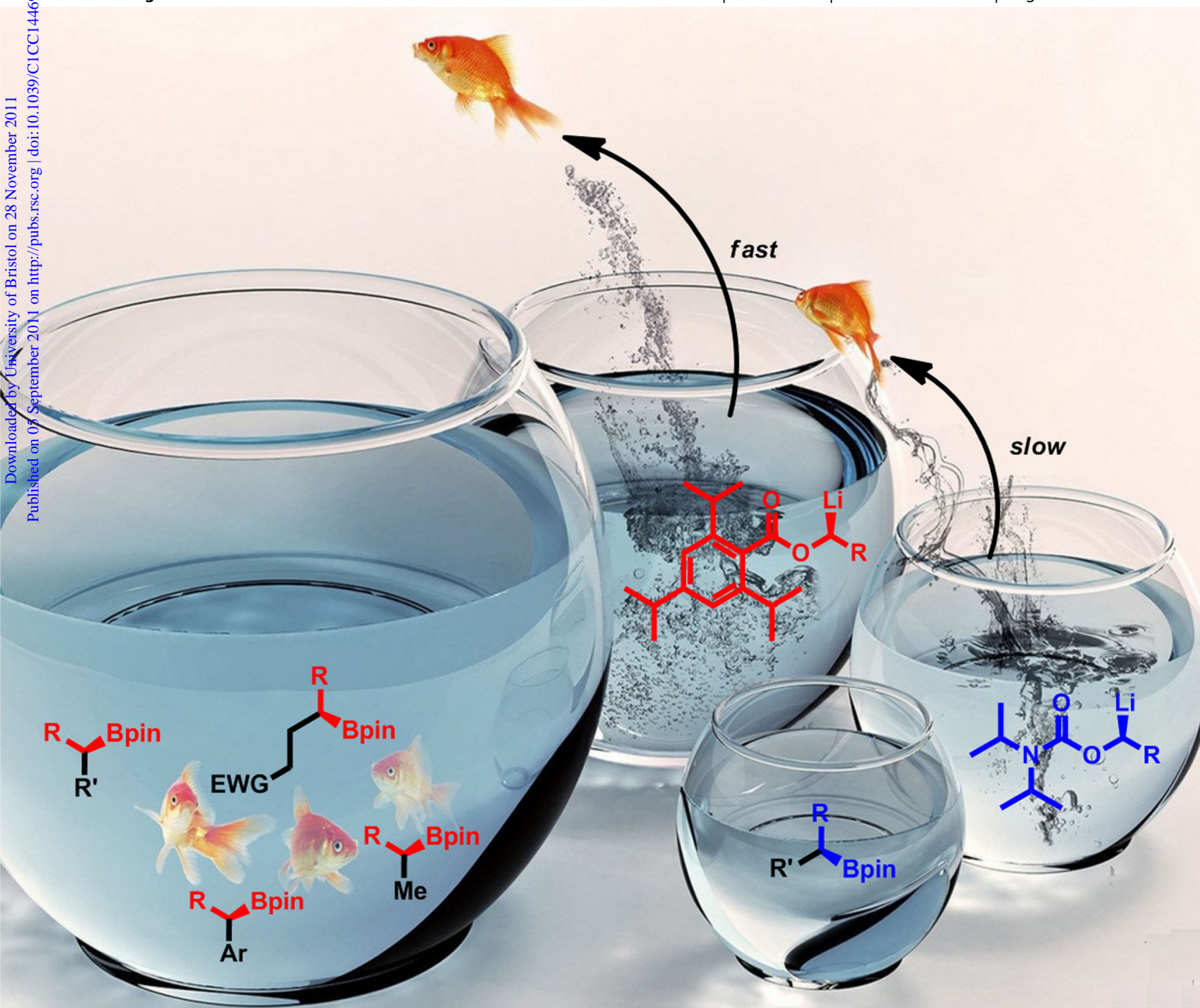
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## Use of alkyl 2,4,6-triisopropylbenzoates in the asymmetric homologation of challenging boronic esters†

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(–)-Sparteine induced lithiation of primary 2,4,6-triisopropylbenzoates and subsequent homologation of boronic esters is reported. A comparative study with lithiated *N,N*-diisopropylcarbamates has demonstrated the superiority of the hindered benzoate.

