A Practical Synthetic Approach to Chiral (α-Chloroalkyl)boronic Esters via Iridium-Catalyzed Chemoselective Hydrogenation of Chloro-Substituted Alkenyl Boronates

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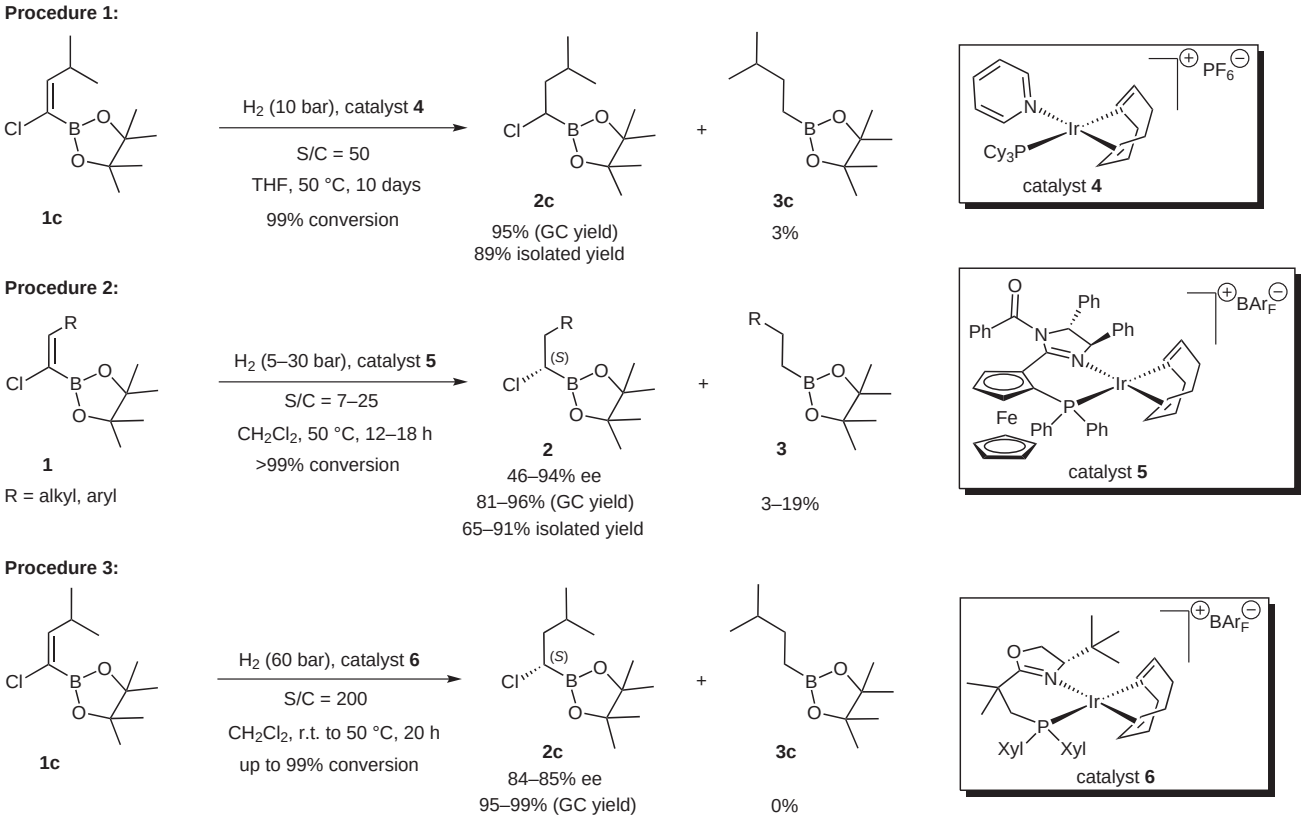
Dedicated to Prof. Dr. Dominique Lorcy (University of Rennes 1, France) on the occasion of her birthday

Abstract: Chiral (α-chloroalkyl)boronic esters are obtained by homogeneous asymmetric iridium-catalyzed chemoselective hydrogenation of (1-chloro-1-alkenyl)boronic esters. P,N–Iridium catalysis provides low level of dehalogenation during the hydrogenation, while the catalyst activity and enantioselectivity essentially depends on the applied P,N ligand features. Fine tuning of P,N ligand structures enables high conversions, broad substrate acceptance, and high to excellent enantioselectivities with enantiomeric excess values up to 94% along with low levels of dechlorination. Low catalyst loading with S/C = 200 can also be achieved for the preparation of an industrially important isobutyl derivative.

