Synthesis of Benzyl Alcohol Building Blocks Bearing an Aldehyde, Pinacol Borane or Carboxylic Acid Motif via Lithium–Bromide Exchange

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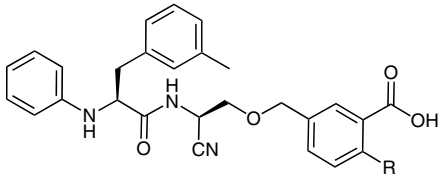
Abstract: A range of useful disubstituted benzyl alcohol building blocks have been synthesised in multigram quantities in a lithium–bromide exchange to give aldehyde, carboxylic acid and pinacol boranes in high yields.

Key words: aldehyde, carboxylic acid, lithiation, pinacol borane, protection groups, exchange reaction

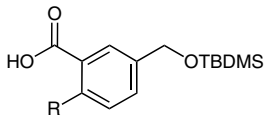
Highly substituted benzyl alcohol aromatics bearing a carboxylic acid motif are key structures in many natural products and drug molecules.[1] For example Greenspan et al. have synthesised *N*-arylamino nitriles **1** and **2** (Figure 1) bearing such benzyl alcohol/carboxylic acid motifs, which are potent inhibitors of cathepsin B,[2] a lysosomal cysteine protease that has been implicated in a number of human diseases such as rheumatoid arthritis.[3]



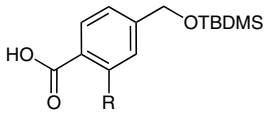
1 R = F (cathepsin B IC_{50} 12 nM)
2 R = Cl (cathepsin B IC_{50} 8.7 nM)

Figure 1

As part of an ongoing drug discovery project, we required a range of substituted carboxylic acids bearing a fixed benzyl alcohol motif in the *meta* (**3**) and *para* (**4**) positions (Figure 2).



3a R = Me
3b R = Cl
3c R = F
3d R = CN

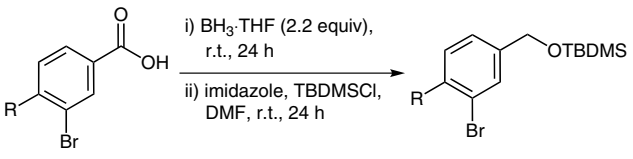


4a R = Me
4b R = Cl
4c R = F

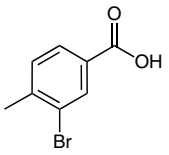
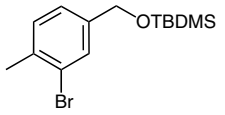
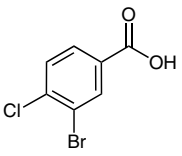
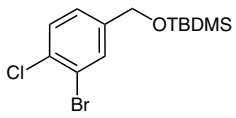
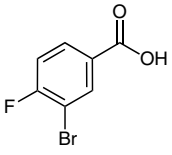
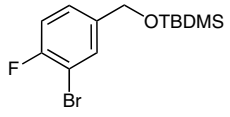
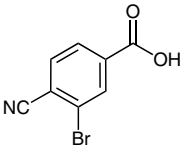
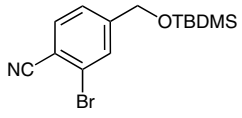
Figure 2

Searching the literature we found routes to acid **3a** that were achieved through lithium–bromide exchange on the unprotected primary alcohol,[4] and acid **4a** utilising high-pressure palladium carbonylation.[5] Marzi et al. demonstrated that carboxylic acids **3c** and **4c** can be prepared through *ortho* fluoro-directed metalation with *sec*-butyllithium and *N*,*N*,*N*′,*N*′′-pentamethylene triamine in 84 and 31% yield, respectively.[6] To the best of our knowledge, no routes to the chloro compounds **3b** and **4b** or the cyano analogue **3d** have been described.

Table 1 Synthesis of Bromo Precursors



5 **6**

Entry	Starting material **5**	Bromo derivative **6**	Yield (%)[a]
1	 **5a**	 **6a**	92
2	 **5b**	 **6b**	87
3	 **5c**	 **6c**	93
4	 **5d**	 **6d**	91[b]

[a] Isolated yield over two steps.
[b] Benzyl alcohol purchased from Aldrich.

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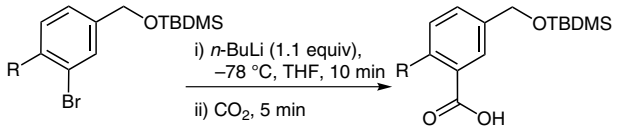
Due to the low number of published methods, we wanted to develop a simple, robust, high-yielding procedure towards such carboxylic acids by using a classical lithium–bromide exchange as the key step. Further expansion of this methodology has allowed us to synthesise a range of aldehydes and pinacol boranes in moderate to excellent yields from readily available starting materials.