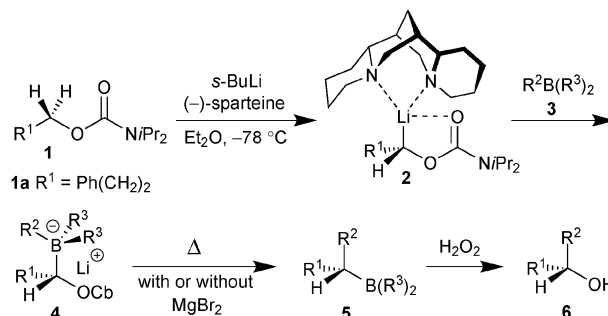
The enantioselective homologation of boronic esters has established itself as highly useful methodology in asymmetric synthesis. Matteson, a pioneer in the field, reported the homologation of chiral boronic esters with  $\text{LiCHCl}_2$  followed by the addition of a Grignard reagent, a process governed by substrate control.<sup>1</sup> An alternative approach is to use reagent control in the homologation of boron compounds which requires access to chiral carbanions bearing suitable leaving groups (carbenoids). In this context, sulfur ylides<sup>2</sup> and  $\alpha$ -chloro Grignard/organolithium reagents<sup>3</sup> have been used successfully for the homologation of boron compounds. The former carbenoid gave good enantioselectivities for boranes but was unreactive towards boronic esters, limiting their applicability.  $\alpha$ -Chloro Grignard reagents were found to react well with boronic esters, but were limited in scope and some degree of racemisation occurred during the homologation process.

Recently, we reported that Hoppe's lithiated carbamates<sup>4</sup> could be used for the homologation of both boranes and boronic esters with very high stereoselectivities (Scheme 1).<sup>5</sup> In this process, *s*-BuLi/(–)-sparteine induced asymmetric deprotonation of a primary carbamate **1** to give lithiated carbamate **2**, which reacted with a boron electrophile **3** to give an ate complex **4**, which finally underwent 1,2-metallate rearrangement to give the homologated boron compound **5**. This could be oxidised to the alcohol **6** or utilized in further homologations. Products of opposite enantioselectivity could be easily obtained by replacing (–)-sparteine with O'Brien's (+)-sparteine surrogate.<sup>6</sup> However, in exploring synthetic applications of this methodology, we have encountered certain boronic esters which were very slow to migrate. For example, we found that the synthetically important Me and  $(\text{CH}_2)_2\text{COO}t\text{Bu}$

boronic esters required Lewis acids to promote the 1,2-metallate rearrangement and yields were low. We have therefore explored alternative leaving groups and now report that using hindered benzoates, in place of carbamates, results in substantially faster 1,2-metallate rearrangement, allowing even the most reluctant of migrating groups to engage in the process.

Based on the problems highlighted above, we sought a carbenoid with a better leaving group than a carbamate and so considered the use of 2,4,6-triisopropylbenzoates. Beak had reported the  $\alpha$ -lithiation of 2,4,6-triisopropylbenzoates mediated by *s*-BuLi and TMEDA, demonstrating that deprotonation was possible with a strong base.<sup>7</sup> Hammerschmidt demonstrated that these lithiated species, generated by tin-lithium exchange from the corresponding stannanes, were configurationally stable at low temperature ( $-78^\circ\text{C}$ ).<sup>8</sup> However, no example of asymmetric lithiation of a primary 2,4,6-triisopropylbenzoate had been reported, which was therefore our first task.

