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VIP

Iridium-Catalyzed Enantioselective Hydrogenation of Alkenylboronic Esters

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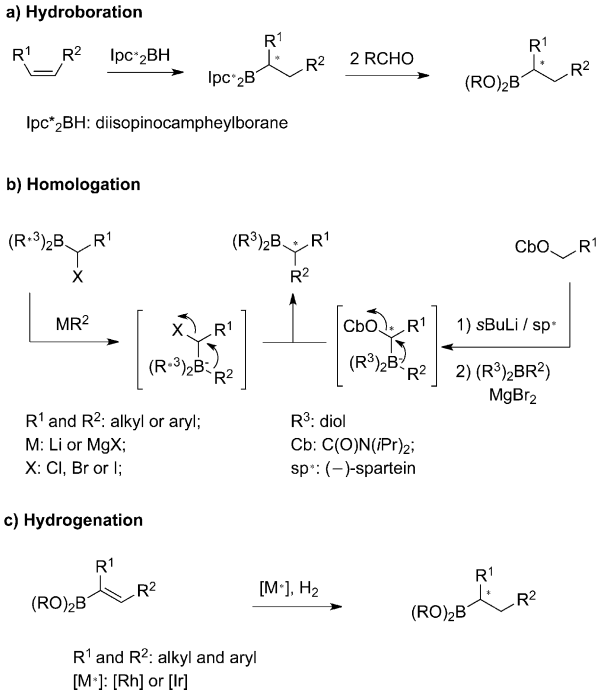
Chiral boronates represent highly versatile building blocks in organic synthesis,[1] since carbon–boron bonds can be readily converted into C–O, C–N, and C–C bonds in a stereospecific manner.[2] Therefore, enantioselective routes to these compounds are of great value. The most widely used method for the synthesis of enantioenriched chiral boronic esters is the hydroboration of C=C bonds with chiral hydroboranes pioneered by Brown (Scheme 1a). The method works particularly well with 1,2-disubstituted *cis* olefins, whereas the corresponding *trans* isomers and trisubstituted olefins usually react with much lower enantioselectivity.[2a–c] On the other hand, the homologation reaction involving a stereoselective migration–displacement process, originally developed by Matteson[3] and further investigated by Aggarwal,[4] yields chiral secondary boron compounds directly from α-haloboronic esters or primary alcohols. Although these approaches have proved very useful in complex molecule synthesis, it was desirable to develop catalytic methods that do not require stoichiometric quantities of chiral reagents. The discovery of Männig and Nöth that rhodium complexes catalyze the addition of catecholborane to alkenes paved the way toward enantioselective catalytic hydroboration.[5] Subsequently, rhodium,[6] and to a lesser extent other transition-metal complexes with chiral ligands have been successfully used as catalysts to prepare chiral organoboranes in high enantiomeric purity.[7,8] However, the substrate scope of these reactions is still limited. With few exceptions, high enantio- and regioselectivities are only obtained with aryl-substituted alkenes.



Scheme 1. Enantioselective routes to chiral secondary alkyl boronates.

In this respect, asymmetric hydrogenation of alkenylboronic esters offers an attractive alternative, because it avoids the regioselectivity problems often encountered in catalytic and stoichiometric hydroborations. Moreover, asymmetric hydrogenation is one of the best established reactions in organic synthesis with a wide range of potential catalysts available. Morken and co-workers reported the first successful enantioselective hydrogenations of 1,2-bis(boronates)[9] and alkenylboronates,[10] using a Rh-Walphos[11] complex (Scheme 1c; $R^2 = H$ or $B(OR)_2$). In this way chiral secondary boronates that are not accessible by hydroboration were obtained in high enantiomeric purity. However, relatively high catalyst loadings of 5 mol% and long reaction times were required. More recently, Andersson and coworkers found that iridium complexes with chiral N,P-ligands are more active catalysts in reactions of this type, giving full conversion with only 0.5 mol% catalyst loading. With certain alkenylboronates with an aryl group at the C=C bond, excellent enantioselectivities were achieved, whereas analogous alkyl-substituted substrates gave unsatisfactory enantiomeric excess (*ee*) values.[12] Overall, the scope of these Rh- and Ir-catalyzed hydrogenations is still limited, so the search for other catalysts that enhance the application range will continue. Herein, we report two efficient Ir catalysts for the enantioselective hydrogenation of a wide range of pinacol-derived alkenylboronic esters.

