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# Enantioselective Syntheses of (+)-Sertraline and (+)-Indatraline Using Lithiation/Borylation–Protodeboronation Methodology

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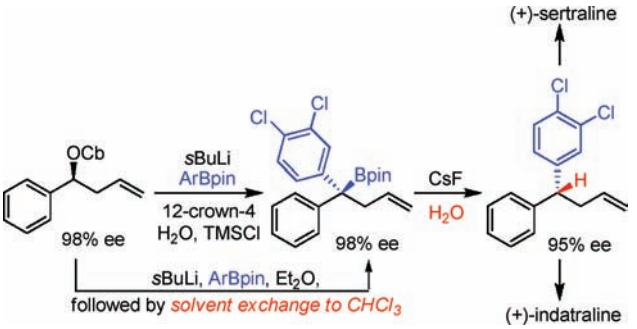
## ABSTRACT




**The lithiation/borylation–protodeboronation of a homoallyl carbamate was applied to the synthesis of (+)-sertraline and (+)-indatraline. Due to the presence of the alkene, significant modifications of the methodology were required (use of 12-crown-4, TMSCl, $H_2O$), or a solvent switch to $CHCl_3$, to achieve high yields and high selectivities.**

The enantioselective synthesis of *gem*-diarylalkyl compounds, a motif which is present in many therapeutically important molecules,[1] is challenging due to the lack of proximal functional groups. Examples of these compounds include (+)-sertraline (**1**, Zoloft), (+)-indatraline (**2**, Lu 19-005), tolterodine, and podophyllotoxin (Figure 1). In this paper we describe the application of our lithiation/borylation[2]–protodeboronation methodology[3] to the synthesis of both (+)-sertraline (**1**) and (+)-indatraline (**2**), although unexpected but significant hurdles were encountered en route that required significant changes to our standard protocol.

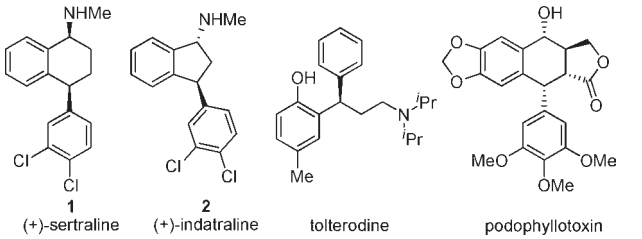



**Figure 1.** Therapeutically important molecules containing the *gem*-diarylalkyl substructure.

(+)-Sertraline (**1**) is a potent competitive selective serotonin reuptake inhibitor (SSRI), which has become a commonly prescribed pharmaceutical for the treatment of

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(2) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778–783. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142–5145. These reactions are based on the seminal studies by Hoppe on the lithiation and trapping of secondary benzylic carbamates. See: (c) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424–1425. (d) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097–6108.

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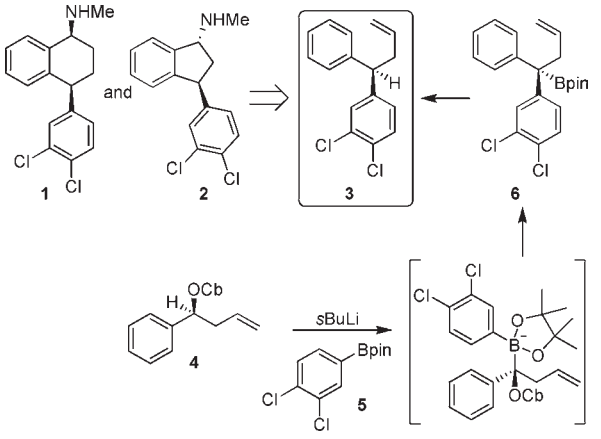
depression and other anxiety-related disorders.[4] In 2004, sertraline was the ninth top-selling drug worldwide ($3.36 billion).[5] (+)-Sertraline has become a popular target for asymmetric synthesis due to its small but challenging structure.[6]

