Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates


**Lithiation–Borylation of Secondary Alkyl Benzoates**

1. s-BuLi (1.6 equiv) TMEDA (6 equiv) CPME, –60 °C, 2 h
2. R^2B(R^3)2, 1 h
3. to 50 °C, 16 h

\[ R^1 \text{OTIB} \rightarrow R^1R^2B(R^3)2 \rightarrow R^1R^2\text{OH} \]

**TIB** = 2,4,6-trisopropyl benzoate
**CPME** = cyclopentyl methyl ether
**R^1 = CH}_2Bn, (CH}_2)2CHCH}_2, (CH}_2)_3OTHP**
**R^2 = Me, Et**
**R^3 = Et, i-Pr, Ph, allyl, 3-(2-fluoropyridyl), (CH}_2)2CO₂Bu, CHCH}_3**
**(R^4)2 = pin, neo, Et}_2**

**Selected examples:**

80% yield
er = 99:1

78% yield
er = 99:1

77% yield
er = 99:1

78% yield
er = 99:1

73% yield
er = 99:1
(TMSCl was added after
ate complex formation)

69% yield
er = 98:2
(MeOH was added after
ate complex formation)

72% yield
er = 99:1

74% yield
er = 99:1

**Significance:** Against common wisdom, Aggarwal and co-workers have now shown that secondary 2,4,6-trisopropyl benzoates (TIP esters) can be deprotonated at –60 °C using a combination of s-BuLi and TMEDA in cyclopentyl methyl ether (CPME). The resulting lithium reagents were allowed to react with various neopentyl boronic esters which after 1,2-metalate rearrangement and oxidation furnished a range of tertiary alcohols in good enantioselectivity.

**Comment:** This lithiation reaction cannot be performed in THF. Simply switching from THF to diethyl ether increased the yield of the lithiated benzoate. The extent of lithiation was increased further by using CPME. Interestingly, the subsequent borylation reaction occurs with complete retention of configuration.