Chemoselective Hydrogenation

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Iridium-Catalyzed Chemoselective and Enantioselective Hydrogenation of (1-Chloro-1-Alkenyl) Boronic Esters**

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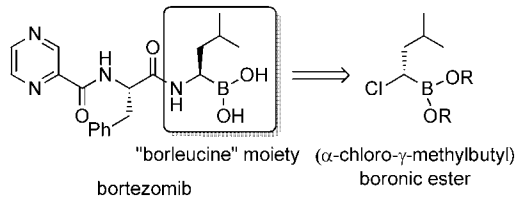
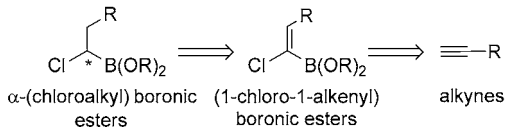
Organoboron compounds[1] play important roles in chemistry, especially in the field of organometallic catalysis[2] where boronic acids, boronic esters,[3] and trifluoroborates[4] are invaluable for the construction of C–O, C–N, or C–C bonds through various coupling reactions.[3,5–8] α-Amino boronic acids,[9] primarily obtained from (α-chloroalkyl) boronic esters,[10] are a recent addition to this class of compounds, expanding them into completely new areas of use.[11] They are a crucial structural element in a new class of anti-cancer peptide drugs.[12] One member of this class of drugs, which contains a "borleucine" moiety, is marketed under the name bortezomib (Scheme 1).[13,14]



Scheme 1. Retrosynthetic analysis of bortezomib synthesis.

The importance of (α-chloroalkyl) boronic esters lies in their versatility as chiral building blocks, which can be further functionalized to asymmetric boronic esters incorporating various functionalities and structural motifs.[3,10,15] To date, access to (α-haloalkyl) boronic esters has been limited to three different approaches, of which only one proceeds in a stereoselective fashion (for a detailed discussion, see the Supporting Information).[3,10] The synthetic versatility of (α-chloroalkyl) boronic esters, and particularly their utility for the preparation of drugs such as bortezomib, prompted us to consider new possibilities for their construction. We envisioned that a very attractive route to (α-chloroalkyl) boronic esters could be based on the asymmetric catalytic hydrogenation of (1-chloro-1-alkenyl) boronic esters, which are easily obtained by a two-step process from readily available alkynes (Scheme 2).



Scheme 2. Retrosynthetic analysis for (α-chloroalkyl) boronic esters.

In the past decade, remarkable progress in the asymmetric catalytic hydrogenation of olefins has been achieved, and this technique has now become a part of the general repertoire of synthetic organic chemistry.[16,17] Although some interesting examples of rhodium[18] and iridium-catalyzed[19] asymmetric hydrogenation of prochiral vinyl boronates have recently been described, the reduction of (1-chloro-1-alkenyl) boronic esters was expected to be a very challenging endeavor, because these substrates tend to undergo dechlorination and lack functional groups with an established mode of coordination to the transition metal catalysts. The asymmetric hydrogenation of vinyl fluorides with both rhodium[20] and iridium catalysts[21] bearing chiral P^N ligands has also been recently investigated. High chemo- and enantioselectivities were reported for selected experiments; however, substantial defluorination was observed for some substrates. Furthermore, only a limited number of studies related to the homogenous asymmetric hydrogenation of vinyl chlorides have thus far been reported[22,23] and only examples of single substrates bearing functional groups capable of coordination to ruthenium catalysts were given. To the best of our knowledge, catalytic asymmetric hydrogenation studies of substrates bearing a vinyl chloride moiety and encompassing a broader range of substrates have not yet been reported.

