Enantioselective synthesis of (*R*)-tolterodine using lithiation/borylation–protodeboronation methodology

Stefan Roesner and Varinder K. Aggarwal

Abstract: The synthesis of the pharmaceutical (*R*)-tolterodine is reported using lithiation/borylation–protodeboronation of a homoallyl carbamate as the key step. This step was tested with two permutations: an electron-neutral aryl Li-carbamate reacting with an electron-rich boronic ester and an electron-rich aryl Li-carbamate reacting with an electron-neutral boronic ester. It was found that the latter arrangement was considerably better than the former. Further improvements were achieved using magnesium bromide in methanol leading to a process that gave high yield and high enantioselectivity in the lithiation/borylation reaction. The key step was used in an efficient synthesis of (*R*)-tolterodine in a total of eight steps in a 30% overall yield and 90% ee.

Key words: asymmetric synthesis, boronic esters, *gem*-diarylalkyl, lithiation/borylation reaction, tolterodine.

Résumé : La synthèse du médicament : la (*R*)-toltérodine a été réalisé suivant une étape clé de lithiation/borylation-protodéboronation d'un carbamate homoallilyque. Deux permutations ont été évalué. Premièrement un carbamate d'aryle et de lithuim éléctronqiuement neutre réagissant sur un estre boronique riche en électron et deuxièmement un carbamate d'aryle et de lithium riche en électron réagissant sur un ester boronique électroniquement neutre. Cette dernière s'est révélée être la meilleure. D'autres améliorations ont été obtenues : notament en utilisant le bromure de magnésium en solution dans le méthanol. Cette méthodologie donne un rendement et une énantiosélectivité élevé pour la réaction de lithiation/borylation. L'étape clé permet de réaliser une synthèse éfficace de la (*R*)-toltérodine en huit étapes avec un rendement global de 30% et un ee de 90%.

Mots-clés : synthèse asymétrique, esters boroniques, *gem*-diarylalkyle, réaction de lithiation/borylation, toltérodine.

Introduction

The enantioselective synthesis of pharmaceuticals and biologically active natural products is a major theme for synthetic chemists. In particular, the formation of chiral *gem*-diarylalkyl compounds, a motif that is present in many therapeutically important molecules, is especially challenging owing to the lack of nearby functional groups that might be enlisted to enable the formation of C–C bonds.[1] Examples of these compounds include (*R*)-tolterodine (**1**, Detrol), (+)-sertraline (**2**, Zoloft), and (+)-indatraline (**3**) (Fig. 1).

(*R*)-Tolterodine (**1**) is a potent competitive muscarine receptor antagonist for the treatment of urinary incontinence and other symptoms related to an overactive bladder,[2] a compound that has achieved blockbuster status ($1.21 billion in sales in 2008[3]). Because of its importance and challenging *gem*-diarylalkyl stereocenter, it has become a popular target for asymmetric synthesis. Whereas the original route relied on optical resolution to separate (*R*)-tolterodine from the racemate,[4] initial asymmetric routes used chiral auxiliaries[5] or asymmetric Me-CBS (Corey–Bakshi–Shibata) reduction[6] to introduce the stereogenic center. More recently, asymmetric strategies have utilized transition-metal-catalyzed processes including hydrogenation,[7] hydroformylation,[8] or arylboration.[9]

Recently, we reported the highly enantioselective syntheses of (+)-sertraline (**2**) and (+)-indatraline (**3**) using a lithiation/borylation[10]–protodeboronation[11] strategy (Scheme 1). (+)-Sertraline (**2**), a potent competitive selective serotonin reuptake inhibitor (SSRI), is a commonly prescribed therapeutic for the treatment of depression and other anxiety-related disorders and has also achieved blockbuster status[12] ($3.36 billion in sales in 2004[13]). The related molecule, (+)-indatraline (**3**), is a potent psychoactive compound that acts as a monoamine reuptake inhibitor[14] and has the potential to be used in maintenance therapy to treat cocaine abuse.[15] A lithiation/borylation reaction and subsequent protodeboronation gave access to both **2** and **3** in high yield and excellent enantioselectivity. In contrast with other substrates devoid of the alkene function, for homoallylic carbamate **4** it was found necessary to add a crown ether or to carry out a solvent exchange to $CHCl_3$ to achieve 1,2-metalate rearrangement of the intermediate ate complex.[11b] The requirement for such unusual conditions has made us probe this type of rearrangement further with a view to applying it in the asymmetric synthesis of (*R*)-tolterodine. Once again, we found that modifications of

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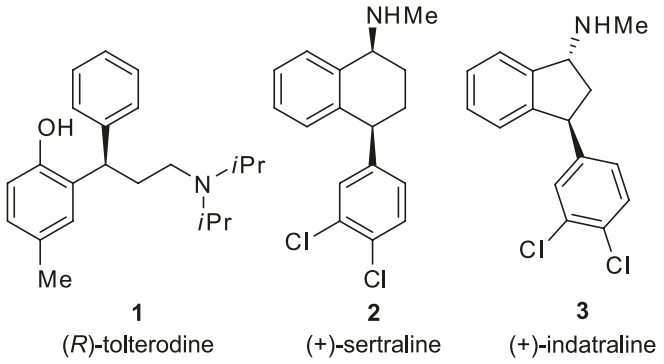
This paper is part of a Special Issue dedicated to Professor Derrick Clive and is for his many creative contributions to synthetic chemistry.

Fig. 1. Pharmaceutically important molecules containing the *gem*-diaryl substructure.



1 (*R*)-tolterodine **2** (+)-sertraline **3** (+)-indatraline

the improved conditions for this class of substrates were required to promote 1,2-metallate rearrangement, but this did ultimately enable us to complete a successful synthesis of (*R*)-tolterodine using our lithiation/borylation–protodeboronation strategy.

Results and discussion

Encouraged by the results for the synthesis of (+)-sertraline and (+)-indatraline, we applied a similar strategy for the synthesis of (*R*)-tolterodine (**1**). The retrosynthetic analysis for **1** (Scheme 2) involves, as a key step, the lithiation/borylation of benzylic carbamate **4** with boronic ester **7** to form **8**. Subsequent protodeboronation of tertiary boronic ester **8** would lead to olefin **9**. Both the lithiation/borylation[10] and protodeboronation[11] have been found to be highly stereoselective, occurring with retention of the stereochemistry. Functional group manipulation of the key intermediate **9** would then provide (*R*)-tolterodine (**1**).

However, attempts to realize this in practice were not straightforward: when we carried out the lithiation/borylation of carbamate **4** with boronic ester **7**, using 12-crown-4, trimethylsilyl chloride (TMSCl), and H_2O as additives, no product was formed (Scheme 3). A solvent switch after ate complex formation from diethyl ether to $CHCl_3$ gave only trace amounts of tertiary boronic ester **8**. Both sets of conditions had been successfully employed in the synthesis of sertraline; the only difference here was the use of 2-methoxy-5-methylphenyl boronic ester in place of 3,4-dichlorophenyl boronic ester. Monitoring the reaction by ^{11}B NMR revealed that an intermediate boron–ate complex (**A**) formed (~5 ppm), but instead of a 1,2-migration to the product, ate complex **A** decomposed over time returning some starting material.

Previous experiments in the syntheses of **2** and **3** revealed that the double bond can interfere in the lithiation/borylation process, presumably by formation of a Li–π complex, as the saturated compound underwent smooth lithiation/borylation under standard conditions (either (*i*) no additives were required, simply warming to room temperature (RT) or (*ii*) the addition of $MgBr_2$/MeOH prior to warming to RT).[11b] To determine whether the problem was related to the double bond, propylcarbamate **10** was tested in the lithiation/borylation reaction with pinacol boronic ester **7** (Scheme 4). The formation of a boron–ate complex was confirmed by ^{11}B NMR, but again no product could be isolated. We believed that the extra steric hindrance of the aryl boronic ester (bearing an ortho substituent) was perhaps responsible for the low reactivity. We therefore investigated the use of the less-hindered neopentyl boronic ester **12**, instead of the pinacol boronic ester **7**, under the same reaction conditions. Utilizing carbamate **10** and neopentyl boronic ester **12** in the lithiation/borylation reaction gave tertiary boronic ester **13** in 62% isolated yield after column chromatography. To our delight, lithiation/borylation of homoallylic carbamate **4** (99% enantiomeric excess (ee)) and neopentyl boronic ester **12** gave tertiary boronic ester **14** in good yield and high enantioselectivity (Table 1, entry 1). This showed that the presence of the double bond was not interfering in the reaction. However, attempts to improve both yield and enantioselectivity by the addition of additives after ate complex formation were not successful (Table 1, entries 2–8).

