Asymmetric Catalysis

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Catalytic Enantioselective Synthesis of Secondary Alkylboronate Building Blocks With and Without Metals**

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On the journey to a world where any desired organic compound may be formed by the simple and controlled combination of stable enantiopure building blocks, a great many steps forward have been taken in the last few years. Yet, to reach this promised land progress is required in both 1) the accessibility of stable building blocks and 2) the ability to combine these in a controlled and diverse manner.

Stable organoboronates bear many desirable aspects of ideal building blocks and, with their surrogate derivatives [e.g. B(pin), BF_3K, B(MIDA), B(dan)], have come to the forefront of synthetic planning.[1,2] Secondary alkylboronates promise off-the-shelf chirality for the construction of bonds to sp^3 carbon atoms. The C–B bond provides a stable stereogenic center which reacts as a nucleophilic component. Importantly, secondary alkylboronate derivatives have been shown to participate in the Suzuki–Miyaura reaction with aryl halides with excellent enantiospecificity. Effective reaction conditions have been developed for cross-coupling with both retention[3,4] and inversion of stereochemistry,[5,6] though the outcome remains substrate defined. Furthermore, the C–B bond of organoboronates may be readily converted into alcohols or amines by oxidation with retention of configuration,[7] and Aggarwal and co-workers have recently developed methods to access a variety of C–X bonds proceeding with inversion via the ate complex.[8] To extend methods of controlled functionalization, and ultimately to achieve universally applicable chiral building blocks, access to organoboronates in high yield and with high *ee* values is essential. Highlighted herein is the very recent progress in catalytic methods for the preparation of non-allylic chiral secondary alkylboronates by the metal-free conjugate addition of boron pinacolate, as well as the iridium-catalyzed hydrogenation of vinyl boronates. These advances promise to open the field to further developments in the versatile chemistry of a wide range of chiral boronates.

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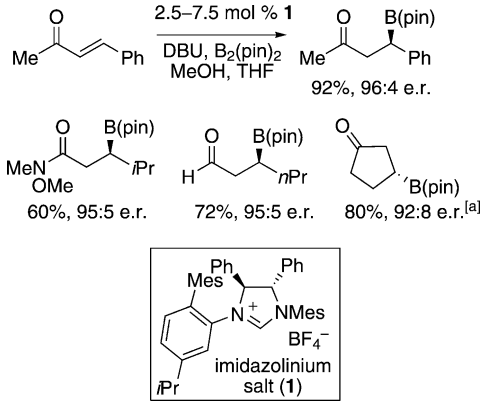
Historically, access to secondary alkylboronates has been achieved by the powerful Matteson homologation approach,[9] which has received modern makeovers in the last few years.[10,4] Excellent stoichiometric chiral hydroboration reactions have also been developed for a variety of substituted alkenes.[11] Catalytic enantioselective hydroboration reactions were then developed, largely using rhodium catalysis,[12] and recently copper catalysts have been employed very successfully with styryl substrates.[4,13] The enantioselective diboration of alkenes has also been developed.[14]

The last few years have seen the emergence of efficient catalytic enantioselective conjugate addition reactions of boronate nucleophiles, which have been recently reviewed.[15] Transition-metal catalysis with chiral ligands provides access to β-boryl carbonyls with excellent enantioselectivity from α,β-unsaturated esters, ketones, amides, and nitriles.[15] Lee and Hall have reported the inverse, that is, the conjugate addition of Grignard reagents to a Michael acceptor bearing a B(dan) group,[16] and the subsequent amalgamation of these approaches, using $B_2(pin)_2$ with a copper(I)-Walphos catalyst, to form 1,1-diboron compounds in up to 99% *ee*.[17] Subsequent consecutive and chemoselective Suzuki–Miyaura couplings with a variety of aryl and vinyl halides were successful, with inversion of stereochemistry in both steps.

A very significant and recent development from Hoveyda and co-workers was the highly enantioselective metal-free conjugate addition of B(pin) using a bulky chiral N-heterocyclic carbene (NHC) catalyst formed from the C_1-symmetric imidazolinium salt **1** (Scheme 1).[18] This impressive result was successful for α,β-unsaturated ketones, esters, Weinreb amides, and aldehydes, thus providing diverse secondary alkylboronates. A preliminary mechanistic proposal involved conjugate addition of a rapidly formed NHC·$B(OR)_2B(OR)_2$ complex.[19] Methanol, required as a cosolvent, was proposed to exchange with pinacol to afford a less sterically demanding complex, so enabling an efficient reaction. Notably, improved chemoselectivity was displayed in the metal-free systems versus the copper-catalyzed reaction. Direct comparison showed much better tolerance to aldehydes, allenes, and terminal alkynes.[18]

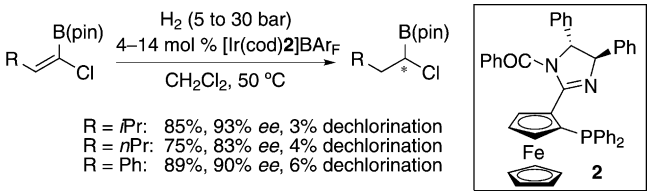
Major advances in the enantioselective hydrogenation of vinyl boronates using iridium catalysis have also been seen in 2012. This approach, using substrates with a pre-installed



Scheme 1. Hoveyda's metal-free, NHC-catalyzed enantioselective conjugate addition. [a] Modified catalyst employed for cyclic enones.[18] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = mesityl, THF = tetrahydrofuran.

boronate unit, avoids regioselectivity issues, and also the requirement for a Michael acceptor substrate and thus the associated functionality in the product.