Primary 2,4,6-triisopropylbenzoates were easily obtained from their corresponding alcohols by direct acylation with 2,4,6-triisopropylbenzoyl chloride (TIBCl)<sup>9</sup> (Scheme 2). We explored the asymmetric lithiation of primary 2,4,6-triisopropylbenzoates by reacting **7a** with *s*-BuLi and (–)-sparteine in  $\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$  followed by  $\text{Bu}_3\text{SnCl}$  and were pleased to isolate stannane (*S*)-**8** in high yield and 96:4 e.r. This indicated that the benzoate behaved similarly to the corresponding carbamate **1a** in promoting asymmetric deprotonation, albeit with slightly lower e.r.<sup>10</sup> Furthermore, treatment of the stannane (*S*)-**8** with *n*-BuLi followed by *i*-PrBpin (**9a**) gave,

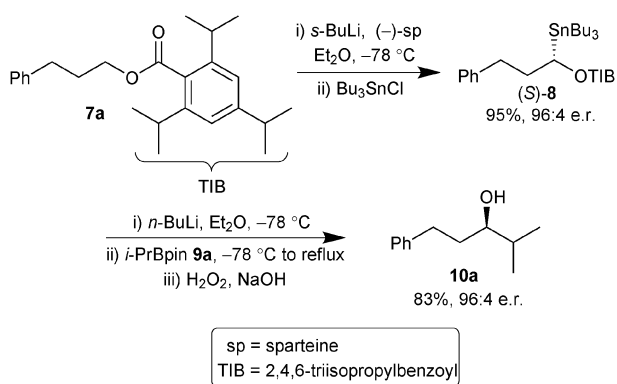


**Scheme 1** Homologation of boron compounds with lithiated primary *N,N*-diisopropylcarbamates, Cb =  $-\text{C}(\text{O})\text{NiPr}_2$ .

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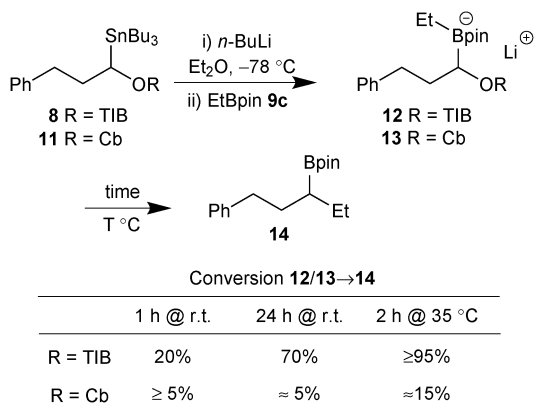


**Scheme 2** Preparation of 2,4,6-triisopropylbenzoates and homologation of boronic esters.

after oxidation, secondary alcohol **10a** in 79% yield with complete stereochemical integrity.<sup>11</sup>

The rate of 1,2-migration for boron-ate complexes derived from lithiated 2,4,6-triisopropylbenzoate and lithiated *N,N*-diisopropylcarbamate were qualitatively evaluated (Scheme 3). Stannanes **8** and **11** were treated with *n*-BuLi at  $-78\text{ }^{\circ}\text{C}$  to generate the lithiated species which were subsequently trapped with EtBpin (**9c**) and allowed to warm to RT. The reaction was monitored by  $^{11}\text{B}$  NMR as it was possible to follow the conversion of the boron-ate complexes **12** and **13** ( $\delta \sim 5\text{--}7\text{ ppm}$ ) into the homologated boronic ester **14** ( $\delta = 34\text{ ppm}$ ). After 1 h at room temperature, 20% conversion was observed for ate complex **12** whereas no sign of migration was observed for the related carbamate **13**. After 24 h, 70% conversion was observed for **12** whereas only marginal conversion was observed for **13**. More conveniently, complete conversion of the benzoate-derived boron-ate complex **12** could be achieved after only 2 h at  $35\text{ }^{\circ}\text{C}$ , whereas under the same conditions only 15% conversion of the carbamate-derived ate complex **13** had occurred. These results demonstrate the significant increase in the rate of 1,2-migration of the 2,4,6-triisopropylbenzoate compared to the *N,N*-diisopropylcarbamate.