Our synthetic strategy for the synthesis of (α-chloroalkyl) boronic esters starts with the preparation of (1-chloro-1-alkenyl) boronic esters by expanding upon the method of Srebnik et al.[24] Having prepared (1-chloro-1-alkenyl) boronic esters **1a–j**,[25] we decided to probe their hydrogenation

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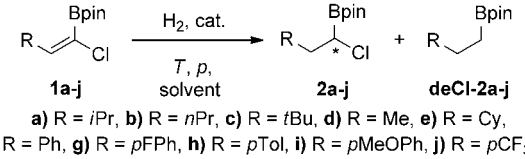
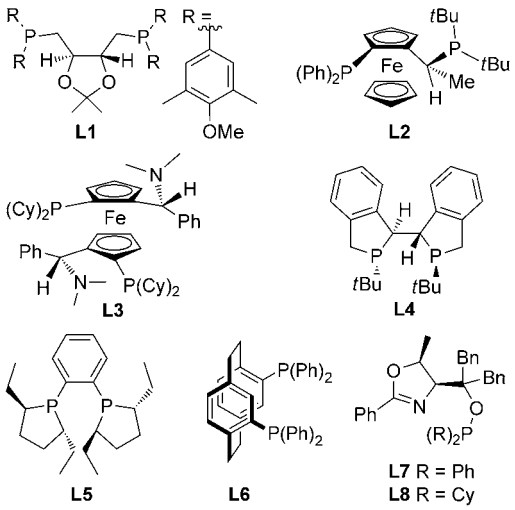
to the corresponding alkyl products **2a–j** with various catalysts (Scheme 3).

We started our hydrogenation experiments with the biologically interesting "borleucine" precursor **1a**. This substrate was subjected to a broad catalyst screening. A large array of P^P and P^N ligands (Scheme 4) in combination with ruthenium, rhodium, and iridium metal precursors were investigated in a range of solvents.[25] Approximately two-thirds of all the reactions gave conversions of less than 10%, but a few encouraging results showed high conversion of **1a** to the alkyl product. Noteworthy results are summarized in Table 1. Dechlorination was the most prominent side reaction. In the presence of ruthenium-based catalysts, this undesired reaction path was followed almost exclusively (Table 1, entry 1). Rhodium-based catalysts provided variable levels of conversion, chemoselectivity, and enantioselectivity. A trend favoring a certain ligand class or solvent preference could not be distinguished (Table 1, entries 2–6). The most remarkable result was the 85% *ee* achieved with a rhodium catalyst bearing Phanephos[27] (ligand **L6**, entry 6), but the conversion was considered too low to be useful. An iridium diphosphine system showed good activity, but gave only moderate chemoselectivity and no enantioselectivity (entry 7). However, a breakthrough result was obtained with Crabtree's catalyst.[28] Indeed, this system gave rise to complete conversion, delivering the expected racemic product in excellent chemoselectivity; only 3% of the dechlorinated byproduct **deCl-2a** (entry 8) was formed. This result directed us to test asymmetric variants of the reaction that involve iridium catalysts bearing chiral P^N oxazolino–phosphinite ligands (**L7** and **L8**). To our delight, these catalysts, originally described by Pfaltz and co-workers for the asymmetric hydrogenation of unfunctionalized alkenes,[29] provided full conversions with excellent chemo- and good enantioselectivities (entries 9 and 10). The best overall results (100% conversion, 96–97% product yield and 62–63% *ee*, without any **deCl-2a** observed) were obtained with the catalyst [Ir(cod)(**L8**)]BAr_F (cod = cyclooctadiene, BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) in either THF or dichloroethane solvent (entries 10 and 11, respectively).

The initial screening experiments shown in Table 1 revealed a clear direction for further research. We explored a wider collection of P^N ligand-based catalysts, primarily aiming towards improvement of the enantioselectivity while preserving the activity and chemoselectivity. Several iridium catalysts bearing PHOX,[30] PyrPHOX,[31] SimplePhox,[32] and ferrocenyl oxazoline ligands[33] were investigated. In all of these experiments, either lower yields or lower enantioselectivities were observed relative to [Ir(cod)(**L8**)]BAr_F. Nevertheless, the chemoselectivities obtained were still high, with less than 5% of **deCl-2a** present in the product.[25] Next, iridium catalysts with ferrocenyl imidazoline ligands were investigated (Scheme 5, Table 2). Remarkably, the catalyst incorporating ligand **L9** with an (*R*,*R*)-configuration for the imidazoline ring (the planar stereogenic element being *S*)[34,35] gave moderate conversion to **2a** (66%), excellent chemoselectivity (4% of **deCl-2a**) and the highest enantioselectivity observed to date (94% *ee*; Table 2, entry 1).[36] Having finally identified a class of catalysts with the potential for a high



Scheme 3. Hydrogenation of (1-chloro-1-alkenyl) boronic esters **1a–j**. pin = pinacolyl, Cy = cyclohexyl.