Key words: alkenes, alkyl halides, asymmetric synthesis, chemoselectivity, hydrogenation



Scheme 1 Iridium-catalyzed chemoselective hydrogenation of chloro-substituted alkenyl boronates

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Introduction

Chiral (α-chloroalkyl)boronic esters, initially discovered by Matteson, represent an important class of chiral building blocks in organic synthesis.[1] Moreover, (α-chloroalkyl)boronic esters proved to be key precursors of α-aminoboronic acids, which attracted considerable interest in recent years in the field of biology.[2,3] Indeed, α-aminoboronic acids constitute a fundamental structural unit in proteasome inhibitors[4] like Bortezomib (FDA approved),[5,6] Ixazomib (Phase III studies),[7] and Delanzomib (Phase II studies)[8] as well as in the dipeptidyl peptidase-4 (DPP-4) inhibitors such as Dutogliptin (Phase III studies) for treatment of type 2 diabetes mellitus.[9] Recently, α-aminoboronic acid derivatives also proved to be useful precursors for the synthesis of enantioenriched benzylamines in the Suzuki–Miyaura coupling reaction.[10] Despite the fact that chiral (α-chloroalkyl)boronic esters were discovered more than three decades ago and proved to be versatile synthetic tools, the only method for their preparation has been Matteson's homologation. This stimulated us to consider a novel method for the preparation of (α-chloroalkyl)boronic esters via chemoselective asymmetric hydrogenation of chloro-substituted alkenyl boronates. However, we were faced with a severe challenge related to the possible C–Cl bond cleavage under the homogeneous hydrogenation reaction conditions.[11] Namely, there was no literature precedent for the homogeneous asymmetric hydrogenation of alkene substrates bearing directly bound chlorine functionality and nonpolar groups that are incapable of coordination to catalyst. To our delight, our initial screening for such a hydrogenation approach revealed that chemoselective hydrogenation of (1-chloro-1-alkenyl)boronic esters can be achieved with P,N–Ir complexes.[12]

Scope and Limitations

Due to the biological significance, **1c** was chosen as the model substrate for the initial investigation of the hydrogenation of (1-chloro-1-alkenyl)boronic esters **1** under homogeneous reaction conditions. During our initial reaction screening,[12a] we surprisingly observed a significant difference in catalytic performance between Crabtree's catalyst **4** and [Rh(cod)DiPFc]BF_4 catalyst.[13] Markedly, while Crabtree's catalyst afforded 99% conversion of **1c** giving 95% of **2c** with less than 3% of **3c** present in 10 days at 50 °C (THF, 10 bar H_2) and substrate/catalyst (S/C) = 50 (Scheme 1, procedure 1), the [Rh(cod)DiPFc]BF_4 catalyst provided only 5% conversion of **1c** giving 4% of dehalogenated product **3c** in 1 day at 50 °C (MeOH, 10 bar H_2) and S/C = 50. Crabtree's catalyst performed equally well in CH_2Cl_2 (50 °C, 10–30 bar H_2, 12–18 h) when tested on other aliphatic substrates **1a** (**2a**/**3a** = 98:2), **1b** (**2b**/**3b** = 95:5), **1e** (**2e**/**3e** = 96:4) with some reduction in chemoselectivity observed with substrate **1d** (**2d**/**3d** = 75:12, 87% GC conversion).