We then explored the asymmetric homologation of a series of boronic esters with the lithiated alkyl 2,4,6-triisopropylbenzoate **7a** and compared it with the *N,N*-diisopropylcarbamate analogue **1a** (Table 1). The carbamate-derived boron-ate



**Scheme 3** Comparative rates of 1,2-migration for 2,4,6-triisopropylbenzoate vs. *N,N*-diisopropylcarbamate.

**Table 1** Comparison of benzoates and carbamates in the homologation of boronic esters

$\text{Ph-CH}_2\text{-CH}_2\text{-CH}_2\text{-OR}^1$ <b>1a</b> R <sup>1</sup> = Cb <b>7a</b> R <sup>1</sup> = TIB			i) <i>s</i> -BuLi, Et <sub>2</sub> O, (–)-sp, –78 °C ii) R <sup>2</sup> Bpin ( <b>9b-g</b> ) iii) Conditions iv) NaOH, H <sub>2</sub> O <sub>2</sub>	$\text{Ph-CH}_2\text{-CH}_2\text{-CH(OH)-R}^2$ <b>10b-g</b>	
Entry	R <sup>1</sup>	R <sup>2</sup>	Conditions <sup>a</sup>	Yield <sup>b</sup> (%)	e.r. <sup>c</sup>
1	Cb	Me <b>9b</b>	A	<10	n.d.
2	Cb	Me <b>9b</b>	B	50	95:5
3	TIB	Me <b>9b</b>	C	76	96:4
4	Cb	Et <b>9c</b>	A	73	99:1
5	Cb	Et <b>9c</b>	B	70	99:1
6	TIB	Et <b>9c</b>	C	84	96:4
7	Cb	<i>c</i> Pr <b>9d</b>	A	71	98:2
8	Cb	<i>c</i> Pr <b>9d</b>	B	n.d.	n.d.
9	TIB	<i>c</i> Pr <b>9d</b>	C	86	96:4
10	Cb	(CH <sub>2</sub> ) <sub>2</sub> COO <i>t</i> Bu <b>9e</b>	A	0	n.d.
11	Cb	(CH <sub>2</sub> ) <sub>2</sub> COO <i>t</i> Bu <b>9e</b>	B <sup>d</sup>	35	93:7
12	TIB	(CH <sub>2</sub> ) <sub>2</sub> COO <i>t</i> Bu <b>9e</b>	A	63	96:4
13	Cb	(CH <sub>2</sub> ) <sub>2</sub> CN <b>9f</b>	A	0	n.d.
14	Cb	(CH <sub>2</sub> ) <sub>2</sub> CN <b>9f</b>	B	0	n.d.
15	TIB	(CH <sub>2</sub> ) <sub>2</sub> CN <b>9f</b>	A	46	97:3
16	Cb	Ph <b>9g</b>	A	<10	n.d.
17	Cb	Ph <b>9g</b>	B	88	99:1
18	TIB	Ph <b>9g</b>	C	79	96:4

<sup>a</sup> Conditions A: 16 h reflux. Conditions B: MgBr<sub>2</sub>·Et<sub>2</sub>O (2 equiv.), 16 h, reflux. Conditions C: 2 h, reflux. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> 5 days, reflux. n.d. = Not determined. *c*Pr = cyclopropyl.

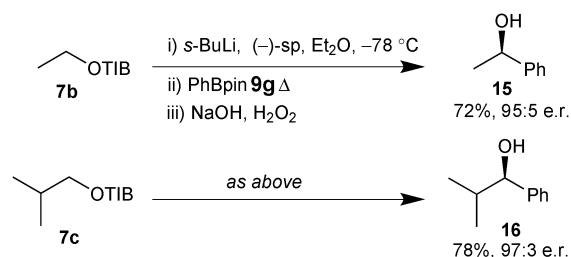
complex was reacted for 16 h at  $35\text{ }^{\circ}\text{C}$  (conditions A), or under the more forcing conditions of 16 h at  $35\text{ }^{\circ}\text{C}$  in the presence of MgBr<sub>2</sub>,<sup>12</sup> (conditions B). The benzoate ester-derived boron-ate complex was reacted for 2 h at  $35\text{ }^{\circ}\text{C}$  (conditions C).

