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Generation of Organolithium Compounds bearing Super Silyl Ester and their Application to Matteson Rearrangement**

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Organolithium compounds are versatile intermediates in organic synthesis. Since they are highly reactive and readily available from organohalides by lithium/halogen exchange, their reaction with various electrophiles is one of the most powerful methods for C–C bond formation.[1] However, their synthetic utility has been restricted by limited functional group compatibility. For example, organolithium compounds bearing an ester group suffer significantly from self-condensation (Figure 1 a). Since direct transformation of ester derivatives provides a concise synthetic route to numerous organic compounds, great efforts have been made to solve this long-standing problem. One way to utilize such an unstable intermediate is the use of a microflow system described by Yoshida et al.[2] They found the microflow reactor allows the direct lithiation of aryl halides bearing an ester group and the subsequent reaction with electrophiles.[2] On the other hand, a wide range of functional groups are compatible with less-reactive organometallic reagents, such as organozinc[3] and organomagnesium[4] reagents. Knochel et al. reported the turbo Grignard reagent (*i*PrMgBr·LiCl) undergoes metal/halogen exchange with aryl halides and the resulting arylmagnesium reagents demonstrate high tolerance toward electrophilic functional groups. Despite the advance of these alternative methods, a general strategy for direct lithiation in a macrobatch reactor that is compatible with the ester functional group has not been accomplished. Toward this end, the utilization of an unaffected ester under highly nucleophilic conditions would be straightforward and advantageous. Even the sterically demanding *tert*-butyl ester, however, requires extremely low temperature to suppress the self-condensation.[5] Therefore, the development of a robust protecting group for carboxylic acids, which can be easily masked and removed, is desirable.

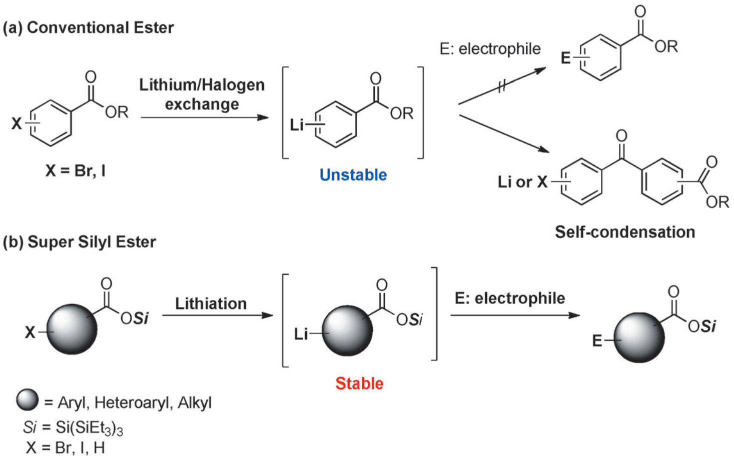

Figure 1. Organolithium compounds bearing ester moieties.

Tris(trialkylsilyl)silyl groups, such as $Si(TMS)_3$ and $Si(TES)_3$, which are called "super silyl" groups, demonstrate unique reactivity owing to their steric bulk and electronic properties. Our group reported Mukaiyama aldol reactions using super silyl enol ethers to afford the mono, double, and triple cross-aldol products with excellent diastereoselectivity.[6] Halogenated super silyl enol ethers were also used to construct the halogenated polyketide-like structures. Recently, we have developed super silyl esters as a new class of protected carboxylic acids and applied them to diastereoselective aldol and Mannich reactions.[7] Therein, the super silyl group plays a crucial role not only as a stereodirecting group to attain high diastereoselectivity, but as a perfect protecting group to stabilize the lithium enolate intermediate. Further, its protection/deprotection process is completed under mild conditions. Encouraged by these results, we envisioned the super silyl group would prevent the organolithium intermediate bearing ester from self-condensation and provide facile synthetic transformations (Figure 1 b).