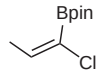
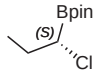
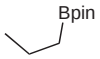
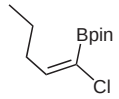
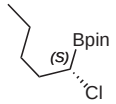
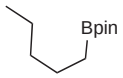
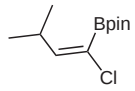
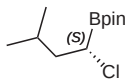
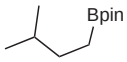
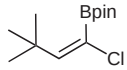
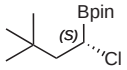
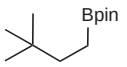
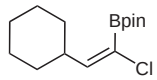
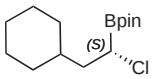
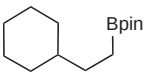
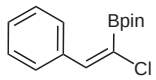
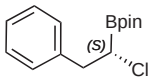
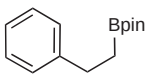
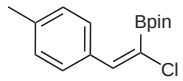
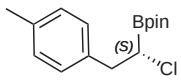
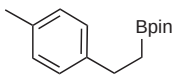
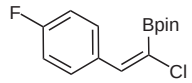
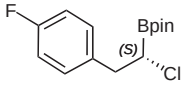
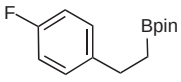
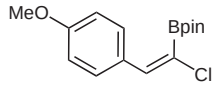
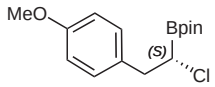
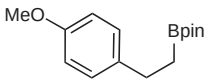
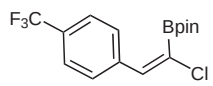
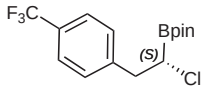
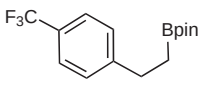
The striking result on the racemic version of the hydrogenation of **1c** prompted us to perform an extended chiral catalyst screening in order to elaborate the asymmetric variant of the protocol. This confirmed the unique activity of P,N–Ir catalysts, since among numerous combinations of P,P; N,N; and P,N ligands with various Rh, Ru, and Ir metal precursors only P,N–Ir based type catalysts assured low levels of dechlorination.[12a] Indeed, P,N–Ir catalysts with phosphinite-oxazoline ligands[14] provided 46–63% ee along with full conversion (S/C = 25) and no **3c** present.[12a] To follow up this lead, related catalyst structures of PHOX,[15] SimplePHOX,[16] PyrPHOX,[17] and ferrocenyl oxazolinylphosphine (phosferrox or Fc-PHOX)[18] were tested. They generally did not deliver improved performance and either partial conversions or lower enantiomeric excesses were obtained, albeit accompanied by low levels of dechlorination.

More encouraging results were obtained with iridium catalyst **6** bearing the *t*-Bu-Xyl-NeoPHOX ligand;[19] at 50 °C and 20 bar of hydrogen pressure, full conversion and 86% ee were achieved applying an S/C ratio of 50 in dichloroethane. Interestingly, the structurally related catalysts bearing phenyl or *o*-tolyl moieties, respectively, instead of the xylyl groups showed significantly worse performance. The comparably lower bulk of the phenyl substituents of the catalyst gave rise to only 35% ee at full conversion, whereas the high steric demand of the *o*-tolyl substituents likely disfavored substrate coordination and resulted in 34% ee and only 50% conversion under otherwise identical conditions.

With a focus on increasing enantioselectivity further, our attention was turned to imidazoline-type P,N–Ir catalysts. To our delight, ferrocenyl-phosphinoimidazoline[20] iridium complexes demonstrated high chemo- and stereoselectivity.[12a] Our modification of the ligand structure by protection of the free imidazoline NH functionality by an acyl moiety was the key to catalysts that also enabled high conversions along with excellent enantioselectivities and low level of dehalogenation.[12a] Among these, P,N–Ir complex **5** proved to be the most promising as evidenced by highly enantioselective hydrogenation of **1c** reaching full conversion and giving the product **2c** in 93% ee. The catalyst loading (S/C = 25) was relatively high but a good yield of **2c** (85%) and low levels of the dechlorinated side-product **3c** (3% by GC area) were obtained, making this reaction a useful method for the synthesis of **2c** with high enantiomeric excess (Table 1, entry 3). The scope of the method was examined by testing asymmetric hydrogenation on a range of aliphatic and aromatic substrates (Scheme 1, procedure 2). Substrate **1a** bearing a methyl substituent on the double bond, instead of the larger isopropyl group present in **1c**, reacted to give the desired product **2a** with a lower ee of 46%, while the amount of dechlorinated side product **3a** remained low (4%) (Table 1, entry 1). The related aliphatic substrate bearing an *n*-propyl group on the double bond gave the hydrogenated product **2b** in 75% yield with 83% ee (Table 1, entry 2). This increased ee in relation to the hydrogenation of **1a** is probably a result of the larger *n*-propyl substituent interacting with the chiral P,N ligand to induce a higher level of asymmetric induction. The higher ee obtained with **1c**,

bearing a more bulky isopropyl group, is also in line with this trend. Hydrogenation of substrate **1d**, bearing a *tert*-butyl group, was possible but a high catalyst loading was needed in this case (S/C = 7). Nevertheless, high yield of the product **2d** was obtained, with a high ee of 93% being achieved (Table 1, entry 4). Hydrogenation of **1e** bearing a cyclohexyl substituent gave the desired product **2e** in good yield (85%) with a high ee of 92% and only 5% of the dechlorinated side-product **3e** (Table 1, entry 5). The aliphatic substrate that did not react well in the desired way was the cyclopropyl-substituted derivative (Scheme 1, compound **1**, R = *c*-Pr; not shown in Table 1). This de-

Table 1 The Scope of Asymmetric Iridium-Catalyzed Chemoselective Hydrogenation of Chloro-Substituted Alkenyl Boronates with Catalyst **5**[a]