To test the feasibility of the key lithium–bromide exchange, we first needed to synthesise the required bromo precursor **6a**–**d** with an alcohol protecting group in place. Commercially available carboxylic acids **5a**–**d** were converted into the desired bromo analogues in a two-step protocol; first, the carboxylic acid was reduced to the primary alcohol by using borane, and the newly formed alcohol was then silyl-protected[7] by treatment with imidazole and TBDMSCl (Table 1).

With the intermediate in hand, the key step was initiated;[8] butyl lithium was added over 10 minutes to a cooled (–78 °C) solution of bromo benzene **6a** in THF. When the addition was complete, the mixture was stirred for 20 minutes before being quenched by bubbling carbon dioxide directly into the reaction mixture over a 5 minute period. Gratifyingly, LCMS analysis revealed complete consumption of the starting material, and product **3a** was isolated in high yield. Encouraged by this result we then carried out the same procedure on our remaining substrates (Table 2).

Table 2 Carboxylic Acid Synthesis



6 **3**

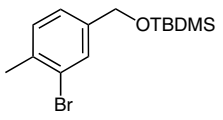
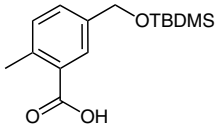
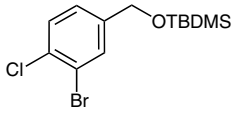
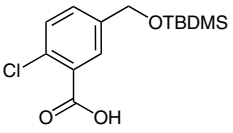
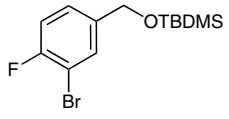
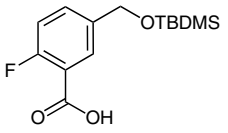
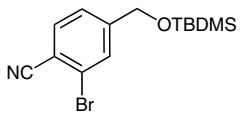
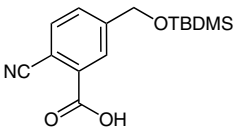
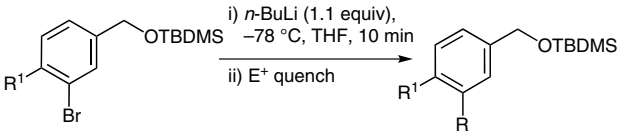
Entry	Bromo derivative	Carboxylic acid	Yield (%)
1	 **6a**	 **3a**	88
2	 **6b**	 **3b**	64
3	 **6c**	 **3c**	87
4	 **6d**	 **3d**	63

Table 3 Aldehyde/Pinacol Borane Synthesis



6

7, R = CHO
8, R = pinacol

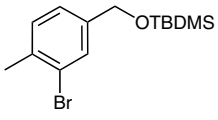
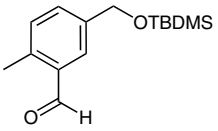
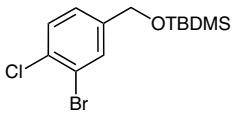
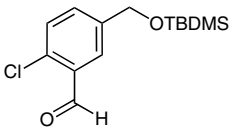
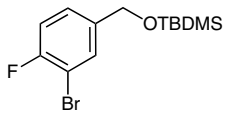
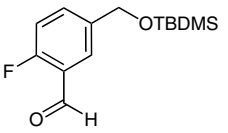
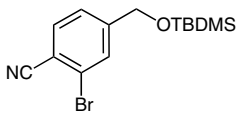
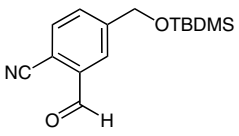
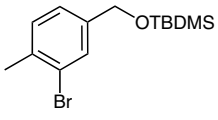
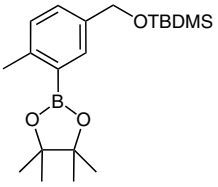
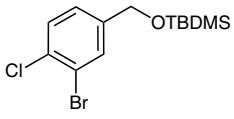
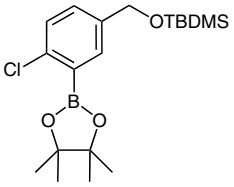
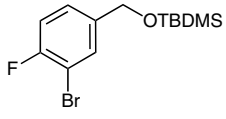
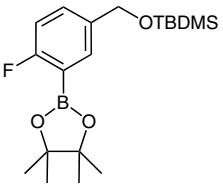
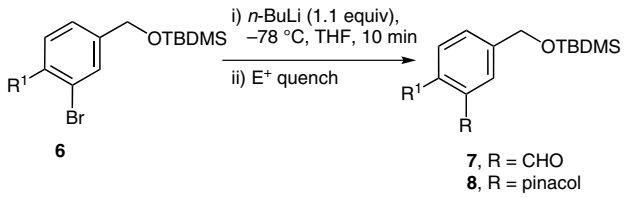
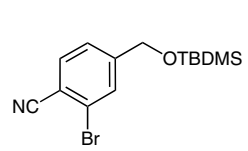
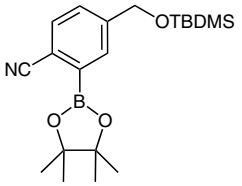
Entry	Bromo derivative	Aldehyde or pinacol	Yield (%)
1	 **6a**	 **7a**	92
2	 **6b**	 **7b**	74
3	 **6c**	 **7c**	91
4	 **6d**	 **7d**	45
5	 **6a**	 **8a**	80
6	 **6b**	 **8b**	88
7	 **6c**	 **8c**	73