A series of super silyl esters were synthesized quantitatively by our reported method[7] from carboxylic acid and tris(triethylsilyl)silane, and the lithiation of super silyl halobenzoate was investigated (Table 1). Treatment of super silyl *para*-iodobenzoate **1a** with *tert*-butyllithium in THF at −78 °C led to *para*-lithiobenzoate intermediate and the subsequent addition of benzaldehyde gave the product **2a** in 80 % yield (entry 1). The use of *para*-bromobenzoate resulted in slightly higher yield (entry 2). The microflow system has relatively low efficiency for lithiation of aryl bromides owing to the sluggish Br/Li exchange[2a] and the present method is complementary in regard to the scope of application. The reaction

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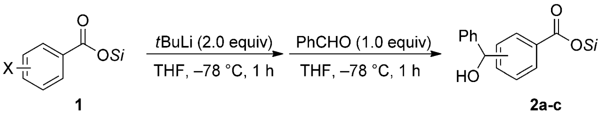
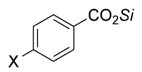
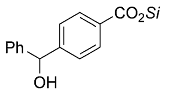
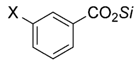
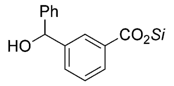
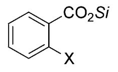
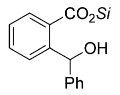
Table 1: Lithiation of super silyl halobenzoate.[a]

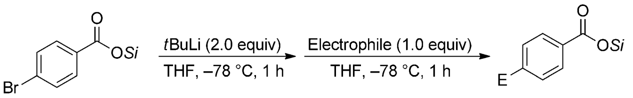


1
Si = Si(SiEt$_3$)$_3$
2a-c

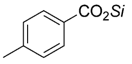
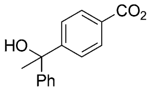
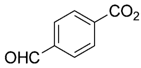
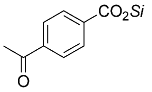
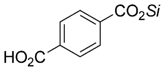
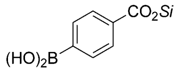
Entry	Super silyl halobenzoate	X	Product		Yield [%][b]
1		I		**2a**	80
2		Br			87
3		Cl			0
4		Br		**2b**	84
5		Br		**2c**	83

[a] All reactions were performed at 0.2 mmol scale. [b] Yield of isolated product.

Table 2: Scope of electrophiles.[a]



1a'
Si = Si(SiEt$_3$)$_3$
3a-f

Entry	Electrophile	Product		Yield [%][b]
1	MeI		**3a**	84
2	acetophenone		**3b**	85
3	DMF		**3c**	66
4	DMA		**3d**	31
5	CO_2		**3e**	49
6	B(OEt)$_3$		**3f**	64

[a] All reactions were performed at 0.2 mmol scale. [b] Yield of isolated product.

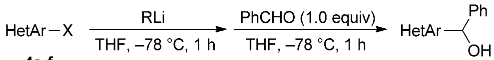
failed with *para*-chlorobenzoate because of the difficulty of the Cl/Li exchange (entry 3).[8] Lithiation of *meta*- and *ortho*-bromobenzoate took place successfully and furnished the desired product in high yield (entries 4 and 5). No self-condensation product was detected. As expected, an aryllithium bearing a super silyl ester is highly stable at low temperature.[9] While reaction of *tert*-butyl *ortho*-lithiobenzoate with benzaldehyde afforded the corresponding lactone through intramolecular cyclization, the super silyl ester gave the products without any of these side reactions.

Next, we screened the scope of electrophiles. As highlighted in Table 2, super silyl *para*-lithiobenzoate was able to react with a variety of electrophiles, such as methyl iodide, ketone, amide, carbon dioxide, and borate in moderate to high yields. Formylation and acylation were achieved by using dimethylformamide (DMF) and dimethylacetamide (DMA) (Table 2, entries 3 and 4). The reaction with carbon dioxide gave the carboxylated product **3e** (entry 5). The use of triethylborate led to the boronic acid **3f** (entry 6).

