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Synthesis of Ortho Substituted Arylboronic Esters by in Situ Trapping of Unstable Lithio Intermediates

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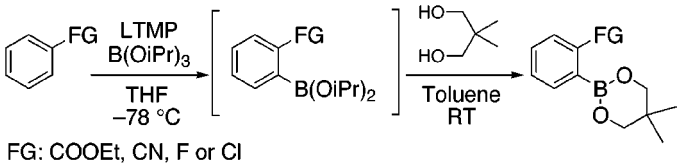
ABSTRACT



FG: COOEt, CN, F or Cl

Ortho lithiation–in situ boration using lithium 2,2,6,6-tetramethylpiperidide (LTMP) in combination with triisopropylborate ($B(OiPr)_3$) is a highly efficient and experimentally straightforward process for the preparation of ortho substituted arylboronic esters. The mild reaction conditions allow the presence of functionalities such as ester or cyano groups or halogen substituents that are usually not compatible with the conditions used in directed ortho metalation of arenes. The arylboronic esters underwent Suzuki-type cross-coupling with a range of aryl halides, furnishing biaryls in 53–94% yield.

The Pd(0)-catalyzed cross-coupling reaction has become one of the most widely used methods of accessing biaryls, and in particular the Suzuki-Miyaura reaction, using arylboronic acids, has emerged as one of the most popular.[1] Catalyst systems that allow coupling with aryl chlorides have been developed, greatly expanding the scope of the reaction.[2] Recently, arylboronic acids have also been used in C−O,[3] C−N,[4] and C−S[5] bond forming reactions. Traditionally, arylboronic acids have been prepared by reacting an aryllithium intermediate, generated by deprotonation or halogen−metal exchange, with a trialkylborate.[6] Alternatively, they can be synthesized from arylhalides via Pd(0)-catalyzed coupling with tetraalkoxydiboron[7] or dialkoxyborane.[8]

In 1983 Krizan and Martin introduced the concept of in situ trapping, i.e., using a sterically hindered base to generate an unstable lithio intermediate while having the electrophile present.[9] In that way they were able to ortho lithiate alkyl benzoates and benzonitrile and trap these intermediates with electrophiles. Recently, Caron and Hawkins applied this methodology to the synthesis of substituted ortho boronyl neopentylbenzoates, using lithium diisopropylamide (LDA) with triisopropylborate ($B(OiPr)_3$) present as in situ trap.[10]

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(7) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

(8) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (c) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268.

(9) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(10) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.

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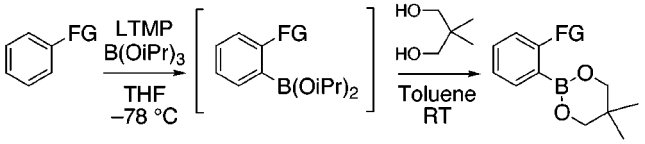
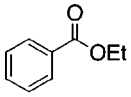
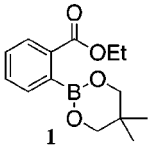
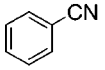
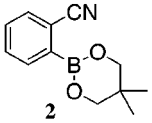
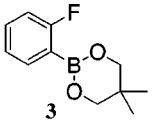
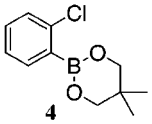
We have found that lithium 2,2,6,6-tetramethylpiperidide (LTMP) in combination with $B(OiPr)_3$ is an excellent reagent system for the synthesis of ortho substituted arylboronic esters. Thus, treatment of ethyl benzoate, benzonitrile, fluorobenzene, or chlorobenzene with 1.5 equiv of LTMP and 2.0 equiv of $B(OiPr)_3$ in THF at −78 °C gave the corresponding ortho substituted boronic esters, which were conveniently isolated as their 2,2-dimethyl-1,3-propandiol (neopentylglycol) adducts in high yields (see Table 1).[11]

Table 1. Preparation of Ortho Substituted Neopentylglycol Arylboronic Esters



entry	substrate	product[a]	yield (%)[b] LDA	LTMP
1		 **1**	0[c]	92
2		 **2**	0[c]	61[d]
3		 **3**	87	98
4		 **4**	< 30[e]	96

[a] For reaction conditions, see representative procedure, ref 26. [b] Isolated yields of analytically pure compound. All reactions performed on 25 mmol scale. [c] *N,N*-Diisopropylbenzamide isolated as only product. [d] Crude product recrystallized from heptane. [e] Crude product ~70% pure.[22]