The related molecule, (+)-indatraline (**2**), is a potent psychoactive compound that acts as a monoamine reuptake inhibitor and affects the dopamine and the serotonin transporter.[7] To date, only three asymmetric syntheses of *trans* (+)/(−)-**2** have been reported.[8]

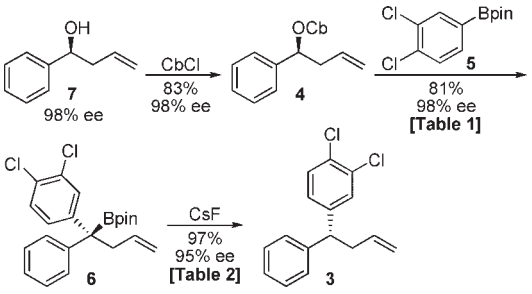
**Scheme 1.** Retrosynthetic Scheme for the Synthesis of Sertraline (**1**) and Indatraline (**2**)[a]




[a] Cb = 2,2-diisopropylcarbamoyl, pin = pinacolato.

Our retrosynthetic analysis of *both* (+)-sertraline and (+)-indatraline led us to a common precursor, diarylalkene **3** (Scheme 1). We envisaged that this intermediate could be obtained from our recently reported methodology of lithiation/borylation−protodeboronation using carbamate **4** and boronic ester **5**.[2,3] This reaction sequence occurs via an intermediate boron-ate complex, which undergoes a stereospecific 1,2-metalate rearrangement to afford a homologated tertiary boronic ester **6**. Subsequent protodeboronation leads to the tertiary stereogenic center. These processes have been found to be highly stereoselective, occurring with retention of stereochemistry in the lithiation/borylation reaction[2] and again retention of stereochemistry in the protodeboronation reaction.[3]

**Scheme 2.** Synthesis of Olefin **3** via Lithiation/Borylation−Protodeboronation Sequence[a]




[a] Cb = 2,2-diisopropylcarbamoyl, pin = pinacolato.

Our synthesis began with commercially available homoallylic alcohol **7**, a substrate which can also be prepared in 98% ee either by enzymatic resolution of the racemate[9] or by asymmetric allylation of benzaldehyde using the (*R*,*R*)-Leighton reagent.[10] The secondary alcohol **7** was initially converted into chiral carbamate **4** in 83% yield (Scheme 2). Thereafter, carbamate **4** was subjected to the lithiation/borylation reaction by treatment with 1.3 equiv of *sec*-butyllithium and a subsequent reaction with 1.5 equiv of aryl pinacol boronic ester **5** (Table 1). The formation of a boron-ate complex between **4** and **5** and its conversion to **6** was monitored by $^{11}$B NMR. However, under our standard reaction conditions, no 1,2-migration occurred, either upon warming to ambient temperature or even by heating the reaction mixture under reflux (Table 1, entry 1). The ate complex stubbornly remained.

To determine whether the problem was related to steric effects, the related propylcarbamate **8** was tested in the lithiation/borylation reaction and this led to the homologated boronic ester **9** in 72% yield and 99% es under standard conditions (Scheme 3). Like previous extensive examples,[2] the 1,2-migration occurred simply upon warming from −78 °C to ambient temperature. This showed that the problem was not steric in origin.

These initial results indicated that the alkene was interfering in the lithiation/borylation process, and we considered the possibility that a Li−$\pi$ coordination complex may be forming (**B**, Figure 2),[11] which would stabilize the ate complex. In this complex, 1,2-metalate rearrangement would be disfavored as the migrating group is not aligned

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(6) For recent asymmetric examples (2005−present), see: (a) Dockendorff, C; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028–15029. (b) Wang, G.; Zheng, C.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2074–2081. (c) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5345–5349. (d) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879–889. (e) Garcia, A. E.; Ouizem, S.; Cheng, X.; Romanens, P.; Kündig, E. P. *Adv. Synth. Catal.* **2010**, *352*, 2306–2314. (f) Krumlinde, P.; Bogar, K.; Bäckvall, J. E. *Chem.—Eur. J.* **2010**, *16*, 4031–4036. (g) Chen, F.; Wang, T.; He, Y.; Ding, Z.; Li, Z.; Xu, L.; Fan, Q. H. *Chem.—Eur. J.* **2011**, *17*, 1109–1113. (h) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510–513.