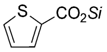
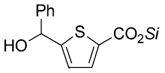
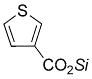
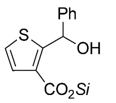
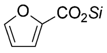
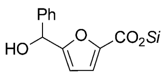
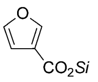
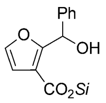
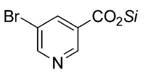
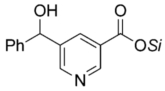
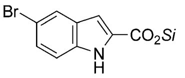
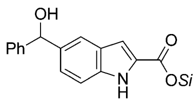
Our method can be applied to heteroaromatic rings:[10] results of lithiation of super silyl heteroaryl esters are shown in Table 3. Thiophene- and furan-derived super silyl esters participated in α-lithiation by using *n*-butyllithium. The reaction of 2-thiophenecarboxylate with benzaldehyde gave the product **5a** in 71% yield (Table 3, entry 1). Notably, 3-thiophenecarboxylate **4b** was selectively functionalized at the sterically congested 2-position, which indicates the super silyl ester has a directing effect analogous to the conventional ester (entry 2). The use of super silyl furyl esters **4c** and **4d** worked as well to give **5c** and **5d** in good yield (entries 3 and 4). Super silyl 5-bromopyridine-3-carboxylate **4e** was converted into the product **5e** in 48% yield (entry 5). The Li/Br exchange reaction proceeded smoothly without the protection of the nitrogen atom. Indole-derived super silyl ester **4f** was also applied to afford the product **5f** by using three equivalents of *tert*-butyllithium (entry 6).

In our prior studies, we found that lithiation of super silyl propionate provides the stable lithium enolate for aldol and

Table 3: Lithiation of heteroaromatic super silyl esters[a].



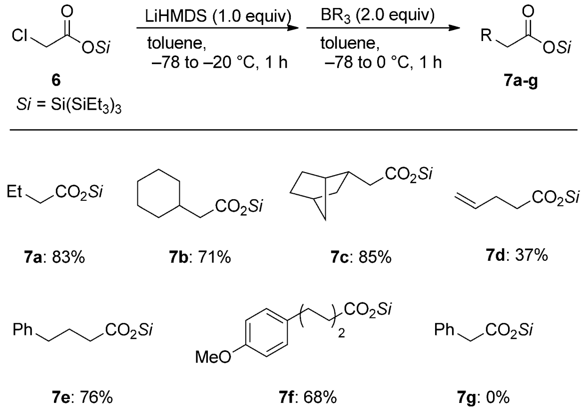
4a-f
X = H, Br
Si = Si(SiEt$_3$)$_3$
5a-f

Entry	HetAr-X	Product[b]		Yield [%][e]
1[b]			**5a**	71
2[b]			**5b**	81
3[b]			**5c**	77
4[b]			**5d**	82
5[c]			**5e**	48
6[d]			**5f**	78

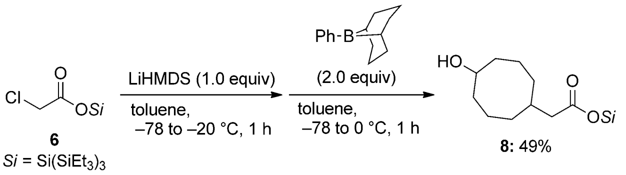
[a] All reactions were performed at 0.2 mmol scale. [b] *n*BuLi (1.0 equiv) was used. [c] *t*BuLi (2.0 equiv) was used. [d] *t*BuLi (3.0 equiv) was used. [e] Yield of isolated product.