Entry	Alkene	S/C	Pressure (bar)	Time (h)	Product **2**	**3**	**2**/**3**[b]	Yield (%) of **2**[c]	ee[b]
1	 **1a**	25	30	18	 **2a**	 **3a**	96:4	73	46
2	 **1b**	25	5	12	 **2b**	 **3b**	96:3.5	75	83
3	 **1c**	25	5	12	 **2c**	 **3c**	95:3	85	93
4	 **1d**	7	10	12	 **2d**	 **3d**	90:10	86	93
5	 **1e**	25	30	18	 **2e**	 **3e**	95:5	85	92
6	 **1f**	10	10	12	 **2f**	 **3f**	94:6	89	90
7	 **1g**	10	30	18	 **2g**	 **3g**	86:14	70	88
8	 **1h**	10	5	12	 **2h**	 **3h**	92:8	91	89
9	 **1i**	10	30	18	 **2i**	 **3i**	88:12	73	88
10	 **1j**	10	30	18	 **2j**	 **3j**	81:19	65	94

[a] Conditions: substrate (0.18–0.22 mmol), catalyst **5**, CH_2Cl_2 (2.5–3 mL), 0.066–0.087 M substrate concentration, 50 °C, full conversion.
[b] Conversions to **2** and **3** as well as enantiomeric excesses were calculated by GC analysis. When the sum of **2** and **3** does not correspond to 100% this is due to the presence of unidentified side products.
[c] Isolated yields.

rivative gave low conversion of 34% within 12 hours (10 bar H_2, S/C = 10) and only 13% of the desired product was obtained. This was probably due to side-reactions resulting from ring-opening of the vinylcyclopropane moiety as demonstrated by the presence of larger amounts of unidentified side-products in GC chromatograms. Interestingly, when this substrate was hydrogenated under identical conditions but in the presence of Crabtree's catalyst **4** in toluene, 86% conversion of the starting material was achieved giving 52% of desired racemic product.

To examine the scope of the synthetic method further, substrates bearing aromatic substituents of various types were prepared and hydrogenated using catalyst **5**. Crabtree's catalyst **4** was again used to prepare the racemic references (S/C = 10:1, CH_2Cl_2, 50 °C, 10–30 bar H_2, 12–18 h). Phenyl-substituted **1f** reacted under standard conditions to give 70% conversion to products **2f** and **3f** in a 64:6 ratio. The presence of electron-withdrawing substituents appeared to increase reactivity: substrates **1h** and **1j** gave full conversion (**2h**/**3h** = 68:5 ratio and **2j**/**3j** = 49:37). The presence of electron-donating substituents caused instead a marked decrease in reactivity: substrates **1g** and **1i** gave respectively 35% conversion (**2g**/**3g** = 16:19) and 21% conversion (**2i**/**3i** = 10:11). Comparable substrate reactivity trends were observed using chiral catalyst **5**. Hydrogenation of the phenyl-substituted **1f** could be achieved at increased catalyst loading (S/C = 10). Good conversion to product **2f** was obtained (89% yield) with 90% ee (Table 1, entry 6). The amount of dechlorinated side-product **3f** was still low at 6%. Even with this less reactive substrate the reaction was performed under mild conditions of temperature and pressure (50 °C, 10 bar H_2). The related substrate **1g** bearing a *p*-tolyl substituent was hydrogenated to give the product **2g** in 70% yield with 88% ee (Table 1, entry 7). In this reaction a higher level of dechlorinated side-product was formed than with the unsubstituted phenyl group and any of the aliphatic substrates. Substrate **1h** bearing a *p*-fluoro aromatic ring was hydrogenated successfully using catalyst **5**. High product yield (91%), high ee (89%) and a low amount of dechlorinated side-product (8%) resulted (Table 1, entry 8). The *p*-OMe analogue **1i** gave 73% yield of the desired product **2i** with 88% ee and about 12% dechlorinated side-product **3i** (Table 1, entry 9). The *p*-CF_3 analogue **1j** gave the highest ee observed at 94%, but more dechlorination occurred in this case resulting in a reduction in the yield of product **2j** (Table 1, entry 10).[12a]