The hydrogenation of the aliphatic boronate **1a**, which so far had given unsatisfactory results with Ir catalysts,[12a] served as a starting point for our study. In a series of chiral N,P-ligand complexes that we screened in this reaction,[13] complex **3a** derived from an imidazoline–phosphinite

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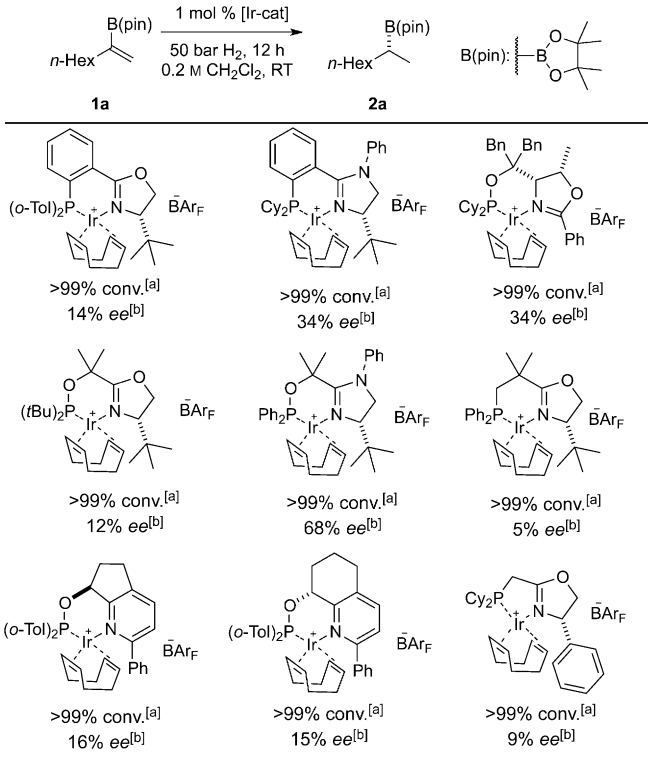
Table 1. Catalyst screening for the hydrogenation of boronic ester **1a**.

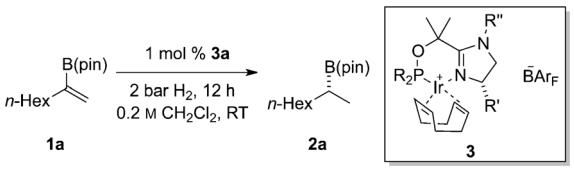


[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Supporting Information for details). [b] Determined by GC analysis on a chiral stationary phase (see the Supporting Information for details).

ligand[14] stood out as the most promising catalyst, providing an *ee* value of 68% at 50 bar hydrogen pressure (Table 1). By lowering the hydrogen pressure to 2 bar the *ee* value increased to 86%.[15] We also investigated the solvent influence, since hydrogenation with rhodium complexes showed a remarkably high solvent dependence for substrates of this type.[10] However, in our case the solvent influence proved to be weak. In dichloromethane, dichloroethane, toluene, and chlorobenzene an *ee* value of 86% was obtained, whereas only slightly lower enantioselectivities were recorded in more polar solvents like cyclopentyl methyl ether (83% *ee*), ethyl acetate (81% *ee*), or trifluoroethanol (78% *ee*). We also found that no special precautions are necessary to exclude oxygen and moisture when setting up the hydrogenation, so the reaction solutions can be conveniently prepared in the laboratory atmosphere without rigorous purification of the solvents.

Next we studied the steric and electronic effects of the substituents at the stereogenic center, at the nitrogen atom in the imidazoline ring and at the phosphorus atom. As shown in Table 2 the sterically demanding *tert*-butyl group on the imidazole ring is necessary for achieving high enantioselectivity (Table 2, entries 1 and 2). Introduction of electron donor or acceptor substituents in the *N*-phenyl group led to lower *ee* values (Table 2, entries 3–6). Replacement of the *P*-phenyl groups by *ortho*-tolyl groups also lowered the

Table 2. Ligand optimization performed in the hydrogenation of vinyl boronate **1a**.