Table 3 Aldehyde/Pinacol Borane Synthesis (continued)

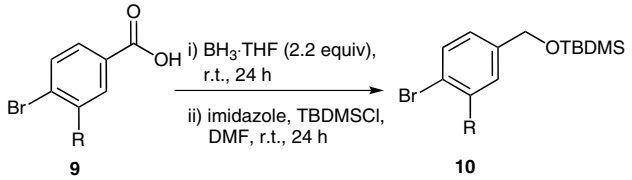


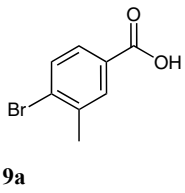
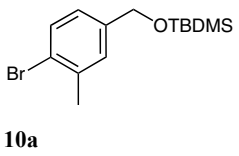
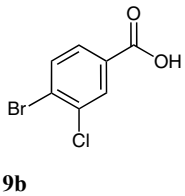
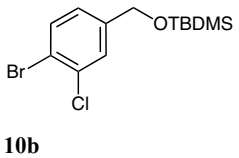
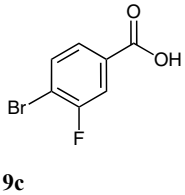
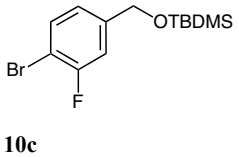
Entry	Bromo derivative	Aldehyde or pinacol	Yield (%)
8	 **6d**	 **8d**	80

It can be seen that, in all cases, the synthesis of the carboxylic acids occurred smoothly in moderate to excellent yield.

Following on from the success of the carboxylic acid synthesis, we decided to increase the scope of the reaction by investigating the feasibility of synthesising both the aldehyde analogue through a DMF quench and also the pinacol borane by quenching with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Table 4 Synthesis of Bromo Precursors



Entry	Starting material	Bromo derivative	Yield (%)[a]
1	 **9a**	 **10a**	93
2	 **9b**	 **10b**	93
3	 **9c**	 **10c**	90

[a] Isolated yield over two steps.

Aldehydes **7a**, **7b** and **7d**, and pinacol boranates **8c** and **8d** have not been reported previously in the literature. Aldehyde **7c** has been synthesised by using a similar methodology to that reported here with *sec*-butyllithium, but in a moderate 47% yield.[9] The synthesis of compounds similar to pinacol boranes **8a** and **8b** have been reported in the patent literature by using palladium cross-coupling chemistry.[10,11]

Utilisation of our general lithium–bromide exchange methodology and quenching with the appropriate electrophile generated the desired aldehydes **7a**–**d** and pinacol boranes **8a**–**d** in moderate to excellent yields (Table 3).

We then turned our attention to the *p*-benzyl carboxylic acid products **4a**–**c**. The required bromo precursors **10a**–**c** were again synthesised through the same two-step protocol from readily available carboxylic acids **9a**–**c** (Table 4). The cyano precursor was not commercially available and thus was not included in this study.

Lithium–bromide exchange at –78 °C followed by the appropriate quench generated the carboxylic acid **4a**–**c**, aldehyde **11a**–**c**, or pinacol borane **12a**–**c** building blocks in moderate to good yields (Table 5).