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(8) Asymmetric indatraline syntheses: (a) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951–4953. (b) Yoo, K.; Kim, H.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 11134–11138. (c) Taylor, J. C.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 857–869.

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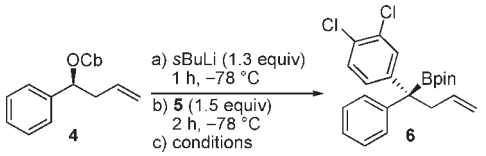
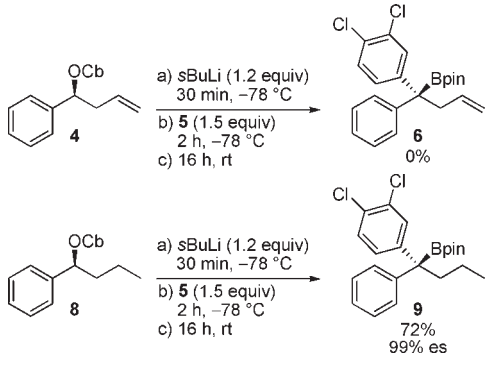
**Table 1.** Optimization of the Lithiation/Borylation Reaction Conditions[a]




| entry | conditions | yield (%) | es (%)[b] |
|---|---|---|---|
| 1 | 64 h, rt or 16 h, reflux | 0 | – |
| 2 | 12-crown-4, 16 h, rt | 0 | – |
| 3 | (i) 12-crown-4, 0.1 equiv $H_2O$, 1 h, −78 °C<br>(ii) TMSCl, 16 h, rt | 81 | 100 |
| 4 | (i) 12-crown-4, 1 h, −78 °C<br>(ii) TMSCl, 16 h, rt | 65 | 80 |
| 5 | (i) 0.1 equiv $H_2O$, 1 h, −78 °C<br>(ii) TMSCl, 16 h, rt | 31 | 99 |
| 6 | (i) 12-crown-4, 0.1 equiv $H_2O$, 1 h, −78 °C<br>(ii) 16 h, rt | 31 | 96 |
| 7 | Remove $Et_2O$, add $CHCl_3$, rt, 16 h | 62 | 98 |
| 8 | Remove $Et_2O$, add $PhCF_3$, rt, 16 h | 57 | 91 |

[a] Reaction conditions: **4** (0.3 M in diethyl ether), *s*BuLi (1.3 M in cyclohexane/hexane 98:2), **5** (0.9 M in toluene). Where applicable, 1.2 equiv of 12-crown-4 and/or 1.2 equiv of TMSCl were used. The enantiomeric excess was determined after oxidation of an aliquot of the tertiary boronic ester by chiral HPLC (see Supporting Information). [b] es = (product ee/starting material ee) × 100.

**Scheme 3.** Lithiation/Borylation of Carbamate **4** and **8**




antiperiplanar to the carbamate leaving group. Without the alkene, the lithium ion could coordinate to both oxygens of the pinacol ester which in turn places the migrating group antiperiplanar to the carbamate leaving group leading to facile 1,2-metalate rearrangement (**A**, Figure 2). Indeed, it has been reported that a $\pi$-bond can contribute a similar level of stabilization as an ether oxygen to a $Li^+$ complex (ca. 1.7 kcal $mol^{-1}$).[11] By adding 12-crown-4 to the reaction mixture, we hoped to break up the complex by sequestering the lithium ions and, therefore, allow the 1,2-migration to occur. Unfortunately, still no migration of the aryl group in the ate complex was observed (entry 2). However, this issue was ultimately solved by the addition of both TMSCl (1.2 equiv) and water (0.1 equiv). Under these conditions, the desired product **6** was indeed obtained with high es and high yield (entry 3). The necessity of each component was established since without the $H_2O$ (entry 4) or the crown ether (entry 5), or TMSCl (entry 6), lower yields or lower es were obtained.[12]