In this study we largely focussed on boronic esters that did not migrate easily and began with MeBpin (**9b**). As is evident from entry 1, the Me group is a very slow migrating group indeed and hardly migrated at all after 16 h at  $35\text{ }^{\circ}\text{C}$  when the carbamate group was employed. The addition of MgBr<sub>2</sub> improved the yield to 50% (entry 2) but the reaction employing the benzoate produced the desired alcohol in 76% yield after only 2 h under reflux (conditions C) (entry 3).

For groups on boron with good migratory aptitude (Et and *c*Pr, entries 4–9), we found only moderate improvement in yields when the benzoate ester was employed compared to the carbamate. Nonetheless, the shorter reaction times for the homologations involving the benzoate are noteworthy (2 h vs. 16 h).

Boronic esters bearing  $\beta$ -electron withdrawing groups [ester (**9e**) or nitrile (**9f**)] turned out to be very slow migrating groups (entries 10–15). Even under the most forcing conditions using MgBr<sub>2</sub>·Et<sub>2</sub>O these groups hardly migrated when carbamate leaving groups were employed (entries 11,14). Even after 5 days under reflux in the presence of MgBr<sub>2</sub>·Et<sub>2</sub>O, the ester **9e** had only migrated to a limited extent and gave the desired alcohol **10d** in only 35% yield (entry 11). In contrast, using the lithiated benzoate the alcohol **10d** was produced in 63% after 16 h at  $35\text{ }^{\circ}\text{C}$  (without any Lewis acid) and in 96:4 e.r. (entry 12). A similar trend was observed in the homologation of cyano substituted boronic ester **9f**, which only worked with the lithiated benzoate (entry 15).





**Scheme 4** Effect of alkyl substituent's bulk on stereoselectivity.

Boronic esters bearing aryl groups also emerged as slow migrating groups (entry 16). Heating at reflux for 16 h in the presence of Lewis acid was required with the lithiated carbamate, to obtain the alcohol **9g** (entry 17). Once again, the benzoate showed remarkable reactivity, allowing the production of the desired alcohol in similar yield and selectivity after only 2 h under reflux without any Lewis acid assistance (entry 18).

The factors that affect the rate of migration of boron substituents are complex and include steric, conformational and electronic effects.<sup>13</sup> In the examples of the slow migrating groups, we believe that the following issues may be operative. In the case of the small Me substituent, the short C–B bond length in the boron-ate complex will make it a stronger bond and so the barrier to migration will be greater.<sup>14</sup> Substituents bearing electron withdrawing groups will be less nucleophilic and so will migrate less rapidly. Although Ph is usually a good migrating group, it had been found to be poor when sulfonium ions were leaving groups but this was due to conformational effects.<sup>15</sup> Such effects are absent here and as such it is not easy to account for its poor migrating ability.

We finally explored the scope of the primary alkyl substituent of the 2,4,6-triisopropylbenzoate in the homologation of PhBpin (**9g**) (Scheme 4). Both the less hindered ethyl (**7b**) and the more hindered isobutyl (**7c**) benzoate esters worked well giving high yields and high enantioselectivities (95:5 and 97:3 e.r. respectively) in the lithiation-borylation reaction, similar to the levels observed with the corresponding carbamates (97:3 and 98:2 e.r. respectively<sup>5a</sup>).

In summary, we have found that  $\alpha$ -lithiated alkyl 2,4,6-triisopropylbenzoates can be easily generated using s-BuLi/(-)-sparteine and subsequent addition to boronic esters leads to boron-ate complexes which rapidly undergo 1,2-metallate rearrangement to give homologated products. The significant increase in rate of the 1,2-metallate rearrangement compared to carbamates now enables the homologation of the most challenging boronic esters including those that were essentially unusable before. The increased scope now broadens the range of chiral secondary boronic esters that can be prepared,<sup>16</sup> and these constitute important substrates in asymmetric synthesis in general.<sup>17</sup>

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