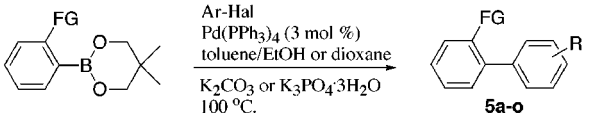
These boronic esters are stable,[12] nonhygroscopic, and easy to characterize.[13] The reactions were generally very clean, since the crude products obtained after aqueous workup in the reactions with ethyl benzoate, fluorobenzene, and chlorobenzene were analytically pure. As seen from Table 1, the choice of base is very important for the success of the reaction. Treatment of ethyl benzoate with LDA/$B(OiPr)_3$ yields exclusively *N,N*-diisopropylbenzamide resulting from the addition of LDA to the ester. In accordance with this result, Caron and Hawkins[10] reported that the attempted lithiation−in situ trapping of the more sterically hindered neopentyl benzoate and 4-*tert*-butyl-neopentyl benzoate with

(11) Attempts to use benzaldehyde, nitrobenzene, bromobenzene, or iodobenzene under similar conditions did not produce the corresponding ortho substituted arylboronic esters in significant amounts.

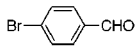
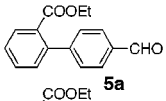
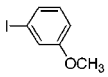
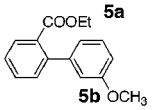
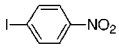
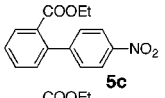
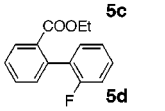
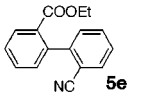
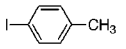
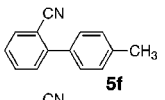
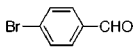
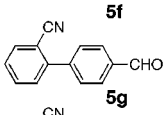
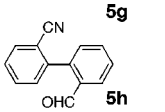
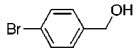
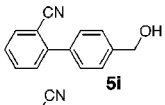
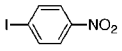
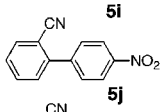
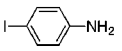
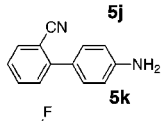
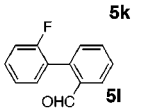
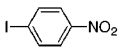
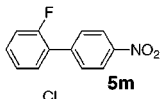
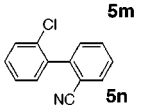
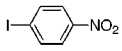
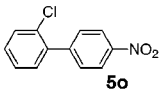
(12) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51.

(13) Characterization of free arylboronic acids is often hampered by the formation of anhydrides.

Table 2. Suzuki Cross-Couplings of Arylboronic Esters **1**−**4**



5a-o

Entry	Boronic ester	Arylhalide	Product	Reaction[a] conditions	Yield[b] (%)
1	**1**		 **5a**	A	80
2	**1**		 **5b**	A	75
3	**1**		 **5c**	A	84
4	**1**		 **5d**	A	72
5	**1**		 **5e**	A	70
6	**2**		 **5f**	B	72
7	**2**		 **5g**	B	73
8	**2**		 **5h**	B	91
9	**2**		 **5i**	B	76
10	**2**		 **5j**	B	84
11	**2**		 **5k**	B	53
12	**3**		 **5l**	B	85
13	**3**		 **5m**	B	86
14	**4**		 **5n**	B	94
15	**4**		 **5o**	B	80

[a] Cross-coupling conditions: (A) $Pd(PPh_3)_4$, dioxane, $K_3PO_4 \cdot 3H_2O$, 100 °C. (B) $Pd(PPh_3)_4$, toluene/EtOH, K_2CO_3, 100 °C. [b] Yields of chromatografically pure products.