In line with experiments conducted by others on fluoro derivatives,[21] we established that pure, racemic **2c** and **2e** did not dechlorinate under the reaction conditions in the presence of catalyst **5**. While aromatic substrates **1f–j** could be successfully hydrogenated using catalyst **5**, they generally showed reduced reactivity and higher levels of dechlorination. Electronic factors related to the nature of the substituents on the aromatic rings appear to play a role. When samples of product mixtures of **2g**, **2i**, and **2j** were resubmitted to hydrogenation conditions (10% catalyst **5**, CH_2Cl_2, 30 bar H_2, 50 °C, 18 h) a different result was obtained in comparison to the aliphatic substrates. A small, but noticeable increase in the amount of dehalogenated side-products **3g**, **3i**, and **3j** (ranging from 4% on **2g** to 11–16% on **2i** and **2j**) was detected. The origin of this, in some cases (e.g., **2g** and **2i**), can be ascribed to the thermal instability of products **2** as evidenced by detectable dechlorination in experiments without catalyst under the identical conditions as described above. A moderate background dechlorination of the products, detectable irrespective of the electronic nature of the substituents on the aromatic ring, would explain the observed trend for substrates/products bearing aromatic substituents to give slightly higher amounts of dechlorinated side products.

In addition to optimizing catalyst selectivity, catalyst productivity was also explored. Unfortunately, it was not possible to increase the activity of catalyst **5**. The use of different reaction temperatures and hydrogen pressures generally made little difference to the reaction outcome. Reactions in toluene at 80 °C provided an acceptable alternative to reactions at 50 °C in CH_2Cl_2 but, in all cases, catalyst loadings lower than S/C = 25/1 caused a slight reduction in enantioselectivity and a significant drop in conversion. We therefore decided to reconsider the use of iridium catalyst **6**, bearing the *t*-Bu-Xyl-NeoPHOX ligand,[19] which, during the catalyst optimization phase had given promising results in the hydrogenation of substrate **1c** (S/C = 50, 86% ee in dichloroethane, 50 °C, 20 bar). A switch to dichloromethane as solvent brought noticeable improvement in reactivity and S/C ratios of 100 were feasible. Alternative solvents and mixtures such as trifluoroethanol or 2-methyltetrahydrofuran–dichloromethane (1:1) proved counter-productive, as did the addition of 0.1 equivalent versus substrate of triethylamine or acetic acid. Reducing the reaction temperature to ambient did neither significantly improve productivity, nor enantioselectivity. An increase in pressure to 60 bar at ambient temperature, however, enabled 99% conversion and 85% ee of **1c** at S/C = 200 (Scheme 1, procedure 3). Equivalent experiment at 50 °C provided 95% conversion to **2c** and 84% ee. In all experiments, product selectivity proved excellent with <1% of dehalogenated by-product **3c** observed.

In conclusion, we have developed a new catalytic and asymmetric route to enantiomerically enriched (α-chloroalkyl)boronic esters. The methodology has been applied to a variety of substrates bearing both alkyl and aryl substituents. While significant changes in reactivity have been detected depending on the steric and electronic nature of the alkyl and aryl residues in substrates **1**, it has been proven that catalyst **5** provides high enantioselectivity with reasonably broad substrate acceptance. In addition, catalyst **6** has proven its value in the hydrogenation of a key aliphatic substrate providing slightly reduced enantioselectivity but at significantly lower catalyst loadings, which can make its use valuable from an applied perspective.

Products **2a–j** were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy, and HRMS. NMR spectra were recorded on a Varian VNMRS 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts are reported in δ ppm referenced to TMS as an internal standard. High-resolution mass spectra (HRMS) were acquired on a Bruker BioApex II 4.7e FTICR mass spectrometer. The chromatographic and optical purity of products **2a–j** was determined by gas chromatography on the following instruments: a) Varian CP3800 Gas Chromatograph, b) Agilent 7890A Gas Chromatograph, and c) Agilent 6890N Gas Chromatograph. Gas chromatograph was equipped with a flame ionization detector on the capillary column. Retention times for eluting peaks of compounds **1a–j**, *rac*-**2a–j**, (*R*)-**2a–j**, (*S*)-**2a–j**, and **3a–j** are reported. All chemicals and solvents were purchased from commercially sources and were used without further purification. Anhyd THF and CH_2Cl_2 were obtained from Sigma-Aldrich. Starting materials **1a–j** were prepared according to the literature procedure as well as standards of dechlorinated products **3a–j**.[12a] Column chromatography was performed with silica gel (Merck, type 60, 0.063–0.2 mm). Catalyst **4** was supplied by Johnson Matthey and stored under inert atmosphere prior to use. Catalyst **5** was synthesized according to literature data.[12a] Catalyst **6** was supplied by Solvias and stored under inert atmosphere prior to use.