We therefore considered an alternative protocol. Instead of using carbamate **4** with 2-methoxy-5-methylphenyl boronic ester we decided to switch the two aryl groups. In other words, we considered the possibility of the reaction of homoallylic carbamate **18** with phenyl boronic ester in a lithiation/borylation reaction. Although the two ate complexes have similar steric properties, we believed that the presence of the *ortho*-methoxy group might assist in the expulsion of the carbamate, thereby promoting the 1,2-metallate rearrangement.

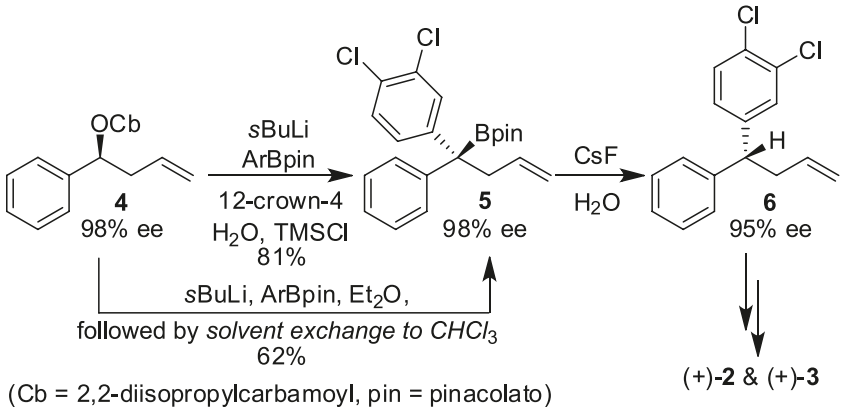
Homoallylic carbamate **18** was synthesized in a three-step sequence starting from the commercially available aldehyde **15** (Scheme 5). The phenolic hydroxyl group was protected as the methyl ether to give aldehyde **16**. Subsequent, Brown-mediated asymmetric allylation using (+)-B-allyl (diisopinocampheyl)borane ((+)-Ipc_2Ball) gave alcohol **17** in 92% ee,[16] which was followed by carbamoylation furnishing the desired carbamate in 97% yield and 92% ee.

The lithiation/borylation reaction between racemic homoallylic carbamate **18** and phenyl pinacol boronic ester **19** now proceeded well to give tertiary boronic ester **8** in 40% yield (Table 2, entry 1). In contrast with our earlier work, the reaction gave only a poor yield when neopentyl boronic ester **20** was used (Table 2, entry 2). Therefore, an optimization of the lithiation/borylation reaction of carbamate **18** with phenyl pinacol boronic ester **19** was carried out. Better results were obtained with the Lewis acidic additives TMSCl or $MgBr_2$ in anhydrous MeOH (Table 2, entries 6 and 8). The optimum conditions/additives of the lithiation/borylation reaction ($MgBr_2$/MeOH; Table 2, entry 8) were applied to the enantioenriched carbamate **18** and we were pleased to find that the reaction proceeded with 98% es (Scheme 6). Hence, we used these optimized conditions to complete the synthesis of (*R*)-tolterodine.

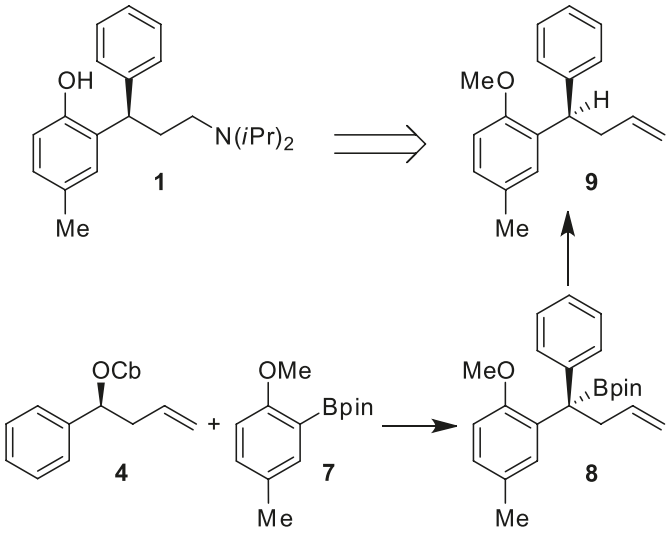
Interestingly, when we reinvestigated the lithiation/borylation reaction as applied in the synthesis of sertraline, the reaction with an electron-rich aryl group associated with carbamate **4** and an electron-deficient aryl group (3,4-$Cl_2C_6H_4$) on boronic ester **21** worked much better than having an electron-deficient aryl group associated with carbamate **22** and an electron-rich aryl group on boronic ester **19** (Scheme 7). This suggests that this arrangement of electronic substitution of the aryl rings is likely to be general.

With the lithiation/borylation problem solved, we focused on the next step: protodeboronation of tertiary boronic ester **8**.

Scheme 1. Enantioselective syntheses of (+)-sertraline (**2**) and (+)-indatraline (**3**) using a lithiation/borylation–protodeboronation strategy.



Scheme 2. Retrosynthetic scheme for the synthesis of (*R*)-tolterodine (**1**).



Unfortunately, our standard procedure for the protodeboronation of diarylalkyl boronic esters (1.5 equiv CsF, 2.5 equiv H_2O, 1,4-dioxane)[11] proceeded very sluggishly and it took 48 h at 80 °C until full conversion of **8** was achieved. This is probably due to the electron-rich aryl ring, which makes deboronation more difficult. In the case of protodeboronation of aryldialkyl boronic esters, we also found that CsF/H_2O was very slow, but that tetrabutylammonium fluoride trihydrate (TBAF·3H2O) was considerably superior.[11a] Using these previously reported conditions (1.5 equiv TBAF·3H_2O, toluene), tertiary boronic ester **8** was smoothly protodeboronated at ambient temperature within 90 min in excellent yield and enantioselectivity to give key intermediate **9** (Scheme 6).

The remaining synthesis was completed in a three-step sequence (Scheme 6). The double bond in olefin **9** was successfully cleaved by a Lemieux–Johnson oxidation,[17] with in situ generated osmium tetroxide, to the corresponding aldehyde **23**. Subsequent reductive amination with diisopropylamine and sodium triacetoxyborohydride gave the protected tolterodine precursor **24** in a good yield. Finally, removal of the methyl group by acidic hydrolysis resulted in the formation of (*R*)-tolterodine (**1**) in an excellent yield. The *R* configuration was confirmed by comparison of the optical rotations, $[\alpha]_D^{20}$ +28.0 (*c* 0.50, MeOH) for **1** with that reported in the literature ($[\alpha]_D^{20}$ +32.5 (*c* 0.89, MeOH)).[7e] Thus, using our lithiation/borylation–protodeboronation methodology as a key step, (*R*)-tolterodine was synthesized through an eight-step sequence in an overall yield of 30%.

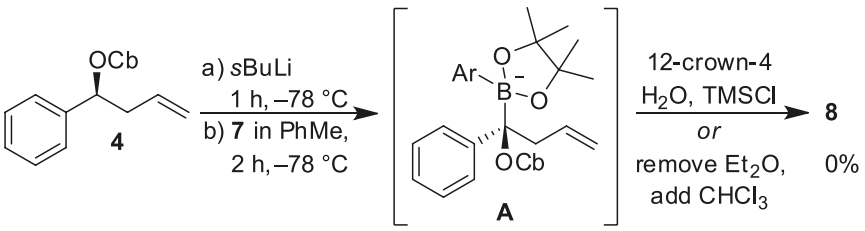
Conclusion

In conclusion, lithiation/borylation and subsequent protodeboronation has been used in the generation of *gem*-diarylalkyl stereocenters in both high yield and high enantioselectivity. More importantly, we have found that the optimum arrangement of groups is to have an electron-rich aryl group associated with the carbamate to promote the 1,2-metallate rearrangement, otherwise, reversion to starting materials tends to dominate. This methodology has been applied to a highly enantioselective synthesis of (*R*)-tolterodine.