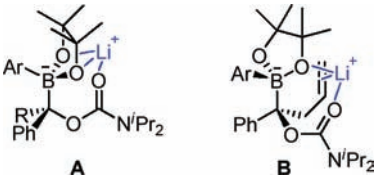
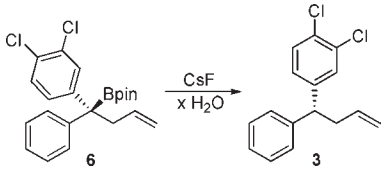



**Figure 2.** Structure of boron-ate complex with and without proposed Li–$\pi$ complexation.

During mechanistic studies to probe the structure of the intermediate boron-ate complex, we surprisingly discovered that, after carrying out a solvent exchange from $Et_2O$ to dry $CHCl_3$, complete migration of the aryl group occurred, leading to tertiary boronic ester **6** in high yield and high es (entry 7). Of the solvents explored for the exchange ($CH_2Cl_2$, $PhCH_3$, and $PhCF_3$), $PhCF_3$ also worked well, albeit with lower es (entry 8). Thus, the simple expediency of carrying out a solvent exchange provides an alternative method for effecting the 1,2-metalate rearrangement in this case. The use of a nonpolar solvent is essential in this process, where it may now begin to favor the lithiated complex **A** required for 1,2-metalate rearrangement over complex **B**.

**Table 2.** Optimization for the Amount of Water in the Protodeboronation Reaction of **6**[a]




| entry | amount of $H_2O$ | yield (%) | es (%)[b] |
|---|---|---|---|
| 1 | 0 equiv | 88 | 16 |
| 2 | 1.1 equiv | 93 | 79 |
| 3 | 1.5 equiv | 92 | 82 |
| 4 | 2.0 equiv | 88 | 94 |
| 5 | 2.5 equiv | 87 | 97 |
| 6 | 3.0 equiv | 81 | 97 |
| 7 | 4.0 equiv | 76 | 97 |
| 8 | 8.0 equiv | 12 | 88 |

[a] Reaction conditions: 0.1 M in $CH_2Cl_2$, 1.5 equiv of CsF and specified equiv of water, room temperature, overnight. [b] es = (product ee/starting material ee) × 100. Determined by chiral HPLC (see Supporting Information).