Mannich reactions.[7] Taking advantage of the inactive Cl/Li exchange, we envisioned lithiation of super silyl α-chloroacetate would give α-chloro lithium enolate, which can be used for a Matteson rearrangement[11] to attain α-functionalization of the ester moiety.[12] α-Arylation is, in particular, a valuable method to give access to α-aryl carboxylic acids, an important structural class for pharmaceuticals. While a number of transition-metal-catalyzed α-arylations has been reported,[13] the direct reaction of easy accessible boron and organolithium compounds is still attractive. Aggarwal et al. accomplished a great achievement in the asymmetric homologation of boron compounds by using lithiated carbamates.[14]

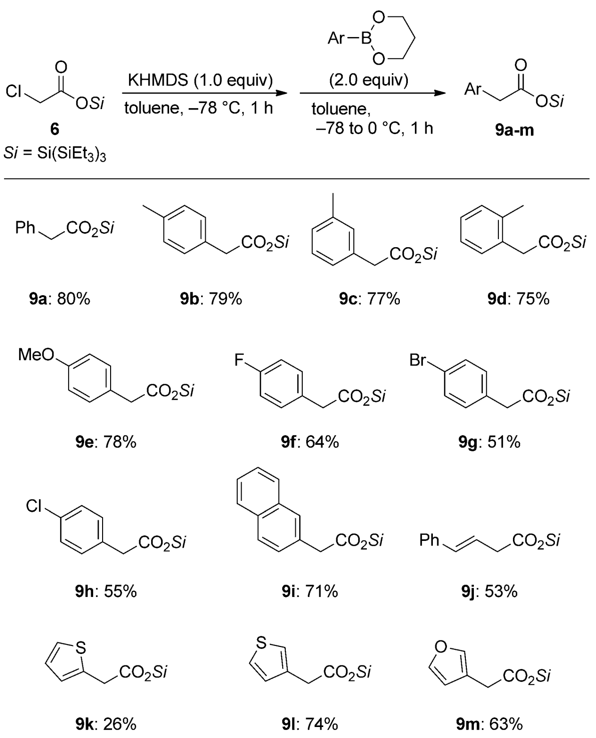
Super silyl chloroacetate **6** was treated with lithium bis(trimethylsilyl)amide (LiHMDS) to form α-chloro lithium enolate, followed by the addition of trialkyl borane (BR_3). α-Alkylation of super silyl chloroacetate is summarized in Scheme 1. Super silyl butyrate **7a** was obtained in 83 % yield by using triethyl borane. Secondary alkyl boranes, such as cyclohexyl and norbornyl borane were also applicable. While the reaction with triallylborane gave a complex mixture of side-products, 2-phenethyl and hydrocinnamyl borane furnished **7e** and **7f** in good yields. No product was observed with the use of triphenyl borane. Surprisingly, when lithiated **6** was treated with a 9-BBN (9-BBN = 9-borabicyclo-[3.3.1]nonane) derived phenylborane, the alkyl-migration product **8** was obtained (Scheme 2). Although it has been demonstrated to give aryl-migration product in Aggarwal's report,[14b] the cyclooctyl group migrated presumably because it positions *anti*-periplanar against the σ* orbital of the C–Cl bond due to steric repulsion between 9-BBN and the super silyl group (see Scheme 4B).[14f]



Scheme 1. α-Alkylation of super silyl chloroacetate by Matteson rearrangement. All reactions were performed at 0.2 mmol scale. The yields are of isolated products.



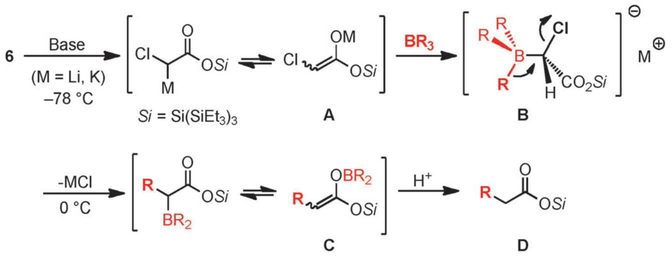
Scheme 2. The reaction of super silyl chloroacetate with 9-BBN derived phenyl borane.