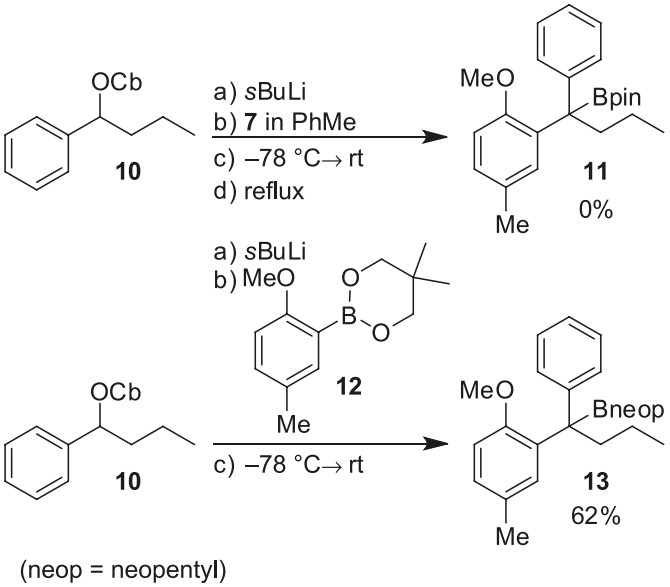
Experimental

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under argon atmosphere using standard Schlenk manifold technique. All required fine chemicals were purchased from Acros Organics, Alfa Aesar, Inochem-Frontier Scientific, or Sigma-Aldrich and used as received unless otherwise mentioned. Anhydrous solvents were prepared using anhydrous solvent drying columns.[18] Microwave reactions were carried out in a Biotage Initiator EXP EU microwave synthesizer. Analytical thinlayer chromatography (TLC) was performed on aluminum-backed silica plates (Merck, silica gel 60 F_{254}, 0.25 mm). Compounds were visualized by exposure to UV light or by staining the plates with a 5% solution of phosphomolybdic acid ($H_3PMo_{12}O_{40}$) in EtOH followed by heating. Flash column chromatography was performed on silica gel (Sigma-Aldrich, silica gel 60, 40–63 μm). ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 or 500 MHz on a Joel ECP 400, a Varian 400, or a Varian 500 Fourier transform (FT) spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referred to $CHCl_3$ (7.27 ppm). ^{1}H NMR coupling constants are reported in hertz and refer to apparent multiplicities. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet,

Scheme 3. Lithiation/borylation of carbamate **4** and boronic ester **7**.

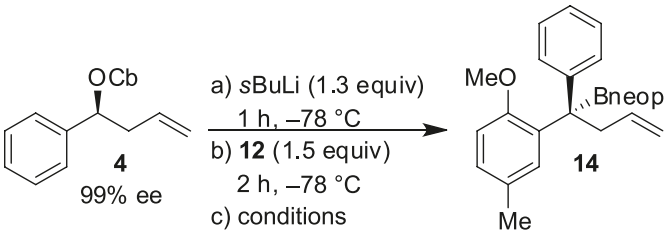


Scheme 4. Lithiation/borylation of carbamate **10**, pinacol boronic ester **7**, and neopentyl boronic ester **12**.



t = triplet, m = multiplet, dd = doublet of doublet, etc.), coupling constant, integration, and assignment. ^{13}C NMR spectra were recorded at 101 or 126 MHz on a Jeol ECP 400, a Varian 400, or a Varian 500 instrument. Chemical shifts (δ_C) are quoted in ppm and referenced to $CHCl_3$ (77.0 ppm). ^{11}B NMR spectra were measured using quartz NMR tubes at 96 or 128 MHz on a Jeol Lambda 300, a Joel ECP (Eclipse) 300, or a Varian 400 with complete proton decoupling using $BF_3{\cdot}Et_2O$ (0.0 ppm) as an external standard. Mass spectra were recorded by the University of Bristol, School of Chemistry departmental mass spectrometry service using chemical ionization (CI) or electrospray ionization (ESI) techniques for low- and high-resolution mass spectra (LR-MS and HR-MS, respectively). All IR spectra were recorded on the neat compounds using a PerkinElmer Spectrum One FT-IR spectrometer. Optical rotations were obtained using a Bellingham + Stanley Ltd. ADP220 polarimeter. Melting points were measured with a Reichert hot stage apparatus and are uncorrected. Chiral HPLC separations were performed on an Agilent 1100 Series HPLC unit equipped with a UV–vis diode array detector using a Daicel Chiralpak IB column (4.6 × 250 mm^2, 5 μm) fitted with a guard (4 × 10 mm^2). (Chiral HPLC traces and ^1H and ^{13}C NMR spectra can be found in the Supplementary data).

Table 1. Optimization of the lithiation/borylation reaction conditions for carbamate **4**.

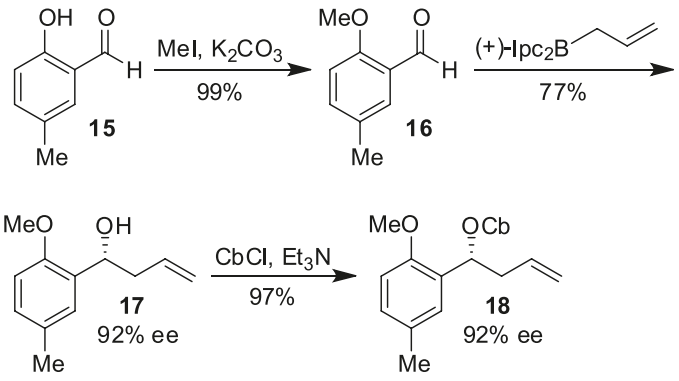


Entry	Conditions	Yield (%)	es (%)[a]
1	No additives	52	94
2	Solvent exchange to $CHCl_3$	10	90
3	Reaction in toluene	19	45
4	12-Crown-4	32	53
5	TMSCl	8	93
6	12-Crown-4, TMSCl	1	93
7	$MgBr_2$/MeOH	1	96
8	$MgBr_2{\cdot}Et_2O$	50	13

Note: es, enantiospecifity. Reaction conditions: **4** (0.3 mol/L in diethyl ether), *s*-BuLi (1.3 mol/L in cyclohexane/hexane, 98:2), **12** (0.9 mol/L in diethyl ether). Where applicable, 1.2 equiv of additive were used. The enantiomeric excess (ee) was determined after oxidation of an aliquot of the tertiary boronic ester by chiral HPLC.

[a]es = (product ee/starting material ee) × 100.

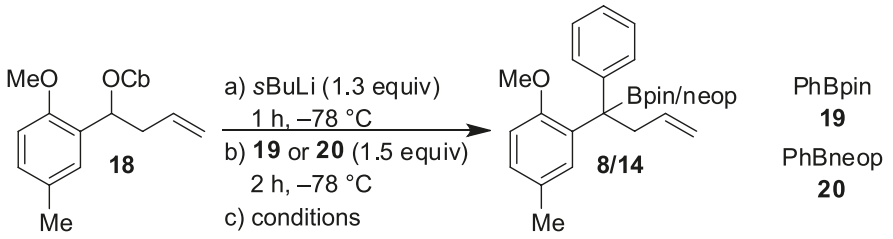
Scheme 5. Synthesis of carbamate **18**.



2-(2-Methoxy-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)

This compound was synthesized following a literature procedure performed on a different substrate.[19] Boronic ester **7** (2.02 g, 8.14 mmol, >99%) was obtained as a white solid, which was used without further purification; mp 75–76 °C

Table 2. Optimization of the lithiation/borylation reaction conditions for carbamate **18**.