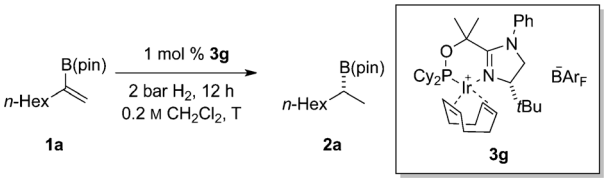
Entry	[Ir-cat.]	R	R′	R″	conv. [%][a]	*ee* [%][b]
1	**3a**	Ph	*t*Bu	Ph	>99	86
2	**3b**	Ph	*i*Pr	Ph	>99	46
3	**3c**	Ph	*t*Bu	*o*-Tol	>99	79
4	**3d**	Ph	*t*Bu	*p*-F_3C-Ph	>99	80
5	**3d**	Ph	*t*Bu	3,5-$(MeO)_2$-Ph	>99	59
6	**3f**	*o*-Tol	*t*Bu	Ph	>99	81
7	**3g**	Cy	*t*Bu	Ph	>99	91
8	**3h**	*t*Bu	*t*Bu	Ph	>99	77

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Supporting Information for details). [b] Determined by GC analysis on a chiral stationary phase (see the Supporting Information for details).

enantioselectivity (Table 2, entry 6), whereas the more electron-donating dicyclohexylphosphino group improved the *ee* value to 91% (Table 2, entry 7). The sterically more demanding di-*tert*-butylphosphino group, on the other hand, caused a decrease of the *ee* value to 77% (Table 2, entry 8). Thus, catalyst **3g** that seemed to have an optimal balance between the electronic and steric properties was selected for further studies.

The enantioselectivity of catalyst **3g** could be further improved by lowering the temperature. The best result was achieved at −20°C with an *ee* value of 96%, while still maintaining full conversion (Table 3). A series of experiments at this temperature with different catalyst loadings and a reaction time of 4 h demonstrated that a 0.1 mol%

Table 3. Optimization of reaction parameters (temperature, time, catalyst loading).



Entry	*T* [°C]	Ir-cat.[mol%]	*t* [hours]	Conv. [%][a]	*ee* [%][b]
1	25	1.00	12	>99	91
2	40	1.00	12	>99	77
3	0	1.00	12	>99	95
4	−20	1.00	12	>99	96
5	−20	1.00	4	>99	96
6	−20	0.50	4	>99	96
7	−20	0.25	4	>99	96
8	−20	0.10	4	>99	96
9	−20	0.05	4	58	96

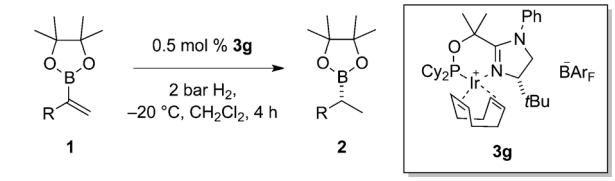
[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Supporting Information for details). [b] Determined by GC analysis on a chiral stationary phase (see the Supporting Information for details).

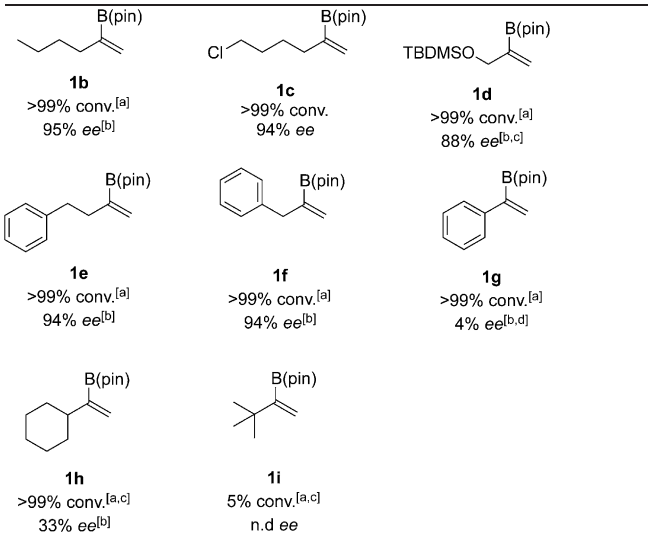
catalyst loading is sufficient to achieve full conversion and retain the *ee* value at 96%. Lower catalyst loadings led to incomplete conversion although the enantioselectivity was not affected (Table 3, entry 9).