Procedure 1: Gram Scale Hydrogenation with Crabtree's Catalyst 4

The (1-chloro-1-alkenyl)boronic ester **1c** (1.84 g, 8.0 mmol), (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (**4**; Crabtree's catalyst, 129 mg, 0.16 mmol, S/C = 50) and anhyd THF (50 mL) were rapidly placed in the 75 mL stainless steel autoclave under N_2 atmosphere. The autoclave was sealed and pressurized/depressurized: first, three times with 6 bar of N_2, then three times with 6 bar of H_2. The mixture was stirred for 10 days at 50 °C under 10 bar of H_2. Once the autoclave had cooled to r.t., the autoclave was carefully depressurized, and the solution was poured into a round bottomed flask. The crude product analysis by GC revealed the 99% conversion with 95% of **2c** and 3% of **3c** present. The solvent was removed under the reduced pressure and the residue was passed through a short column of silica gel (eluent: *n*-hexane) to remove the catalyst. The racemic product **2c** was isolated in 89% (1.65 g) yield.

Procedure 2: Hydrogenation with Catalyst 5; (α-Chloroalkyl)boronic Esters 2a–j; General Procedure

The respective (1-chloro-1-alkenyl)boronic ester **1a–j** was placed in a vial suitable for the Biotage Endeavour and the P,N–Ir complex **5** was added. The vial was placed into the Endeavour and sealed. The system was purged with N_2 five times and then solvent was added. The system was purged five more times with N_2 and ten times with H_2. The reaction mixture was heated to adequate temperature and pressurized with H_2 for 12–18 hours. The system was vented and the resulting reaction crude was purified by flash column chromatography using as eluent a mixture of *n*-hexane and EtOAc (v/v).

Procedure 3: Hydrogenation with Catalyst 6

The (1-chloro-1-alkenyl)boronic ester **1c** (115.2 mg, 0.5 mmol) was placed in a Schlenk flask, set under argon by three vacuum/argon cycles and dissolved in degassed CH_2Cl_2 (2 mL). (*S*)-Ir-*t*-Bu-Xyl-NeoPHOX catalyst precursor **6** (2.5 μmol, 4.13 mg, S/C = 200) was placed in a Schlenk flask, set under argon by three vacuum/argon cycles and dissolved in degassed CH_2Cl_2 (1 mL). Both solutions were stirred for 15 min at r.t. and subsequently transferred into an inertized 50 mL stainless steel autoclave via syringe under a slight overpressure of argon. The autoclave was closed, purged three times with argon and three times with H_2 and the pressure was set to 60 bar. Heating and stirring was started and as soon as the temperature of 50 °C was reached, the pressure was readjusted and the reaction was stirred for 20 h. Afterwards, the autoclave was vented, flushed with argon, unloaded, and the product solution was analyzed.

(*S*)-2-(1-Chloro-2-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2a)

Following the general procedure with catalyst **5** (S/C = 25) using **1a** (40 mg, 0.20 mmol) in anhyd CH_2Cl_2 (3 mL), **2a** was obtained as a colorless oil; yield: 30 mg (73%); 46% ee.

GC: Both conversion and ee were established using chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate: 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature: 100 °C for 30 min; Total run time: 20 min; **1a** = 8.4 min; **3a** = 2.8 min; (*R*)-**2a** = 7.5 min; (*S*)-**2a** = 7.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.6 Hz, 3 H), 1.31 (12 H, s), 1.89 (m, 2 H), 3.39 (t, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 24.6, 27.5, (C–B not observed), 84.4.

HRMS-ESI$^+$: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{18}BClO_2$ + Na: 227.0981; found: 227.0979.

(*S*)-2-(1-Chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2b)

Following the general procedure with catalyst **5** (S/C = 25) using **1b** (50 mg, 0.22 mmol) in anhyd CH_2Cl_2 (2.5 mL), **2b** was obtained as a colorless oil; yield: 38 mg (75%); 83% ee.

GC: Both chromatographic purity and the ee were established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature: 100 °C for 30 min; Total run time: 30 min; **1b** = 20.3 min; (*R*)-**2b** = 21.9 min; (*S*)-**2b** = 22.6 min; **3b** = 6.7 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.30 (s, 12 H), 1.36 (m, 3 H), 1.48 (m, 1 H), 1.83 (m, 2 H), 3.42 (dd, *J* = 6.8, 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.2, 24.6, 29.5, 33.8, 43.5 (br), 84.3.

HRMS-ESI$^+$: *m*/*z* $[M - CH_3]^+$ calcd for $C_{10}H_{19}BClO_2$: 217.1167; found: 217.1161.