Entry	Boronic ester	Conditions	Yield (%)
1	**19**	No additives	40
2	**20**	No additives	13
3	**19**	Solvent exchange to $CHCl_3$	44
4	**19**	Reaction in toluene	16
5	**19**	12-Crown-4	33
6	**19**	TMSCl	51
7	**19**	12-Crown-4, TMSCl	17
8	**19**	$MgBr_2$/MeOH	74
9	**19**	$MgBr_2{\cdot}Et_2O$	15

Note: Reaction conditions: **18** (0.3 mol/L in diethyl ether), *s*-BuLi (1.3 mol/L in cyclohexane/hexane, 98:2), **19** or **20** (0.9 mol/L in diethyl ether). Where applicable, 1.2 equiv of additive were used.

(diethyl ether). IR (neat, cm^{-1}) ν_{max}: 2981, 1605, 1585, 1243. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.49 (d, J = 2.3 Hz, 1H, H_{Ar}), 7.20 (dd, J = 8.4, 2.3 Hz, 1H, H_{Ar}), 6.77 (d, J = 8.4 Hz, 1H, H_{Ar}), 3.81 (s, 3H, OCH_3), 2.29 (s, 3H, $C_{Ar}CH_3$), 1.36 (s, 12H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 162.2 ($COCH_3$), 137.1 (CH), 132.9 (CH), 129.2 (C), 110.5 (CH), 83.4 ($OC(CH_3)_2$), 56.0 (OCH_3), 24.8 (CH_3), 20.2 ($C_{Ar}CH_3$). ^{11}B NMR (96 MHz, $CDCl_3$, ppm) δ_B: 30.0 (br s). MS *m/z* (%) (CI^+): 249 ($[M + H]^+$, 100), 248 ($[M]^+$, 60), 247 (18), 145 (15), 123 ($[Ar + H]^+$, 15), 101 (24). HR-MS (CI^+) calcd for $C_{14}H_{22}O_3{}^{11}B$ $[M + H]^+$: 249.1662; found: 249.1664.

2-(2-Methoxy-5-methylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (12)

This compound was synthesized following a literature procedure performed on a different substrate.[19] Boronic ester **12** (3.51 g, 14.4 mmol, 96%) was obtained as a white solid, which required no further purification; mp 59–61 °C (diethyl ether). IR (neat, cm^{-1}) ν_{max}: 2936, 1603, 1584, 1241. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.47 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.17 (dd, J = 8.4, 2.2 Hz, 1H, H_{Ar}), 6.78 (d, J = 8.4 Hz, 1H, H_{Ar}), 3.82 (s, 3H, OCH_3), 3.80 (s, 4H, OCH_2), 2.29 (s, 3H, $C_{Ar}CH_3$), 1.05 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 161.7 ($COCH_3$), 136.2 (CH), 132.0 (CH), 129.1 (C), 110.4 (CH), 72.4 (OCH_2), 55.9 (OCH_3), 31.7 ($C(CH_3)_2$), 21.9 (CH_3), 20.3 ($C_{Ar}CH_3$). ^{11}B NMR (96 MHz, $CDCl_3$, ppm) δ_B: 26.3 (br s). MS *m/z* (%) (CI^+): 235 ($[M + H]^+$, 100), 234 ($[M]^+$, 53), 233 (19), 123 ($[Ar + H]^+$, 31), 75 (53). HR-MS (CI^+) calcd. for $C_{13}H_{20}O_3{}^{11}B$ $[M + H]^+$: 235.1506; found: 235.1500.

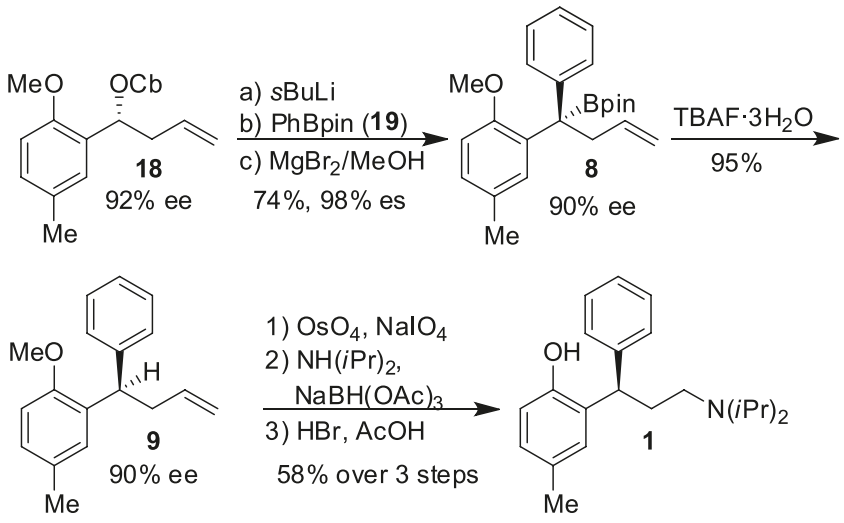
1-Phenylbutyl diisopropylcarbamate (10)

To a suspension of sodium hydride (60% dispersion in mineral oil, 300 mg, 7.50 mmol, 1.5 equiv) in anhydrous tetrahydrofuran (THF; 20 mL), 1-phenylbutan-1-ol (751 mg, 5.00 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 75 min at RT. A solution of *N*,*N*-diisopropylcarbamoyl chloride (982 mg, 6.00 mmol, 1.2 equiv) in anhydrous THF (5.0 mL) was added and the reaction mixture was heated under reflux for 44 h. The solvent was removed in vacuo and the residue was portioned between water and diethyl ether. The phases were separated and the aqueous layer was re-extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, pentane/EtOAc, 6:1) to obtain carbamate **10** (1.13 g, 4.07 mmol, 81%) as a colourless oil. TLC (pentane/EtOAc, 6:1): 0.46. IR (neat, cm^{-1}) ν_{max}: 2962, 1687. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.37–7.29 (m, 4H, H_{Ar}), 7.29–7.23 (m, 1H, H_{Ar}), 5.71 (t, J = 6.9 Hz, 1H, CHOCb), 4.04 (br m, 1H, $CH(CH_3)_2$), 3.84 (br m, 1H, $CH(CH_3)_2$), 1.94 (m, 1H, $CHHCHO$), 1.76 (m, 1H, CHH-CHO), 1.44–1.27 (m, 2H, CH_2CH_3), 1.22 (br m, 12H, $CH(CH_3)_2$), 0.92 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 155.1 (NCO), 141.8 (C), 128.2 (CH), 127.3 (CH), 126.5 (CH), 76.4 (CHOCb), 46.1 (br, $CH(CH_3)_2$), 39.0 (CH_2CHO), 21.4 (br, $CH(CH_3)_2$), 18.9 (CH_2CH_3), 13.9 (CH_2CH_3). MS *m/z* (%) (CI^+): 278 ($[M + H]^+$, 77), 236 (11), 218 (10), 146 ($[CbOH + H]^+$, 100), 133 ($[Ph(CH_2)_4]^+$, 57), 128 (16), 102 (12), 91 ($[PhCH_2]^+$, 30). HR-MS (CI^+) calcd for $C_{17}H_{28}NO_2$ $[M + H]^+$: 278.2120; found: 278.2116.

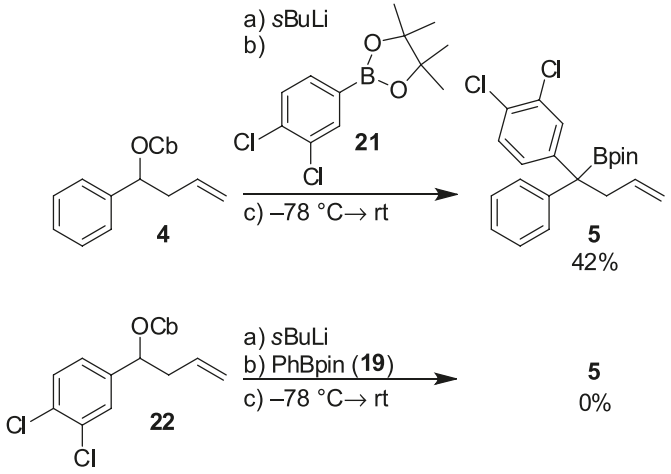
2-(1-(2-Methoxy-5-methylphenyl)-1-phenylbutyl)-5,5-dimethyl-1,3,2-dioxaborinane (13)

1-Phenylbutyl diisopropylcarbamate (**10**; 139 mg, 0.50 mmol, 1.0 equiv) was dissolved in anhydrous diethyl ether (1.5 mL) and chilled to −78 °C. *s*-BuLi (500 μL, 1.3 mol/L solution in cyclohexane/hexane, 98:2, 0.65 mmol, 1.3 equiv) was added dropwise and the mixture was stirred at this temperature for 1 h. A solution of neopentyl ester **12** (176 mg, 0.75 mmol, 1.5 equiv) in anhydrous diethyl ether (0.5 mL)

Scheme 6. Synthesis of (*R*)-tolterodine (**1**).