For the di-*tert*-butylphosphino-imidazoline ligand complex **3h** the temperature had a similar effect with an increase in *ee* value from 68% at 40°C to 81% at −20°C. Remarkably, the di-*ortho*-tolyl analogue **3f** showed strikingly different behavior. In this case, the enantioselectivity dropped from 81 to 15% *ee* when the temperature was lowered from 25 to −20°C. The enantioselectivity of the corresponding catalyst **3a** with a diphenylphosphino group, on the other hand, remained in a narrow range of 80 to 85% *ee* between −20 and 40°C (for details, see the Supporting Information).

Having established the optimal conditions for substrate **1a**, the scope of catalyst **3g** in the hydrogenation of boronic esters with a terminal C=C bond was investigated (Table 4).

Table 4. Substrate scope of the hydrogenation of terminal boronic esters.



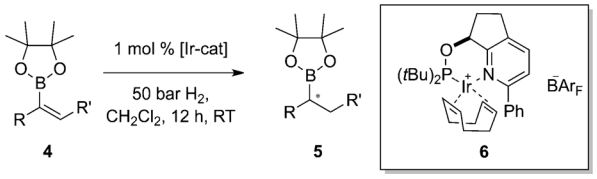


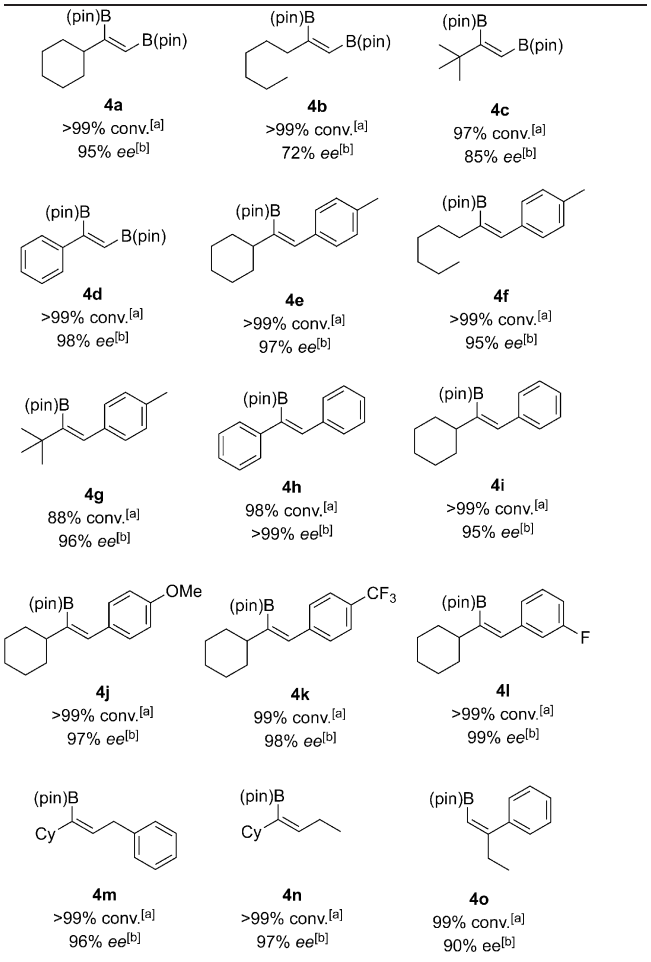
[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Supporting Information for details). [b] Determined by GC analysis on a chiral stationary phase (see the Supporting Information for details). [c] Reaction time 12 h.

All substrates that have a CH_2 group next to the double bond were well tolerated. Excellent activity and enantioselectivity were obtained for a variety of different substrates with additional functional groups (chloride **1c**, protected allylic alcohol **1d**, or phenyl groups **1e**–**f**). Sterically more demanding substituents next to the C=C bond (**1g**–**i**) required higher catalyst loadings (1 mol%) and longer reaction times (>12 h) to achieve full conversion, and a dramatic drop in enantioselectivity was observed. In this respect, catalyst **3g** strongly differed from Andersson's Ir catalysts that gave enantioselectivities of up to 89% *ee* with substrate **1g**, but only 18% *ee* with **1a**.[12a]

The next substrates targeted were bisboronic esters **4a**–**d** (Table 5). However, for this substrate class the phosphinite–

Table 5. Substrate scope of trisubstituted pinacol derived boronic esters.