Scheme 3. α-Arylation of super silyl chloroacetate by Matteson rearrangement. All reactions were performed at 0.2 mmol scale. The yields are of isolated products.

To our delight, aryl migration took place with the use of aryl propanediol boronate.[15] For these reactions, potassium bis(trimethylsilyl)amide (KHMDS) was found to be suitable and α-arylation of super silyl chloroacetate proceeds smoothly (Scheme 3). The reaction demonstrated high tolerance to the substituent of aromatic ring at the *ortho*, *meta*, and *para* positions. Electron-rich aryl boronates resulted in higher yield than electron-deficient aryl boronates. The reaction with haloaryl boronates left the halogen atom intact, proving an opportunity for further transformations. The rearrangement occurred with the use of sterically hindered naphthyl boronate and vinyl-derived cinnamyl boronate to provide **9i** and **9j**. Although the use of 2-thienyl boronate gave **9k** in low yield, 3-thienyl boronate afforded **9l** effectively, indicating the coordination of the thiophene ring has negative effect on the migration. 3-Furylboronate also worked to furnish **9m** in 63 % yield.

A proposed mechanism is shown in Scheme 4. Super silyl chloroacetate is deprotonated by base (LiHMDS or KHMDS) to generate metal enolate **A**, and the reaction with a boron compound leads to the formation of boron ate complex **B**. 1,2-Metallate rearrangement occurs to give the boron enolate **C**. Finally, the desired product **D** is obtained after being quenched with NH_4Cl aqueous solution. The super silyl group is indispensable to protect the intermediates **A** and **C** and inhibit their self-condensation. While LiHMDS succeeded for α-alkylation, the decomposition of intermediate **B** was observed with warming up to 0 °C for α-arylation. Thus,



Scheme 4. Proposed mechanism for Matteson rearrangement of super silyl chloroacetate.

1,2-metallate rearrangement of boronic esters is slower than boranes.[14b] The use of KHMDS might help to stabilize the intermediate **B** and promote the aryl migration.[16]

In summary, super silyl haloesters and heteroaromatic super silyl esters were synthesized in high yields. By treating with an alkyllithium reagent, the lithium/halogen exchange or deprotonation reaction gave the organolithium reagents bearing a super silyl ester group. They were found to react with a variety of electrophiles, such as aldehyde, ketone, amide, carbon dioxide, and borate. Moreover, α-functionalization of super silyl chloroacetate was successful by a Matteson rearrangement. Thus, the super silyl group is a strong and robust protecting group even against highly reactive anionic species. Further application of super silyl ester is under investigation.

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Keywords: arylation · matteson rearrangement · organolithium reagents · super silyl · synthetic methods

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[1] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975–3984; c) M. Schlosser, *Angew. Chem.* **2005**, *117*, 380–398; *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393; d) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256–2276; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.

[2] a) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167–11177; b) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem.* **2008**, *120*, 7951–7954; *Angew. Chem. Int. Ed.* **2008**, *47*, 7833–7836.

[3] a) X.-J. Wang, X. Sun, L. Zhang, Y. Xu, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2006**, *8*, 305–307; b) Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717–4718.

[4] a) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336; b) L. Boymond, M. Rottländer, G. Chiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801–1803; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701–1703; c) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024–3027; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961.

[5] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704–2706; b) W. E. Parham, Y. A. Syed, *J. Org. Chem.* **1974**, *39*, 2053–2056; c) W. E. Parham, C. K. Bradsher, *Acc. Chem. Res.* **1982**, *15*, 300–305.