Scheme 7. Lithiation/borylation of carbamates **4** and **22**.



was added dropwise and the mixture was stirred for 2 h at −78 °C. The cooling bath was removed and stirring was continued at RT overnight (15 h). The reaction mixture was cooled to 0 °C and 1 mol/L KH_2PO_4(aq) (2.0 mL) was added slowly. After stirring for 10 min at RT, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 30:1) to give tertiary boronic ester **13** (114 mg, 0.31 mmol, 62% or 92% based on recovered starting material (BRSM)) as a colourless oil, which crystallized upon standing to white cubes; mp 86–87 °C (pentane/EtOAc). TLC (pentane/EtOAc, 30:1): 0.22. IR (neat, cm^{-1}) ν_{max}: 2955, 2873, 1494, 1244. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.42–7.38 (m, 2H, H_{Ar}), 7.28–7.23 (m, 2H, H_{Ar}), 7.16–7.11 (m, 1H, H_{Ar}), 6.97 (ddd, J = 8.2, 2.2, 0.6 Hz, 1H, H_{Ar}), 6.82–6.79 (m, 2H, H_{Ar}), 3.85 (s, 3H, OCH_3), 3.53 (s, 4H, OCH_2), 2.25–2.17 (m, 1H, C*H*HCH_2), 2.19 (s, 3H, $C_{Ar}CH_3$), 2.02–1.93 (m, 1H, CH*H*CH_2), 1.31–1.21 (m, 1H, C*H*HCH_3), 0.87–0.78 (m, 4H, CH_2CH_3, CH*H*CH_3), 0.65 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.9 (C), 144.0 (C), 136.3 (C), 130.9 (CH), 129.4 (CH), 129.3 (C), 127.2 (CH), 126.7 (CH), 124.5 (CH), 110.4 (CH), 72.3 (OCH_2), 56.1 (OCH_3), 34.8 (CH_2CH_2), 31.6 ($C(CH_3)_2$), 21.5 (CH_3), 20.8 ($C_{Ar}CH_3$), 17.9 (CH_2CH_3), 14.8 (CH_2CH_3). ^{11}B NMR (96 MHz, $CDCl_3$, ppm) δ_B: 27.9 (br s). MS *m*/*z* (%) (CI^+): 367 ($[M + H]^+$, 16), 366 ($[M]^+$, 30), 351 ($[M – Me]^+$, 14), 323 ($[M – n\text{-}Pr]^+$, 5), 289 ($[M – Ph]^+$, 30), 253 ($[M – Bneop]^+$, 7), 245 ($[M – Ar]^+$, 100), 203 (28), 177 (16), 149 (12), 131 (34), 123 (46), 105 (15), 93 (99). HR-MS (CI^+) calcd for $C_{23}H_{32}O_3{}^{11}B$ $[M + H]^+$: 367.2445; found: 367.2457.

2-(1-(2-Methoxy-5-methylphenyl)-1-phenylbut-3-enyl)-5,5-dimethyl-1,3,2-dioxaborinane (14)

Following the experimental procedure for tertiary boronic ester **13**, 1-phenylbut-3-enyl diisopropylcarbamate (**4**) (139 mg, 0.50 mmol, 1.0 equiv) in anhydrous diethyl ether (1.5 mL), *s*-BuLi (570 μL, 1.14 mol/L solution in cyclohexane/hexane, 98:2, 0.65 mmol, 1.3 equiv), and neopentyl ester **12** (176 mg, 0.75 mmol, 1.0 equiv) in anhydrous diethyl ether (0.75 mL) gave, after purification by column chromatography (SiO_2, pentane/EtOAc, 30:1), tertiary boronic ester **14** (94 mg, 0.26 mmol, 52% or 97% BRSM) as a colourless oil. TLC (pentane/EtOAc, 30:1): 0.12. IR (neat, cm^{-1}) ν_{max}: 2928, 1495, 1245. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.49–7.42 (m, 2H, H_{Ar}), 7.30–7.23 (m, 2H, H_{Ar}), 7.18–7.13 (m, 1H, H_{Ar}), 6.98 (ddd, J = 8.1, 2.2, 0.6 Hz, 1H, H_{Ar}), 6.85–6.78 (m, 2H, H_{Ar}), 5.68 (dddd, J = 17.3, 10.2, 7.4, 6.2 Hz, 1H, C*H*CH_2), 4.97–4.84 (m, 2H, CHC*H*$_2$), 3.86 (s, 3H, OCH_3), 3.56 (s, 4H, OCH_2), 3.13 (ddt, J = 15.4, 7.4, 1.2 Hz, 1H, C*H*H), 2.84 (ddt, J = 15.4, 6.2, 1.6 Hz, 1H, CH*H*), 2.20 (s, 3H, $C_{Ar}CH_3$), 0.71 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.8 (C), 143.7 (C), 137.1 (*C*HCH$_2$), 135.8 (C), 130.7 (CH), 129.6 (CH), 129.4 (C), 127.3 (CH), 126.9 (CH), 124.8 (CH), 115.6 (CH*C*H$_2$), 110.4 (CH), 72.3 (OCH_2), 56.1 (OCH_3), 37.5 (CH_2), 31.6 ($C(CH_3)_2$), 21.6 (CH_3), 20.8 ($C_{Ar}CH_3$). ^{11}B NMR (96 MHz, $CDCl_3$, ppm) δ_B: 28.1 (br s). MS *m*/*z* (%) (CI^+): 365 ($[M + H]^+$, 89), 364 ($[M]^+$, 75), 349 ($[M – Me]^+$, 49), 323 ($[M – allyl]^+$, 49), 287 ($[M – Ph]^+$, 32), 243 ($[M – Ar]^+$, 100), 203 (12), 149 (36), 131 (33), 123 (19), 105

(24), 93 (77). HR-MS (CI^+) calcd for $C_{23}H_{30}O_3{}^{11}B$ $[M + H]^+$: 365.2288; found: 365.2278.

2-Methoxy-5-methylbenzaldehyde (16)

This compound was synthesized following a literature procedure[20] and yielded a pale yellow oil (4.44 g, 29.6 mmol, 99%), which was used without further purification. IR (neat, cm^{-1}) ν_{max}: 2863, 1676, 1494, 1250. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 10.45 (s, 1H, CHO), 7.64 (d, J = 2.5 Hz, 1H, H_{Ar}), 7.36 (dd, J = 8.6, 2.5 Hz, 1H, H_{Ar}), 6.90 (d, J = 8.6 Hz, 1H, H_{Ar}), 3.91 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 190.0 (CHO), 160.0 (C), 136.6 (CH), 130.0 (C), 128.6 (CH), 124.5 (C), 111.6 (CH), 55.7 (OCH_3), 20.2 (CH_3). MS *m/z* (%) (CI^+): 151 ($[M + H]^+$, 100), 123 ($[Ar + H]^+$, 26), 89 (68). HR-MS (CI^+) calcd for $C_9H_{11}O_2$ $[M + H]^+$: 151.0759; found: 151.0756.