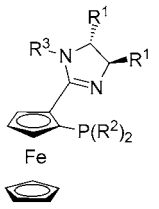


Scheme 4. Ligands used in the initial hydrogenation experiments. Cy = cyclohexyl, Bn = benzyl.

Table 1: Catalyst screening for the hydrogenation of **1a** to **2a**.

Entry	Catalyst[a]	Conv.	**2a**	**deCl-2a** [%][b]	*ee*
1	[Ru(cod)$(CF_3CO_2)_2$]/**L1**	73	1	68	n.d.[c]
2	[Rh(nbd)$_2$]BF_4/**L2**	13	5	2	32(*S*)
3	[Rh(nbd)$_2$]BF_4/**L3**	18	11	2	21(*S*)
4	[Rh(cod)(**L4**)]BF_4	53	12	26	5(*S*)
5	[Rh(cod)(**L5**)]CF_3SO_3	65	20	42	rac.
6	[Rh(nbd)$_2$]BF_4/**L6**	13	8	3	85(*R*)
7	[Ir(cod)$_2$]BAr_F/**L1**	97	52	11	rac.
8	[Ir(cod)(PCy_3)(Py)]PF_6	100	97	3	rac.
9	[Ir(cod)(**L7**)]BAr_F	100	97	1	46(*R*)
10	[Ir(cod)(**L8**)]BAr_F	100	96	0	62(*R*)
11	[Ir(cod)(**L8**)]BAr_F	100	97	0	63(*R*)

[a] Standard conditions: 4 mol% of catalyst precursor or 4 mol% of metal precursor with 1.2 equiv of ligand per metal, 50°C, 20 bar H_2, 20 h, and 0.08 M substrate concentration in given solvent (except entry 8, where 10 bar H_2 was applied over 10 days). Entries 1, 8, and 10 in THF; entries 6, 7, 9, and 11 in $ClCH_2CH_2Cl$; entries 2, 3, and 5 in MeOH; and entry 4 in CF_3CH_2OH.[25] [b] Conversions, yields, and enantiomeric excesses calculated by GC analysis[25,26] and confirmed by ^1H NMR. A standard of the dechlorinated product **(deCl-2a)** was prepared by reaction of alkyl boronic acids with pinacol.[25] [c] n.d.: not determined. cod = cyclooctadiene, nbd = norbornadiene, BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, Cy = cyclohexyl, Py = pyridine.



L9: R^1 = Ph, R^2 = Ph, R^3 = H
L10: R^1 = Cy, R^2 = Ph, R^3 = H
L11: R^1 = *p*MeOPh, R^2 = Ph, R^3 = H
L12: R^1 = Ph, R^2 = Cy, R^3 = H
L13: R^1 = Ph, R^2 = Xyl, R^3 = H
L14: R^1 = Ph, R^2 = *o*Tol, R^3 = H
L15: R^1 = Ph, R^2 = Ph, R^3 = CF_3CO
L16: R^1 = Ph, R^2 = Ph, R^3 = PhCO
L17: R^1 = Ph, R^2 = Xyl, R^3 = PhCO

Scheme 5. Imidazoline-type P^N-ligands used for hydrogenation of **1a**. Cy = cyclohexyl, Xyl = xylyl.

Table 2: Investigation of iridium catalysts bearing ferrocenyl imidazoline ligands for the hydrogenation of **1a** to **2a**.