(*S*)-2-(1-Chloro-3-methylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c)

Following the general procedure with catalyst **5** (S/C = 25) using **1c** (50 mg, 0.22 mmol) in anhyd CH_2Cl_2 (2.5 mL), **2c** was obtained as a colorless oil; yield: 43 mg (85%); 93% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature: 120 °C for 8 min; Total run time: 8 min; **1c** = 6.6 min, **2c** = 5.7 min, **3c** = 2.8 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature gradient: 60 °C for 40 min, increase 0.5 °C min^{-1} until 90 °C, hold 2 min, decrease 15 °C min^{-1} until 60 °C, hold 1 min; Total run time: 105 min; **1c** = 83.8 min; (*R*)-**2c** = 94.5 min; (*S*)-**2c** = 95.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H), 1.21 (s, 12 H), 1.52 (m, 1 H), 1.70 (m, 1 H), 1.79 (m, 1 H), 3.40 (dd, *J* = 6.0, 9.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 22.9, 24.6, 25.6, 41.5 (br), 42.5, 84.3.

HRMS-ESI$^+$: *m*/*z* $[M - C_3H_6O]^+$ calcd for $C_8H_{16}BClO$: 174.0986; found: 174.0977.

(*S*)-2-(1-Chloro-3,3-dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2d)

Following the general procedure with catalyst **5** (S/C = 7) using **1d** (49 mg, 0.20 mmol) in anhyd CH_2Cl_2 (2.5 mL), **2d** was obtained as a colorless oil; yield: 44 mg (86%); 93% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature: 120 °C for 12 min; Total run time: 12 min; **2d** = 8.4 min, **3d** = 4.0 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 90 °C; Temperature: 90 °C for 60 min; Total run time: 60 min; (*R*)-**2d** = 52.7 min; (*S*)-**2d** = 53.3 min; **1d** = 54.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9 H), 1.30 (s, 12 H), 1.77 (dd, *J* = 6.3, 13.7 Hz, 1 H), 1.98 (dd, *J* = 10.3, 13.7 Hz, 1 H), 3.47 (dd, *J* = 5.5, 9.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 29.6, 31.3, (C–B not observed), 48.0, 84.2.

HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{24}BClO_2$ + Na: 269.1456; found: 269.1450.

(*S*)-2-(1-Chloro-2-cyclohexylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2e)

Following the general procedure with catalyst **5** (S/C = 25) using **1e** (54 mg, 0.20 mmol) in anhyd CH_2Cl_2 (3 mL), **2e** was obtained as a colorless oil; yield: 46 mg (85%); 92% ee.

GC: Chromatographic purity was determined by GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 160 °C; Total run time: 15 min; **1e** = 8.4 min, **2e** = 9.5 min, **3e** = 4.8 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 100 °C; Total run time: 180 min; (*R*)-**2e** = 165.9 min; (*S*)-**2e** = 166.9 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 2 H), 1.20 (m, 15 H), 1.71 (m, 8 H), 3.55 (dd, *J* = 6.0, 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 26.3, 26.5, 26.8, 32.0, 33.6, 35.1, 41.2, 84.3.

HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ calcd $C_{14}H_{26}BClO_2$ + Na: 295.1607; found: 295.1603.

(*S*)-2-(1-Chloro-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2f)

Following the general procedure with catalyst **5** (S/C = 10) using **1f** (50 mg, 0.19 mmol) in anhyd CH_2Cl_2 (2.5 mL), **2f** was obtained as a colorless oil; yield: 45 mg (89%); 90% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 160 °C; Total run time: 15 min; **1f** = 11.6 min, **2f** = 10.7 min, **3f** = 5.4 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 110 °C; Total run time: 120 min; (*R*)-**2f** = 104.5 min; (*S*)-**2f** = 106.0 min; **1f** = 113.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H), 1.27 (s, 6 H), 3.12 (dd, *J* = 8.6, 13.9 Hz, 1 H), 3.21 (dd, *J* = 8.1, 13.9 Hz, 1 H), 3.63 (t, *J* = 8.1 Hz, 1 H), 7.29 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 40.3, 43.0 (br), 84.5, 126.8, 128.4, 129.2, 138.4.

HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}BClO_2$ + Na: 289.1134; found: 289.1137.