(*R*)-1-(2-Methoxy-5-methylphenyl)but-3-en-1-ol (17)

This compound was synthesized following a literature procedure performed on a different substrate.[16] Flash chromatography (SiO_2, pentane/diethyl ether, 9:1) gave alcohol **17** (74 mg, 0.38 mmol, 77%) as white needles; mp 44–45 °C (pentane/diethyl ether). $[\alpha]_D^{20}$ +56.3 (*c* 1.79, $CHCl_3$, for 98% ee). TLC (pentane/diethyl ether, 9:1): 0.08. IR (neat, cm^{-1}) ν_{max}: 3361, 2922, 1498, 1243. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.16 (d, J = 2.0 Hz, 1H, H_{Ar}), 7.05 (dd, J = 8.2, 2.0 Hz, 1H, H_{Ar}), 6.79 (d, J = 8.2 Hz, 1H, H_{Ar}), 5.93–5.81 (ddt, J = 16.9, 10.3, 6.9 Hz, 1H, C*H*CH_2), 5.19–5.10 (m, 2H, CHC*H*$_2$), 4.93 (dt, J = 8.1, 5.3 Hz, 1H, C*H*OH), 3.84 (s, 3H, OCH_3), 2.62–2.47 (m, 3H, CH_2, OH), 2.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.3 (C), 135.3 (*C*HCH_2), 131.4 (C), 129.9 (C), 128.5 (CH), 127.5 (CH), 117.5 (CH*C*H_2), 110.4 (CH), 69.8 (CHOH), 55.4 (OCH_3), 42.0 (CH_2), 20.6 (CH_3). MS *m/z* (%) (ESI^+): 215 ($[M + Na]^+$, 100), 175 ($[M – allyl + Na]^+$, 10), 107 ($[Ar – Me]^+$, 5). HR-MS (ESI^+) calcd. for $C_{12}H_{16}O_2Na$ $[M + Na]^+$: 215.1043; found: 215.1038. HPLC: Chiralpak IB, 20 °C, 0.5% *i*-PrOH in hexane, 0.7 mL/min, UV detection at 210.8 nm, retention times: (*S*)-1-(2-methoxy-5-methylphenyl)but-3-en-1-ol, 27.6 min; (*R*)-1-(2-methoxy-5-methylphenyl)but-3-en-1-ol, 30.1 min; 92% ee.

(*R*)-1-(2-Methoxy-5-methylphenyl)but-3-enyl diisopropylcarbamate (18)

Alcohol **17** (1.32 g, 6.84 mmol, 1.0 equiv), *N*,*N*-diisopropylcarbamoyl chloride (1.34 g, 8.21 mmol, 1.2 equiv), and Et_3N (1.23 mL, 8.89 mmol, 1.3 equiv) were dissolved in anhydrous toluene (7.0 mL) in a microwave vial. The vial was sealed and heated for 2 h at 150 °C. After cooling to ambient temperature, the salts were removed by filtration through a plug of silica and the solids were thoroughly washed with diethyl ether. The solvent was removed in vacuo and the residue was subjected to flash chromatography (SiO_2, pentane/EtOAc, 9:1) to obtain 2.11 g (*R*)-carbamate **18** (6.6 mmol, 97%) as a pale yellow oil. $[\alpha]_D^{21}$ −1.0 (*c* 1.00, $CHCl_3$). TLC (pentane/EtOAc, 9:1): 0.27. IR (neat, cm^{-1}) ν_{max}: 2969, 1686, 1249. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.09 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.02 (dd, J = 8.2, 2.2 Hz, 1H, H_{Ar}), 6.76 (d, J = 8.2 Hz, 1H, H_{Ar}), 6.15 (dd, J = 7.1, 5.3 Hz, 1H, CHOCb), 5.80 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H, C*H*CH_2), 5.08–4.99 (m, 2H, CHC*H*$_2$), 4.01 (br m, 1H, C*H*$(CH_3)_2$), 3.90 (br m, 1H, C*H*$(CH_3)_2$), 3.81 (s, 3H, OCH_3), 2.65–2.53 (m, 2H, CH_2), 2.28 (s, 3H, $C_{Ar}CH_3$), 1.24 (br m, 12H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.9 (NCO), 154.0 (C), 134.7 (*C*HCH_2), 129.6 (C), 129.3 (C), 128.5 (CH), 127.3 (CH), 116.9 (CH*C*H_2), 110.5 (CH), 70.8 (CHOCb), 55.5 (OCH_3), 45.7 (br, *C*$H(CH_3)_2$), 40.1 (CH_2), 21.1 (br, CH_3), 20.7 ($C_{Ar}CH_3$). MS *m/z* (%) (ESI^+): 342 ($[M + Na]^+$, 100), 220 ($[M – Ar + Na]^+$, 4), 175 ($[M – OCb]^+$, 7), 114 (4). HR-MS (ESI^+) calcd for $C_{19}H_{29}O_3NaN$ $[M + Na]^+$: 342.2040; found: 342.2033. HPLC: Chiralpak IB, 0 °C, 0.2% *i*-PrOH in hexane, 0.5 mL/min, UV detection at 210.8 nm, retention times: (*S*)-1-(2-methoxy-5-methylphenyl)but-3-enyl diisopropylcarbamate, 36.3 min; (*R*)-1-(2-methoxy-5-methylphenyl)but-3-enyl diisopropylcarbamate, 40.9 min; 92% ee.

(*R*)-2-(1-(2-Methoxy-5-methylphenyl)-1-phenylbut-3-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8)

(*R*)-Carbamate **18** (515 mg, 1.61 mmol, 1.0 equiv) was dissolved in anhydrous diethyl ether (5.0 mL) and chilled to −78 °C. *s*-BuLi (1.41 mL, 1.49 mol/L solution in cyclohexane/hexane, 98:2, 2.10 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. A solution of PhBpin (4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane, 490 mg, 2.42 mmol, 1.5 equiv) in anhydrous diethyl ether (2.5 mL) was added dropwise and the mixture was stirred for 2 h at −78 °C. Afterwards, a 1.0 mol/L solution of $MgBr_2$ in anhydrous MeOH[10b] (1.93 mL, 1.93 mmol, 1.2 equiv) was added slowly. After 5 min, the cooling bath was removed and stirring was continued at RT overnight (16 h). Then, the reaction mixture was cooled to 0 °C and 1 mol/L KH_2PO_4(aq) (2.0 mL) was added slowly. After stirring for 10 min at RT, the phases were separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 30:1) to give tertiary boronic ester **8** (449 mg, 1.19 mmol, 74%) as a white solid; mp 134–136 °C (pentane/EtOAc). $[\alpha]_D^{21}$ −88.0 (*c* 1.00, $CHCl_3$, for 90% ee). TLC (pentane/EtOAc, 30:1): 0.10. IR (neat, cm^{-1}) ν_{max}: 2974, 1497, 1240. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.46 (d, J = 7.8 Hz, 2H, H_{Ar}), 7.26 (t, J = 7.8 Hz, 2H, H_{Ar}), 7.15 (t, J = 7.8 Hz, 1H, H_{Ar}), 6.96 (dd, J = 8.2, 1.7 Hz, 1H, H_{Ar}), 6.81 (d, J = 1.7 Hz, 1H, H_{Ar}), 6.76 (d, J = 8.2 Hz, 1H, H_{Ar}), 5.65 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H, C*H*CH_2), 4.95 (dd, J = 17.1, 1.4 Hz, 1H, CHCH_{trans}H), 4.87 (dd, J = 10.2, 1.4 Hz, 1H, CHCH_{cis}H), 3.77 (s, 3H, OCH_3), 3.10 (dd, J = 15.2, 6.8 Hz, 1H, C*H*H), 2.94 (dd, J = 15.2, 6.8 Hz, 1H, CH*H*), 2.19 (s, 3H, $C_{Ar}CH_3$), 1.11 (s, 6H, CH_3), 1.10 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.8 (C), 143.0 (C), 136.7 (*C*HCH_2), 134.4 (C), 130.4 (CH), 129.9 (CH), 129.2 (C), 127.3 (CH), 127.1 (CH), 125.1 (CH), 115.7 (CH*C*H_2), 110.1 (CH), 83.0 (C), 55.1 (OCH_3), 38.8 (br, CB), 37.8 (CH_2), 24.6 (CH_3), 24.4 (CH_3), 20.8 ($C_{Ar}CH_3$). ^{11}B NMR (96 MHz, $CDCl_3$, ppm) δ_B: 30.2 (br s). MS *m/z* (%) (ESI^+): 401 ($[M + Na]^+$, 100), 279 (9), 223 (4), 134 (5). HR-MS (ESI^+) calcd for $C_{24}H_{31}O_3Na{}^{11}B$ $[M + Na]^+$: 401.2258; found: 401.2245. The enantiomeric excess of the chiral boronic ester was determined by HPLC analysis of an aliquot oxidized to **25**.