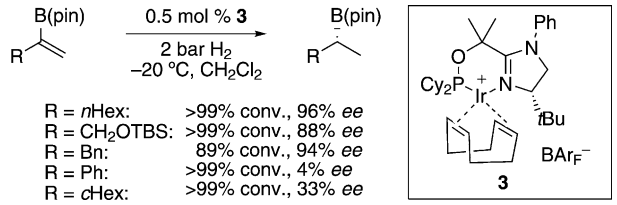
Časar and co-workers reported the first enantioselective hydrogenation of 1-chloro-1-alkenyl boronates to afford α-(chloroalkyl)boronates (Scheme 2).[20] The products, generated here catalytically, are comparable to those obtained by the Matteson homologation using dichloromethyllithium and an alkylboronate, and have been shown to be highly versatile building blocks.[9,10] Iridium catalysts were most effective in preventing dechlorination, which was initially a prominent side reaction. Fine-tuning of a ferrocenyl imidazoline ligand offered excellent stereoinduction for a range of examples. Sterically hindered examples were well tolerated but required an increase in catalyst loading.



Scheme 2. α-(Chloroalkyl)boronates by iridium-catalyzed enantioselective hydrogenation.[20] cod = 1,5-cyclooctadiene.

The first iridium-catalyzed hydrogenation of vinyl boronates was reported by Andersson and co-workers in 2009, and it gave high *ee* values for several substrates.[21,22] This advance introduced low catalyst loadings, low H_2 pressures, and selectivities of up to 98% *ee*. However, terminal alkenes and those without aromatic substituents were less effective. Indeed, obtaining high enantioselectivities in the reactions of 1,1-disubstituted olefins is a general challenge across asymmetric synthesis.[11]

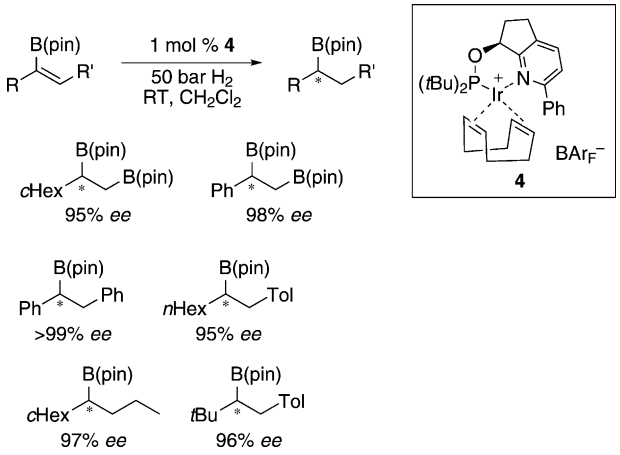
Most recently, Ganić and Pfaltz examined the hydrogenation of terminal vinylboronates, which gave low *ee* values under the previously reported conditions, and have developed a system to afford high *ee* values with these challenging



Scheme 3. Pfaltz iridium-catalyzed enantioselective hydrogenation of terminal vinylboronates.[23] Bn = benzyl, Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl.

substrates.[23] The optimized iridium complex **3**, derived from an oxazolino-phosphinite ligand, was a highly efficient catalyst for the asymmetric hydrogenation of terminal vinyl boronic esters (Scheme 3). A catalyst loading of only 0.5 mol% was required at 2 bar hydrogen pressure to give the highest enantioselectivity. For substrates where the R group was linked through a CH_2 unit, the catalyst gave excellent activity and enantioselectivity and tolerated functional groups such as protected alcohols, phenyl rings, and chlorides. However, the *ee* value was dramatically reduced by aromaticity or branching, thus providing a complementary system to that of Andersson.

In contrast, employing the catalyst **4**, containing a pyridine phosphinite ligand, allowed trisubstituted alkenyl boronates to be efficiently reduced with high activity and excellent enantioselectivity (up to >99% *ee*, Scheme 4).[23] A wide



Scheme 4. Enantioselective hydrogenation of trisubstituted vinyl boronates with varied substituents.[23] Tol = 4-tolyl.

range of alkene substituents, including aromatic and highly branched aliphatics were very well tolerated, and generally showed complete conversion. The hydrogenation of 1,2-bisboronates was also highly efficient, thus affording excellent conversions and enantiomeric excesses.

These new catalytic methods deliver highly enantioenriched secondary alkylboronates, considerably extending the accessible scope of these versatile units. These methods will undoubtedly find numerous applications in synthesis and spur further investigation into the efficient functionalization of alkylboronates, thus taking us much closer to ideal chiral

building blocks for the controlled formation of bonds to sp^3 carbon atoms.

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