Entry	Catalyst[a]	Conv.	**2a**	**deCl-2a** [%][b]	*ee*
1	[Ir(cod)(**L9**)]BAr_F	72	66	4	94 (*S*)
2	[Ir(cod)(**L10**)]BAr_F	20	13	4	65 (*S*)
3	[Ir(cod)(**L11**)]BAr_F	72	66	4	93 (*S*)
4	[Ir(cod)(**L12**)]BAr_F	55	48	4	58 (*S*)
5	[Ir(cod)(**L13**)]BAr_F	79	72	4	92 (*S*)
6	[Ir(cod)(**L14**)]BAr_F	66	59	5	91 (*S*)
7	[Ir(cod)(**L15**)]BAr_F	79	72	4	94 (*S*)
8	[Ir(cod)(**L16**)]BAr_F	>99	95	3	92 (*S*)
9	[Ir(cod)(**L17**)]BAr_F	>99	95	3	87 (*S*)

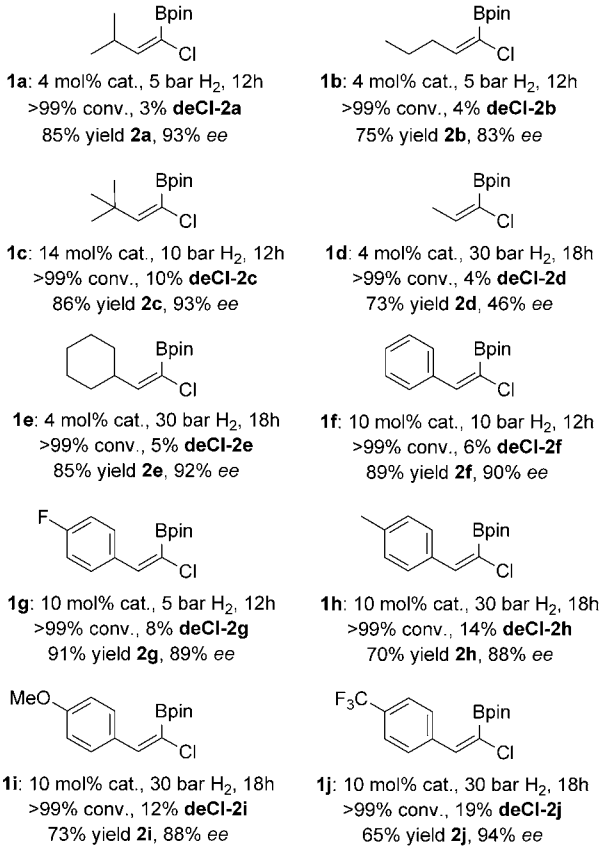
[a] Conditions: substrate, catalyst (4 mol%), CH_2Cl_2 (2.5 mL), 50°C, 10 bar H_2, 10 h and 0.087 M substrate concentration. [b] Conversions, yields, and enantiomeric excesses calculated by GC analysis.[25,26] cod = cyclooctadiene, BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

degree of stereoinduction, several new ligands based on the ferrocenyl–imidazoline backbone were prepared to optimize catalyst performance and identify potential structure–activity relationships. Modifications of the 'parent' **L9** ligand involved changes in the substituents on the imidazoline ring (entries 2 and 3), at the substituents on phosphorus (entries 4–6), and substitution at the sp^3 nitrogen of the imidazoline group (entries 7–9).[25] Increasing electron density on the imidazoline by replacing the phenyl substituent R^1 with a cyclohexyl group in **L10** was detrimental for catalyst productivity as well as *ee* (entry 2). An additional electron-donating methoxy group on the phenyl residue in **L11** had little effect on catalyst performance (entry 3). Analogously, the alkyl substituents on phosphorus in ligand **L12** caused a drop in catalyst reactivity and product *ee* (entry 4). Steric effects are considered the decisive factor in the observed increase of product yield upon changing the R^2 group from phenyl to 3,5-xylyl (**L13**, entry 5), but with the *o*-tolyl substituent of **L14** the useful degree of steric hindrance was exceeded, resulting in a drop in conversion compared to the catalyst bearing only a phenyl phosphine moiety (entry 6).