(*S*)-1-(2-Methoxy-5-methylphenyl)-1-phenylbut-3-en-1-ol (25)

A solution of tertiary boronic ester **8** (38 mg, 0.10 mmol, 1.0 equiv) in THF (5.0 mL) was cooled to 0 °C and a mixture of 2 mol/L NaOH(aq) (2.0 mL) and 30% H_2O_2 (1.0 mL) was added slowly under vigorous stirring. The reaction mixture was stirred at RT for 2 h. The solvent was removed under reduced pressure and the residue was portioned between water and diethyl ether. The phases were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 9:1) to give tertiary alcohol **25** (21 mg, 79 μmol, 79%) as a colourless oil, which crystallized on standing to form a white solid; mp 52–53 °C (pentane/EtOAc). $[\alpha]_D^{24}$ +100.2 (*c* 1.57, $CHCl_3$, for 94% ee). TLC (pentane/EtOAc, 9:1): 0.32. IR (neat, cm^{-1}) ν_{max}: 3517, 2923, 1497, 1237. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.35–7.31 (m, 2H, H_{Ar}), 7.30–7.24 (m, 3H, H_{Ar}), 7.22–7.17 (m, 1H, H_{Ar}), 7.08 (ddd, J = 8.2, 2.2, 0.6 Hz, 1H, H_{Ar}), 6.78 (d, J = 8.2 Hz, 1H, H_{Ar}), 5.86 (ddt, J = 17.2, 10.3, 6.8 Hz, 1H, C*H*CH_2), 5.15–5.05 (m, 2H, CHC*H*$_2$), 4.64 (br s, 1H, OH), 3.56 (s, 3H, OCH_3), 3.14 (ddd, J = 14.5, 6.8, 1.1 Hz, 1H, C*H*H), 2.89 (ddd, J = 14.5, 6.8, 1.1 Hz, 1H, CH*H*), 2.35 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 155.0 (C), 147.7 (C), 134.5 (*C*HCH_2), 134.0 (C), 129.9 (C), 128.8 (CH), 128.1 (CH), 127.5 (CH), 126.3 (CH), 125.6 (CH), 117.6 (CH*C*H_2), 112.5 (CH), 77.5 (COH), 55.8 (OCH_3), 45.8 (CH_2), 20.9 (CH_3). MS *m*/*z* (%) (CI^+): 269 ($[M + H]^+$, 4), 251 ($[M - OH]^+$, 100), 227 ($[M - allyl]^+$, 85), 149 ($[M - Ar + H]^+$, 30), 135 (20), 105 (34). HR-MS (CI^+) calcd for $C_{18}H_{21}O_2$ $[M + H]^+$: 269.1542; found: 269.1545. HPLC: Chiralpak IB, 20 °C, 3.0% *i*-PrOH in hexane, 0.7 mL/min, UV detection at 210.8 nm, retention times: (*R*)-1-(2-methoxy-5-methylphenyl)-1-phenylbut-3-en-1-ol, 8.6 min; (*S*)-1-(2-methoxy-5-methylphenyl)-1-phenylbut-3-en-1-ol, 9.7 min; 90% ee.

(*R*)-1-Methoxy-4-methyl-2-(1-phenylbut-3-enyl)benzene (9)

A solution of tertiary boronic ester **8** (328 mg, 0.87 mmol, 1.0 equiv) and TBAF·$3H_2O$ (411 mg, 1.30 mmol, 1.5 equiv) in anhydrous toluene (9.0 mL) was stirred for 1.5 h at RT. Afterwards, the reaction mixture was washed with 0.5 mol/L NaOH(aq), water, and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give olefin **9** (207 mg, 0.82 mmol, 95%) as a colourless oil, which required no purification. $[\alpha]_D^{20}$ −10.0 (*c* 1.00, $CHCl_3$, for 90% ee). IR (neat, cm^{-1}) ν_{max}: 2922, 1498, 1240. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.30–7.25 (m, 4H, H_{Ar}), 7.19–7.12 (m, 1H, H_{Ar}), 7.02 (d, J = 2.2 Hz, 1H, H_{Ar}), 6.96 (dd, J = 8.3, 2.2 Hz, 1H, H_{Ar}), 6.74 (d, J = 8.3 Hz, 1H, H_{Ar}), 5.75 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H, C*H*CH_2), 5.03 (ddt, J = 17.1, 2.8, 1.3 Hz, 1H, CHCH_{trans}H), 4.93 (ddt, J = 10.2, 2.8, 1.3 Hz, 1H, CHCH_{cis}H), 4.47 (t, J = 7.9 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 2.78 (ddt, J = 7.9, 6.8, 1.3 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.9 (C), 144.5 (C), 137.3 (*C*HCH_2), 132.8 (C), 129.5 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 125.8 (CH), 115.8 (CH*C*H_2), 110.8 (CH), 55.6 (OCH_3), 43.3 (CH), 39.1 (CH_2), 20.7 (CH_3). MS *m*/*z* (%) (ESI^+): 275 ($[M + Na]^+$, 100), 270 ($[M + NH_4]^+$, 18), 211 ($[M - allyl]^+$, 22). HR-MS (ESI^+) calcd for $C_{18}H_{20}ONa$ $[M + Na]^+$: 275.1406; found: 275.1413. The enantiomeric excess of the chiral olefin was determined by HPLC analysis of an aliquot, which has been hydroborated and oxidized to **26**.

(*R*)-4-(2-Methoxy-5-methylphenyl)-4-phenylbutan-1-ol (26)

A solution of 9-borabicyclo[3.3.1]nonane (9-BBN; 390 μL, 0.5 mol/L in THF, 0.20 mmol, 1.75 equiv) was added to a solution of olefin **9** (29 mg, 0.11 mmol, 1.0 equiv) in anhydrous THF (1.0 mL) and stirred for 2 h at ambient temperature. The reaction mixture was cooled to 0 °C and a mixture of 2 mol/L NaOH(aq) (1.0 mL) and 30% H_2O_2 (0.5 mL) was added slowly. The reaction mixture was stirred vigorously for 2 h at RT. The solution was diluted with water and extracted with diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, pentane/EtOAc, 4:1) to give alcohol **26** (23 mg, 85 μmol, 75%) as a colourless oil. $[\alpha]_D^{21}$ +6.5 (*c* 0.62, $CHCl_3$, for 90% ee). TLC (pentane/EtOAc, 4:1): 0.10. IR (neat, cm^{-1}) ν_{max}: 3334, 2937, 1498, 1243. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.31–7.24 (m, 4H, H_{Ar}), 7.19–7.12 (m, 1H, H_{Ar}), 7.03–7.00 (m, 1H, H_{Ar}), 6.96 (dd, J = 8.2, 2.2 Hz, 1H, H_{Ar}), 6.74 (d, J = 8.2 Hz, 1H, H_{Ar}), 4.39 (t, J = 7.8 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.67 (t, J = 6.6 Hz, 2H, CH_2OH), 2.27 (s, 3H, CH_3), 2.14–2.00 (m, 2H, CH_2CH), 1.60–1.51 (dq, J = 8.1, 6.6 Hz, 2H, C$H_2$$CH_2$OH), 1.35 (br s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ_C: 154.8 (C), 144.8 (C), 133.2 (C), 129.6 (C), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.3 (CH), 125.8 (CH), 110.7 (CH), 62.9 (CH_2OH), 55.7 (OCH_3), 42.7 (CH), 31.1 (CH_2), 31.0 (CH_2), 20.7 (CH_3). MS *m*/*z* (%) (ESI^+): 293 ($[M + Na]^+$, 100), 290 (13), 282 (2), 211 ($[M - (CH_2)_3OH)]^+$, 2). HR-MS (ESI^+) calcd for $C_{18}H_{22}ONa$ $[M + Na]^+$: 293.1512; found: 293.1517. HPLC: Chiralpak IB, 20 °C, 1.5% *i*-PrOH in hexane, 0.7 mL/min, UV detection at 210.8 nm, retention times: (*S*)-1-(2-methoxy-5-methylphenyl)-1-phenylbut-3-en-1-ol, 48.8 min; (*R*)-4-(2-methoxy-5-methylphenyl)-4-phenylbutan-1-ol, 50.2 min; 90% ee.