[6] a) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48–49; b) M. B. Boxer, H. Yamamoto, *Nat. Protoc.* **2006**, *1*, 2434–2438; c) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 2762–2763; d) M. B. Boxer, H. Yamamoto, *Org. Lett.* **2008**, *10*, 453–455; e) M. B. Boxer, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 1580–1582; f) M. B. Boxer, B. J. Albert, H. Yamamoto, *Aldrichimica Acta* **2009**, *42*, 3–15; g) B. J. Albert, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 2807–2809; *Angew. Chem. Int. Ed.* **2010**, *49*, 2747–2749; h) Y. Yamaoka, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5354–5356; i) B. J. Albert, Y. Yamaoka, H. Yamamoto, *Angew. Chem.* **2011**, *123*, 2658–2660; *Angew. Chem. Int. Ed.* **2011**, *50*, 2610–2612; j) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 14248–14251; k) P. B. Brady, H. Yamamoto, *Angew. Chem.* **2012**, *124*, 1978–1982; *Angew. Chem. Int. Ed.* **2012**, *51*, 1942–1946.

[7] J. Tan, M. Akakura, H. Yamamoto, *Angew. Chem.* **2013**, DOI: 10.1002/ange.201300102; *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201300102.

[8] a) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Tetrahedron Organic Chemistry Series, Vol. 23; b) M. Yus, R. Ortiz, F. F. Huerta, *Tetrahedron* **2003**, *59*, 8525–8542.

[9] The stability of super silyl *para*-lithiobenzoate was investigated. See the Supporting Information for details.

[10] a) M. A. J. Miah, V. Snieckus, *J. Org. Chem.* **1985**, *50*, 5436–5438; b) R. J. Mills, V. Snieckus, *J. Org. Chem.* **1989**, *54*, 4386–4390; c) M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez, V. Snieckus, *J. Org. Chem.* **2007**, *72*, 1588–1594.

[11] a) D. S. Matteson, D. J. Majumder, *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590; b) D. S. Matteson, D. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591; c) D. S. Matteson, K. M. Sadhu, *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078; d) D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 1529–1535; e) H. C. Brown, M. V. Rangaishenvi, S. Jayaraman, *Organometallics* **1992**, *11*, 1948–1954; f) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535–1551.

[12] a) H. C. Brown, M. M. Rogic, M. W. Rathke, G. W. Kabalka, *J. Am. Chem. Soc.* **1968**, *90*, 818–820; b) H. C. Brown, M. M. Rogic, M. W. Rathke, *J. Am. Chem. Soc.* **1968**, *90*, 6218–6219; c) H. C. Brown, H. Nambu, M. M. Rogic, *J. Am. Chem. Soc.* **1969**, *91*, 6852–6854; d) H. C. Brown, H. Nambu, M. M. Rogic, *J. Am. Chem. Soc.* **1969**, *91*, 6854–6855.

[13] a) M. Durandetti, J. Y. Nédélec, J. Périchon, *J. Org. Chem.* **1996**, *61*, 1748–1755; b) M. Durandetti, C. Gosmini, J. Périchon, *Tetrahedron* **2007**, *63*, 1146–1153; c) W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002; d) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541–555; e) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177; f) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5182–5191.

[14] a) J. L. Stymiest, V. Bagutski, R. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782; b) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem.* **2007**, *119*, 7635–7638; *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494; c) V. Bagutski, R. M. French, V. K. Aggarwal, *Angew. Chem.* **2010**, *122*, 5268–5271; *Angew. Chem. Int. Ed.* **2010**, *49*, 5142–5145; d) S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24–39; e) R. Robiette, G. U. Fang, J. N. Harvey, V. K. Aggarwal, *Chem. Commun.* **2006**, 741–743; f) G. Y. Fang, O. A. Wallner, N. D. Blasio, X. Ginesta, J. N. Harvey, V. K. Aggarwal, *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.

[15] The use of more stable boronic esters, such as neopentyl glycol and pinacol gave the product in low yields, presumably due to their steric hindrance.

[16] The use of KHMDS for α-alkylation gave comparable results with LiHMDS.