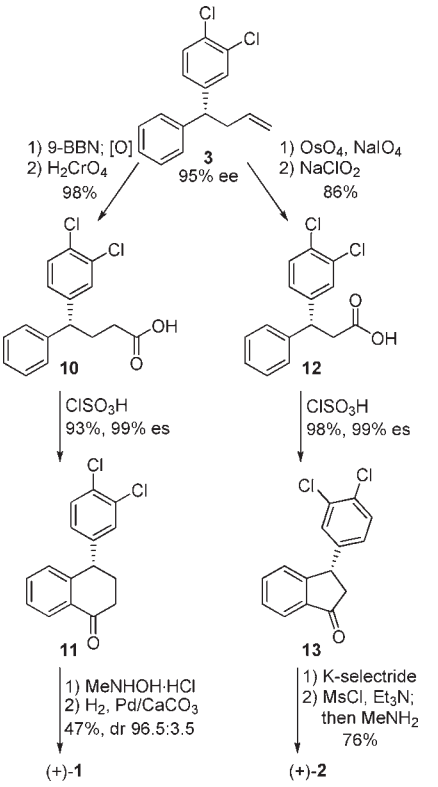
With the lithiation/borylation problem solved, we focused on the next step: protodeboronation of tertiary boronic ester **6**. Unfortunately, our standard conditions for diarylalkyl boronic esters (1.5 equiv of CsF; 1.1 equiv of $H_2O$, 1,4-dioxane)[3] led to partial racemization of the stereocenter. Through a systematic investigation, we found that controlling the amount of water was crucial for this reaction, since the reactivity of fluoride in organic solvents is fundamentally dependent on the water content in the reaction mixture.[13] For optimization, the protodeboronation reaction was performed in dichloromethane with 1.5 equiv of predried cesium fluoride and varying amounts of water (Table 2). While a certain threshold amount of water was critical for obtaining high enantioselectivity (entries 1−4), the best results were obtained with 2.5 and 3.0 equiv of water (entries 5, 6). Further increasing the equivalents of water resulted in diminished yields and reduced es (entries 7−8). Consequently, by performing the protodeboronation with 2.5 equiv of water, olefin **3** could be obtained in excellent yield with almost complete retention of configuration.[14]

With diarylbutene **3** in hand, the double bond was oxidized by a sequence of hydroboration and Jones oxidation to provide carboxylic acid **10** in 98% yield (Scheme 4). Subsequent intramolecular Friedel−Crafts acylation[15] of the chiral carboxylic acid using chlorosulfonic acid afforded known tetralone **11** in 93% yield and 94% ee (99% es from **3**), which was converted to (+)-sertraline by reductive amination in 47% yield with a *cis*/*trans* ratio of 96.5:3.5.[16] Thus, sertraline (+)-**1** was synthesized in eight steps from readily accessible homoallylic alcohol **7** with an overall yield of 28%.

For the synthesis of (+)-indatraline (Scheme 4), oxidation[17] of olefin **3** with *in situ* generated osmium tetroxide gave the desired aldehyde, which was further oxidized by a Pinnick oxidation to furnish carboxylic acid **12**. Intramolecular Friedel−Crafts acylation gave indenone **13** in 93% ee (99% es from **3**) and nearly quantitative yield.[18] The ee of **13** could be improved to >98% by recrystallization from hot heptane. Indenone **13** was reduced to the alcohol, which was subsequently converted to (+)-indatraline (**2**) in 76% yield for both steps.[8a,19] Thus, (+)-indatraline **2** was synthesized in eight steps with an overall yield of 42% starting from alcohol **7**.

In conclusion, lithiation/borylation and subsequent protodeboronation give access to functionalized chiral 1,1-diaryl compounds in high enantioselectivity. For our homoallylic carbamate, it was found to be necessary to break up the lithium/boron-ate complex with a crown ether or to carry out a solvent exchange to achieve 1,2-metalate rearrangement in order to obtain the tertiary boronic ester in high yield and high es.

**Scheme 4.** Syntheses of (+)-Sertraline and (+)-Indatraline[a]




[a] 9-BBN = 9-borabicyclo[3.3.1]nonane, Ms = methanesulfonyl.

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**Supporting Information Available.** Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) The optimized conditions found here are specific to this substrate. Application of these conditions to the saturated carbamate **8** gave the corresponding tertiary alcohol in low yield (26% over two steps) and with reduced chirality transfer (91% es).

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(14) Protodeboronation of tertiary boronic ester **9** under the previously reported conditions (1.5 equiv of CsF, 1.1 equiv of $H_2O$, 1,4-dioxane) gave the protodeboronated product in 67% es. Using the current conditions (1.5 equiv of CsF (predried), 2.5 equiv of $H_2O$, $CH_2Cl_2$) gave the protodeboronated product in 97% es. We believe that different batches of CsF contain different amounts of water and so recommend drying it prior to use and then adding controlled amounts of water (2.5 equiv) in order to get consistently high enantioselectivity.

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