(*R*)-3-(2-Methoxy-5-methylphenyl)-3-phenylpropanal (23)

This compound was synthesized following a literature procedure performed on a different substrate.[17] The crude material was filtered through a plug of silica (pentane/EtOAc, 1:1), and the solvent was removed in vacuo to afford aldehyde **23** (163 mg, 0.64 mmol, 97%) as a pale yellow oil, which required no further purification. $[\alpha]_D^{22}$ +14.0 (*c* 1.00, $CHCl_3$) (lit.[21] value $[\alpha]_D^{20}$ −16.2 (*c* 1.4, $CHCl_3$, for 99% ee of the (*S*)-isomer)). IR (neat, cm^{-1}) ν_{max}: 2919, 1721, 1498, 1241. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 9.70 (t, J = 2.2 Hz, 1H, CHO), 7.32–7.23 (m, 4H, H_{Ar}), 7.22–7.16 (m, 1H, H_{Ar}), 6.98 (dd, J = 8.3, 2.0 Hz, 1H, H_{Ar}), 6.87 (d, J = 2.0 Hz, 1H, H_{Ar}), 6.75 (d, J = 8.3 Hz, 1H, H_{Ar}), 5.00 (t, J = 7.8 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 3.09 (dd, J = 7.8, 2.2 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ_C: 201.9 (CHO), 154.5 (C), 142.9 (C), 131.3 (C), 129.8 (C), 128.8 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 126.3 (CH), 110.8 (CH), 55.5 (OCH_3), 48.5 (CH_2), 38.3 (CH), 20.6 (CH_3). MS *m*/*z* (%) (ESI^+): 277 ($[M + Na]^+$, 38), 237 (11), 211 ($[M - CH_2CHO]$, 100). HR-MS (ESI^+) calcd for $C_{17}H_{18}O_2Na$ $[M + Na]^+$: 277.1199; found: 277.1204. HPLC: Chiralpak IB, 0 °C, 2.0% *i*-PrOH in hexane, 0.5 mL/min, UV detection at 210.8 nm, retention times: (*S*)-3-(2-methoxy-5-methylphenyl)-3-

phenylpropanal, 24.7 min; (*R*)-3-(2-methoxy-5-methylphenyl)-3-phenylpropanal, 27.6 min; 90% ee.

(*R*)-*N*,*N*-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropan-1-amine (24)

A mixture of aldehyde **23** (25 mg, 98 μmol, 1.0 equiv), diisopropylamine (28 μL, 0.20 mmol, 2.0 equiv), and $NaBH(OAc)_3$ (42 mg, 0.20 mmol, 2.0 equiv) in anhydrous THF (1.0 mL) was stirred for 18 h at ambient temperature. Then, saturated $NaHCO_3$(aq) solution (0.5 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 3.0 mol/L HCl(aq) and brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (SiO_2, pentane/EtOAc/Et_3N, 75:24:1) afforded tertiary amine **24** (23 mg, 68 μmol, 69%) as a pale yellow oil. $[\alpha]_D^{20}$ −11.0 (*c* 1.00, $CHCl_3$) (lit.[22] value $[\alpha]_D$ −6.14 (*c* 0.95, $CHCl_3$, for 81% ee). TLC (pentane/EtOAc/Et_3N, 75:24:1): 0.16. IR (neat, cm^{-1}) ν_{max}: 2962, 1497, 1239. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ_H: 7.31–7.22 (m, 4H, H_{Ar}), 7.16–7.12 (m, 1H, H_{Ar}), 7.07 (d, *J* = 2.2 Hz, 1H, H_{Ar}), 6.94 (dd, *J* = 8.2, 2.2 Hz, 1H, H_{Ar}), 6.72 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 4.35 (t, *J* = 7.7 Hz, 1H, CH), 3.75 (s, 3 H, OCH_3), 2.98 (sept, *J* = 6.5 Hz, 2H, C*H*(CH_3)$_2$), 2.37–2.30 (m, 2H, C*H*HN + C*H*HCH), 2.26 (s, 3H, $C_{Ar}CH_3$), 2.16–2.09 (m, 2H, CH*H*N + CH*H*CH), 0.94 (d, *J* = 6.5 Hz, 6H, CH_3), 0.93 (d, *J* = 6.5 Hz, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ_C: 154.9 (C), 145.1 (C), 133.5 (C), 129.5 (C), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.1 (CH), 125.6 (CH), 110.6 (CH), 55.6 (OCH_3), 48.7 (*C*H(CH_3)$_2$), 44.1 (CH_2N), 41.3 ($C_{Ar}CH$), 37.0 (*C*H_2CH), 20.7 (CH_3), 20.5 ($C_{Ar}CH_3$). MS *m*/*z* (%) (ESI^+): 340 ($[M + H]^+$, 100), 298 ($[M - i\text{-}Pr]^+$, 15), 211 ($[M - (CH_2)_2N(i\text{-}Pr)_2]^+$, 7), 113 (4). HR-MS ($ESI^+$) calcd for $C_{23}H_{34}ON$ $[M + H]^+$: 340.2635; found: 340.2625.

(*R*)-Tolterodine (1)

This compound was synthesized following a literature procedure performed on a different substrate.[7e] Flash chromatography (SiO_2, pentane/EtOAc, 70:30, 2% Et_3N) yielded a pale yellow oil, which crystallized upon standing. (*R*)-tolterodine (**1**; 91 mg, 0.28 mmol, 87%) was obtained as an off-white solid; mp 78–79 °C (pentane/EtOAc/Et_3N). $[\alpha]_D^{20}$ +28.0 (*c* 0.50, MeOH) (lit.[7e] value $[\alpha]_D$ +32.5 (*c* 0.89, MeOH, for 99% ee). TLC (pentane/EtOAc, 70:30, 2% Et_3N): 0.18. IR (neat, cm^{-1}) ν_{max}: 3249, 2971, 2927, 1493. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ_H: 10.27 (br s, 1H, $C_{Ar}OH$), 7.36–7.32 (m, 4H, H_{Ar}), 7.26–7.22 (m, 1H, H_{Ar}), 6.87 (dd, *J* = 8.2, 2.0 Hz, 1H, H_{Ar}), 6.82 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{Ar}), 6.57 (s, 1H, H_{Ar}), 4.50 (dd, *J* = 10.8, 3.2 Hz, 1H, CH), 3.25 (sept, *J* = 6.7 Hz, 2H, C*H*(CH_3)), 2.79–2.70 (m, 1H, C*H*HN), 2.46–2.33 (m, 2H, CH*H*N + C*H*HCH), 2.14 (s, 3H, $C_{Ar}CH_3$), 2.13–2.04 (m, 1H, CH*H*CH), 1.15 (d, *J* = 6.7 Hz, 6H, CH_3), 1.10 (d, *J* = 6.7 Hz, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ_C: 153.2 (C), 144.7 (C), 132.3 (C), 129.3 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 126.1 (CH), 118.1 (CH), 48.0 (*C*H(CH_3)$_2$), 42.1 (CH_2N), 39.4 ($C_{Ar}CH$), 33.2 (*C*H_2CH), 20.7 ($C_{Ar}CH_3$), 19.9 (CH_3), 19.5 (CH_3). MS *m*/*z* (%) (ESI^+): 348 ($[M + Na]^+$, 1), 326 ($[M + H]^+$, 100), 284 ($[M - i\text{-}Pr + H]^+$, 2), 197 ($[M - (CH_2)_2N(i\text{-}Pr)_2]^+$, 1), 109 ($[Ar]^+$, 5). HR-MS ($ESI^+$) calcd for $C_{22}H_{32}ON$ $[M + H]^+$: 326.2478; found: 326.2466.

Supplementary data

Supplementary data are available with the article through the journal Web site http://nrcresearchpress.com/doi/supp/10.1139/v2012-069.

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