As the iridium P^N-ligand catalysts are known to deactivate in the presence of coordinating solvents or additives, such as amines and anions, through the formation of inactive, hydride-bridged, trinuclear iridium complexes,[17a,f,37] protection of the mildly acidic NH functionality in the ferrocenyl imidazoline ligands was also explored. Indeed, elimination of the potential for interaction/coordination or hydrogen bonding in combination with the proper steric bulk led to a significant increase in catalytic activity. Protection of the imidazoline ring with a trifluoroacetyl group in ligand **L15** resulted in slightly better catalyst performance ([Ir(cod)(**L15**)]BAr_F, Table 2, entry 7) as compared to the unprotected species ([Ir(cod)(**L9**)]BAr_F; entry 1). However, when the imidazoline was protected with the bulkier benzoyl group ([Ir(cod)(**L16**)]BAr_F; entry 8), full conversion and a high enantioselectivity (92% *ee*) were achieved. The catalyst [Ir(cod)(**L17**)]BAr_F also achieved full conversion, albeit with a reduced enantioselectivity (87% *ee*; entry 9). Remarkably, both catalysts demonstrated excellent chemoselectivities with less than 3% of **deCl-2a** formed. The structurally fine-tuned ligand **L16** thus provided the best balance of steric and electronic effects for the hydrogenation of substrate **1a**. Apart from stereoelectronic catalyst features, only substrate concentration was found to have a significant influence on reaction outcome. Other parameters, such as solvent choice, temperature, and hydrogen pressure had a relatively small effect.[25]

Next, we evaluated the performance of the lead catalyst system [Ir(cod)(**L16**)]BAr_F on a broader range of substrates **1b–j** bearing aliphatic substituents with different steric hindrances and aromatic substituents with different electronic properties. Unsurprisingly, the more sterically hindered substrates (aromatic derivatives **1f–j** and in particular **1c**) required the use of higher catalyst loadings. However, by adjusting the reaction parameters, it was possible to successfully reduce all substrates **1b–j** to products **2b–j**. In all but one case (**1d**), full conversions and high enantioselectivities were achieved. The presence of bulky alkyl moieties or aryl substituents within substrates was found to be beneficial for enantiodifferentiation whereas dechlorination levels appear to be affected by electronic and steric effects with no clear, observable trend (Scheme 6).[25,38]

We envisaged that hydrogenation pathways for chlorovinyl boronates are similar to those followed by unfunctionalized C=C bonds in the presence of P^N-iridium catalysts. A confirmed mechanistic model of these hydrogenations is not yet available.[17] Indeed, catalytic cycles involving Ir^I/Ir^{III} as well as Ir^{III}/Ir^V species as potential intermediates have recently been discussed.[39] Nevertheless, both cycles might be operational depending on the nature of the substrate and the reaction conditions.[17,39i] Knowledge in the area of catalytic dechlorination pathways of vinyl halide substrates in the presence of homogeneous iridium catalysts is also scarce.[40] The results of mechanistic investigations that have been conducted on the dehalogenation of vinyl fluorides and chlorides in the presence of rhodium systems are in favor of a catalytic cycle involving insertion of the halo-olefin into a metal hydride complex, followed by β-chloride elimination to give the dehalogenated alkene substrate.[41] An alternative mechanism involving C–X oxidative addition of the vinyl halide to a metal hydride appears less likely. In such a reaction pathway, faster addition of the haloalkane versus haloalkene would be expected, but this was not observed by Andersson and co-workers for fluoro derivatives.[21b] In order to determine whether dechlorination occurs by oxidative addition of the alkylchloride product, we submitted pure, racemic **2a** to



Scheme 6. Scope of the asymmetric hydrogenation of **1a–j**. pin = pinacolyl.

the hydrogenation conditions with [Ir(cod)(**L16**)]BAr_F as catalyst. The experiments revealed that **2a** did not dehalogenate;[25] results that disfavor dechlorination through oxidative addition of the product to the catalyst and suggest that dechlorination instead takes place in the catalytic cycle from the starting olefin.[25]

In conclusion, our work is the first study in which a broad range of (1-chlorovinyl) boronate substrates, with different steric and electronic properties, have been successfully hydrogenated in the presence of P^N-iridium catalysts without significant cleavage of the C–Cl bond. The rational modification of the structural properties of the P^N ligands has resulted in the preparation of new *N*-acyl-imidazoline ferrocenyl-based iridium catalysts with broad substrate acceptance. Excellent conversions, high chemoselectivities (with dechlorinated byproducts in the range of 3–19%), and enantioselectivities of up to 94% *ee* were achieved. The utility of the hydrogenation method presented was demonstrated by preparation of **2a**, which serves as a key precursor for the construction of the anticancer drug bortezomib.

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