[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Supporting Information for details); [b] Determined by GC or HPLC analysis on chiral stationary phase (see the Supporting Information for details).

imidazoline ligand complex **3g** gave poor enantioselectivities (only 13% *ee* for substrate **4a**). In a brief catalyst screening including the complexes shown in Table 1 (for details, see the Supporting Information) the pyridine–phosphinite complex **6**[16] emerged as the most promising catalyst for substrates of this type. Subsequently, a series of different bisboronic esters was hydrogenated with catalyst **6** without further optimization of the reaction conditions. Various sub-

stituents (cyclohexyl, *n*-hexyl, *tert*-butyl, and phenyl) at the C=C bond were tolerated, giving high conversions for all substrates. The cyclohexyl- and phenyl-substituted bisboronates **4a** and **4d** reacted with excellent enantioselectivities of 95 and 98% *ee*, whereas the sterically less demanding *n*-hexyl derivative gave 72% *ee*.

Bisboronic esters **4a–d** are versatile precursors for the preparation of alkenyl-monoboronic esters with a trisubstituted C=C bond by Suzuki–Miyaura coupling occurring selectively at the more reactive terminal boronate group.[17] In this way a series of alkenylboronates **4e–n** were prepared, in which the terminal boron substituent had been replaced by different groups. Hydrogenation of these substrates led to the corresponding secondary alkylboronic esters with excellent enantioselectivities from 95 up to >99% *ee*. With the exception of the sterically demanding *tert*-butyl derivative **4g**, all other substrates gave >97% conversion. Electron donor or acceptor groups at the aryl substituent had no significant effect on the *ee* value and conversion. Aryl substituents at the C=C bond are not essential for achieving high enantioselectivity, as shown by hydrogenation of the merely alkyl-substituted substrates **4m** and **4n**. Substrate **4o**[18] with a boronic ester residue at the less-substituted olefinic C atom reacted with lower, but still very good enantioselectivity to give the corresponding primary alkylboronate with full conversion and 90% *ee*.

In summary, we have demonstrated that iridium complexes consisting of N,P-ligands are efficient catalysts for the hydrogenation of pinacol-derived boronic esters. Whereas a phosphinoimidazoline ligand was identified as highly efficient for the asymmetric hydrogenation of terminal vinyl boronic esters, trisubstituted bis- and monoboronates could be reduced with high activity and good to excellent selectivity employing a pyridine–phosphinite ligand.

Experimental Section

Procedure for the iridium-catalyzed asymmetric hydrogenation: A solution of the substrate **1a** (303 mg, 1.27 mmol, 1.0 equiv) and the iridium complex **3g** (2.07 mg, 1.28 μmol, 0.1 mol-%) in dichloromethane (6 mL) was placed in an autoclave. The equipment was pressurized with nitrogen (1 bar) and cooled to −20 °C for 1 hour. The autoclave was then pressurized five times with hydrogen (up to 10 bar) and released. The reaction was performed under 2 bar H_2 atmosphere over 4 h at −20 °C. After releasing the hydrogen pressure the reaction mixture was allowed to reach RT and the solvent was removed under reduced pressure. The crude product was taken up in *n*-heptane (3 mL) and purified over a plug of silica gel (0.5 cm × 2 cm *n*-heptane/*tert*-butyl methyl ether (TBME) 10:1) to give analytically pure hydrogenation product **2a** (297 mg, 1.24 mmol, 97%) suitable for analysis.

All the other substrates were hydrogenated on smaller scales (50–100 μmol).

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Keywords: asymmetric catalysis · boron · hydrogenation · iridium · N,P ligands

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Asymmetric Synthesis

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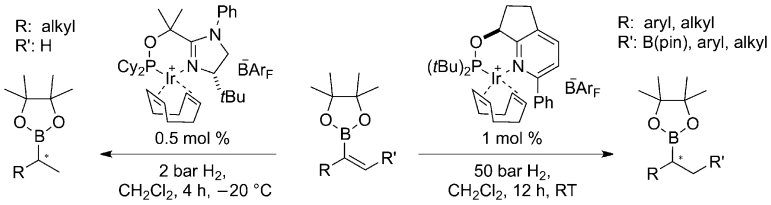

Choose the right ligand: An iridium complex derived from a phosphino–imidazoline ligand is a highly efficient catalyst for the asymmetric hydrogenation of terminal vinyl boronic esters (see scheme). On the other hand, trisubstituted alkenyl-boronates can be reduced with high activity and good to excellent enantioselectivity employing a pyridine-phosphinite ligand.