(*S*)-2-(1-Chloro-2-*p*-tolylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2g)

Following the general procedure with catalyst **5** (S/C = 10) using **1g** (55 mg, 0.20 mmol) in anhyd CH_2Cl_2 (3 mL), **2g** was obtained as a colorless oil; yield: 40 mg (70%); 88% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 160 °C; Total run time: 20 min; **1g** = 15.8 min, **2g** = 13.7 min, **3g** = 7.2 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 120 °C; Total run time: 120 min; (*R*)-**2g** = 75.6 min; (*S*)-**2g** = 77.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H), 1.27 (s, 6 H), 2.32 (s, 3 H), 3.06 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.16 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.59 (t, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 24.5, 24.8, 39.8, 43.0 (br), 84.4, 128.9, 129.0, 135.3, 136.3.

HRMS-ESI$^+$: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}BClO_2$: 281.1474; found: 281.1460.

(*S*)-2-[1-Chloro-2-(4-fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2h)

Following the general procedure with catalyst **5** (S/C = 10) using **1h** (50 mg, 0.18 mmol) in anhyd CH_2Cl_2 (2.5 mL), **2h** was obtained as a colorless oil; yield: 46 mg (91%); 89% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 160 °C; Total run time: 15 min; **1h** = 10.9 min, **2h** = 10.7 min, **3h** = 5.7 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 110 °C; Total run time: 120 min; **1h** + (*R*)-**2h** = 109.5 min, (*S*)-**2h** = 111.6 min. Given the co-elution of **1h** and (*R*)-**2h**, the ee could be established only for the reactions that gave full conversion.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H), 1.26 (s, 6 H), 3.08 (dd, *J* = 8.1, 14.3 Hz, 1 H), 3.16 (dd, *J* = 8.1, 14.3 Hz, 1 H), 3.58 (t, *J* = 8.1 Hz, 1 H), 7.00 (t, *J* = 9.0 Hz, 2 H), 7.24 (dd, *J* = 5.6, 9.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 39.4, 43.0 (br), 84.6, 115.1 ($^2J_{C,F}$ = 23.1 Hz), 130.7 ($^3J_{C,F}$ = 8.0 Hz), 134.0 ($^4J_{C,F}$ = 4.0 Hz), 161.9 ($^1J_{C,F}$ = 243.5 Hz).

HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{19}BClFO_2$ + Na: 307.1053; found: 307.1043.

(*S*)-2-[1-Chloro-2-(4-methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2i)

Following the general procedure with catalyst **5** (S/C = 10) using **1i** (58 mg, 0.20 mmol) in anhyd CH_2Cl_2 (3 mL), **2i** was obtained as a colorless oil; yield: 44 mg (73%); 88% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 180 °C; Total run time: 20 min; **1i** = 13.7 min, **2i** = 11.6 min, **3i** = 6.4 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 130 °C; Total run time: 120 min; (*R*)-**2i** = 101.5 min; (*S*)-**2i** = 103.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H), 1.26 (s, 6 H), 3.06 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.14 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.56 (t, *J* = 8.0 Hz, 1 H), 3.80 (s, 3 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 24.8, 39.4, 43.0 (br), 55.2, 84.4, 113.7, 130.3, 130.4, 158.5.

HRMS-ESI$^+$: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}BClO_3$: 297.1423; found: 297.1414.

(*S*)-2-[1-Chloro-2-(4-trifluoromethyl)phenylethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2j)

Following the general procedure with catalyst **5** (S/C = 10) using **1j** (66 mg, 0.20 mmol) in anhyd CH_2Cl_2 (3 mL), **2j** was obtained as a colorless oil; yield: 43 mg (65%); 94% ee.

GC: Chromatographic purity was determined by GC method under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.0 mL min^{-1}; Detector: T = 250 °C; Temperature 160 °C; Total run time: 15 min; **1j** = 8.6 min and 8.8 min, **2j** = 9.4 min, **3j** = 5.1 min.

The ee was established using a chiral GC under the following conditions: Column: Chrompack capillary column CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.25 μm; Injector: split ratio 30, T = 250 °C; Carrier gas: He, constant flow rate 1.5 mL min^{-1}; Detector: T = 250 °C; Temperature 120 °C; Total run time: 60 min; **3j** = 37.1 min, (*R*)-**2j** = 48.9 min; (*S*)-**2j** = 50.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 6 H), 1.26 (s, 6 H), 3.15 (dd, *J* = 8.8, 14.0 Hz, 1 H), 3.26 (dd, *J* = 7.2, 14.0 Hz, 1 H), 3.62 (dd, *J* = 7.2, 8.8 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 39.8, (C–B not observed), 84.7, 125.1, 128.3, 129.6, 142.5.

HRMS-ESI$^+$: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}BClF_3O_2$: 335.1190; found: 335.1191.

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