In conclusion, we have demonstrated an efficient three-step protocol for the synthesis of highly useful benzyl alcohol building blocks bearing carboxylic acid, aldehyde or pinacol borane motifs. This methodology has proven to be robust, is higher-yielding than current synthetic approaches, and can be performed on a multigram scale.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) A *Reaxys* search of these *meta*/*para* carboxylic acid scaffolds revealed several thousand hits.
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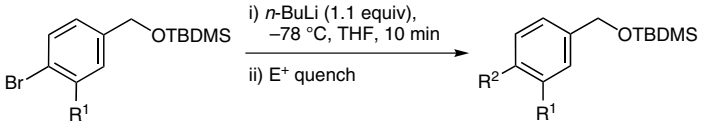
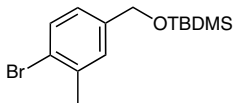
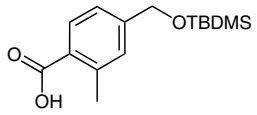
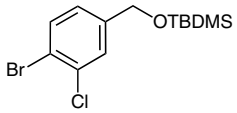
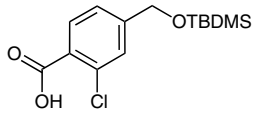
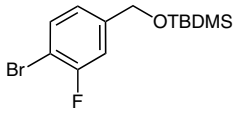
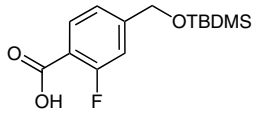
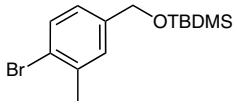
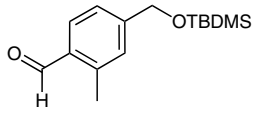
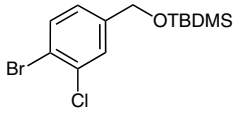
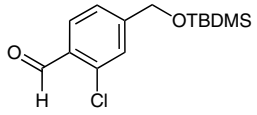
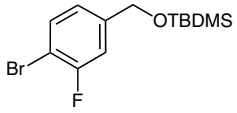
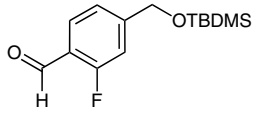
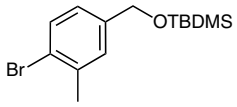
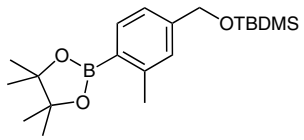
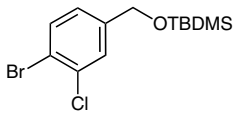
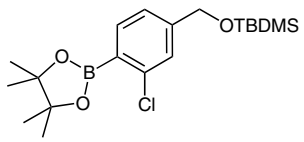
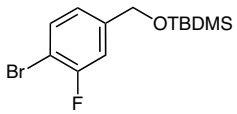
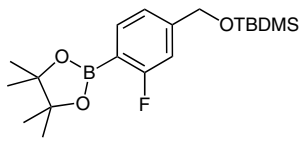
Table 5 Carboxylic Acid, Aldehyde and Pinacol Synthesis



8

4a–c R^2 = COOH
11a–c R^2 = CHO
12a–c R^2 = pinacol

Entry	Bromo derivative	Product	Yield (%)
1	 **10a**	 **4a**	85
2	 **10b**	 **4b**	58
3	 **10c**	 **4c**	74
4	 **10a**	 **11a**	80
5	 **8b**	 **11b**	96
6	 **8c**	 **11c**	90
7	 **10a**	 **12a**	79
8	 **10b**	 **12b**	74
9	 **10c**	 **12c**	65

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(7) There were several reasons for utilizing a TBDMS group; first, it allowed extractions into non-polar solvents such as heptane; second, we were able to purify many of the intermediates by distillation; third, it allowed selective manipulation of the newly formed functionality.
(8) **General Procedure:** (3-Bromo-4-methylbenzyloxy)(*tert*-butyl)dimethylsilane (19.2 g, 60.9 mmol) was dissolved in THF (250 mL) and cooled to –78 °C, and *n*-butylithium (1.6 M in hexanes, 40.0 mL, 63.9 mmol) was added over 10 min. The pale-yellow mixture was stirred at –78 °C for 10 min, then the anion was quenched by bubbling carbon dioxide (472 mL, 6089 mmol) through the reaction for 30 min. The reaction was allowed to warm to r.t., quenched with 0.5 M HCl (100 mL), extracted with EtOAc (3 × 100 mL), and the organic layer was dried over $MgSO_4$, filtered and evaporated to afford 5-[(*tert*-butyldimethylsilyl-oxy)-methyl]-2-methylbenzoic acid (15.0 g, 88%) as a colourless gum. ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ = 0.09 (s, 6 H), 0.93 (s, 9 H), 2.61 (s, 3 H), 4.71 (s, 2 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.94 (s, 1 H); COOH proton missing. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 139.1, 131.8, 130.5, 129.1, 128.8, 64.4, 26.0, 21.7, 18.4, –5.2; COOH missing. MS (ES+): *m*/*z* = 279 $[M - H]^-$; MS: *m*/*z* $[M - CH_3]^+$ calcd for $C_{15}H_{24}O_3Si$: 265.1260; found: 265.1264.
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