LDA/B(O*i*Pr)$_3$ also led to formation of the corresponding diisopropylamides. In contrast to these results, ethyl benzoate devoid of any activating/stabilizing substituents could be converted to the desired arylboronic ester **1** in 92% yield (entry 1, Table 1) when LTMP was employed.[14] Under analogous conditions, benzonitrile gave the expected product **2** (entry 2, Table 1) along with 20−25% of the benzamide resulting from the addition of LTMP to benzonitrile.[15] Attempts to suppress this unwanted side reaction using other sterically hindered bases such as bis(2,2,6,6-tetramethylpiperidino)magnesium[16] or lithium *tert*-butyltritylamide[17] were unsuccessful.[18] However, **2** could be isolated in 61% yield after recrystalization. As in the case of ethyl benzoate it is crucial that LTMP is used for the lithiation of benzonitrile, since *N*,*N*-diisopropylbenzamide was the only detectable product when LDA was employed. Fluorobenzene is readily lithiated either by alkyllithium bases or LTMP at −78 °C.[6b,19] In contrast, there is only a single example of the ortho lithiation of chlorobenzene.[20] The reaction had to be performed at −105 °C to avoid the formation of benzyne. As seen in Table 1 (entries 3 and 4), the ortho lithiation−in situ trapping works remarkably well with LTMP. Thus, fluorobenzene is smoothly converted to the desired arylboronic ester **3** in 98% and 87% yield, using LTMP and LDA, respectively.[21] Chlorobenzene gave arylboronic ester **4** in 96% isolated yield when LTMP was used. Again LDA proved inefficient for the transformation, as **4** was isolated in less than 30% yield along with numerous impurities.[22]

As illustrated in Table 2, the ortho substituted arylboronic esters[23] **1**−**4** were coupled efficiently with sterically hindered, with electron-rich, and with electron-poor aryl halides under standard Suzuki-type conditions, furnishing a range of unknown or otherwise difficultly accessible[24] biaryls, including products (e.g., **5a,f,g,i**) with a potential as intermediates in the synthesis of non-peptide angiotensin II receptor antagonists such as losartan and analogues thereof.[25]

In conclusion, the presented ortho lithiation−in situ trapping of substituted arenes using LTMP/B(O*i*Pr)$_3$ represents an efficient and experimentally simple way of synthesizing ortho substituted arylboronic esters.[26] The mild reaction conditions allow the presence of functionalities such as ester or cyano groups or halogen substituents that are usually not compatible with the conditions used in directed ortho metalation of arenes.[27] The scope and limitations of this method are currently under investigation in our laboratories.

Supporting Information Available: Detailed experimental procedures and full characterization for compounds **1**−**4** and **5a**−**o**. This information is available free of charge via the Internet at http://pubs.acs.org.

OL015598+

(14) Upton and Beak reported that alkyl benzoates can be deprotonated with LTMP and that the resulting anions self-condense: Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094.

(15) See Supporting Information for details.

(16) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016.

(17) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515.

(18) Quenching at −78 °C, increasing the amount of solvent, using trimethylborate, or switching from THF to Et$_2$O did not improve the ratio between **2** and the amide.

(19) (a) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, E. *Tetrahedron Lett*. **1992**, *33*, 7495. (b) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, E. *Tetrahedron Lett*. **1992**, *33*, 7499.

(20) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622.

(21) Rocca et al. prepared 2-(fluorobenzene)boronic acid in 37% yield from fluorobenzene using *n*-BuLi as base, see ref 6b.

(22) GC−MS of the crude product showed the presence of *N*,*N*-diisopropylaniline, clearly indicating the formation of benzyne during the reaction.

(23) For synthesis of biaryls using arylboronic esters, see: ref 8c and Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841.

(24) See Supporting Information for details.

(25) (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermanns, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525. (b) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermanns, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

(26) **Representative Procedure. Preparation of 2-(2-Chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane (4).** B(O*i*Pr)$_3$ (50 mmol, 11.5 mL) was added to a solution of freshly prepared LTMP (37.5 mmol) in THF (40 mL) at −78 °C. Stirring was continued for 5 min before chlorobenzene (24.9 mmol, 2.80 g) was added neat via syringe. The mixture was stirred at −78 °C for 2 h, subsequently warmed to room temperature over 3−4 h, and quenched with saturated NH_4Cl (100 mL). Extraction with EtOAc (3 × 100 mL), drying of the combined organic phases (Na_2SO_4), and evaporation of the solvent produced a crude product, which was dissolved in toluene (100 mL); 2,2-dimethyl-1,3-propandiol (30 mmol, 3.13 g) was then added. The mixture was stirred overnight at room temperature. The toluene phase was washed with water (3 × 50 mL), and the combined aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 phase was washed once with water (50 mL) and combined with the toluene extract from above. Drying (Na_2SO_4) and removal of the solvent gave 5.35 g (96%) analytically pure 2-(2-chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane (**4**) as slightly orange crystals, mp 35 °C. Recrystalization from heptane gave white crystals, mp 36 °C.

(27) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.