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Recent Advances in the Preparation and Application of Allylboron Species in Organic Synthesis

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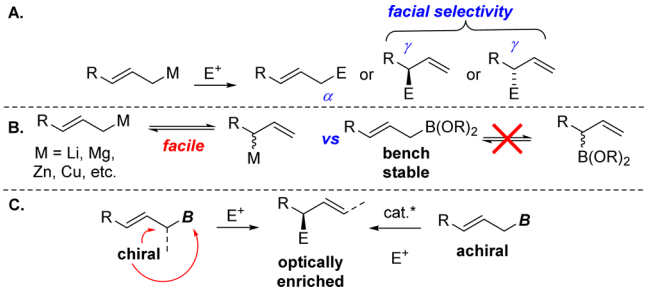
ABSTRACT: In this Perspective we will highlight the most important recent breakthroughs in selective allylboron chemistry (both the synthesis and application of these species). In addition we will provide an outlook toward the future of this promising subfield of organic synthesis.

Recently, the area of selective organic synthesis has benefitted from advances in both the preparation and application of organoboron compounds.[1] Within this broad arena, allylic boronic acids and their esters stand out as a uniquely versatile class of reagents. The ability of allylmetal reagents to react with electrophilic functional groups (or catalysts) in a variety of ways (i.e., α- vs γ-addition and differential facial selectivity) allows a relatively simple fragment to be exploited into a diverse array of complex products (Scheme 1A). Unlike allylic lithium, magnesium, zinc, and

Scheme 1



copper reagents, their boryl analogues generally (excluding allylboranes) benefit from bench stability and, more importantly, avoid the potentially deleterious 1,3-metallotropic shift (Scheme 1B).[2] Allylboron species participate in a range of reactions, including asymmetric catalysis. The most important reactions are the allylboration of carbonyl and imine functionalities.[3] In addition, allylboron species can participate in other C−C bond-forming reactions via cross-coupling reactions. Current applications of allylboronates toward optically enriched chiral molecules include two general approaches: (1) the asymmetric synthesis of a chiral allylboronate followed by chirality transfer, and (2) coupling the synthesis of an *achiral* allylboronate with a subsequent and analogous reaction, this time guided by asymmetric catalysis (Scheme 1C).

In this Perspective we focus on new methods for the selective synthesis of substituted allylboron species, and the application of these compounds in organic synthesis. The main emphasis is on recent enantioselective reactions with carbonyl compounds and imines and the development of new types of cross-coupling reactions reported in the past decade. This Perspective is not comprehensive, and the only works cited from before 2006 are key contributions that directly contribute to the current state of the art. For excellent comprehensive reviews on allylboration, please see recent articles and monographs.[1,3,4]

Allylboronates can be prepared by adding reactive allylic organometallic reagents to borate derivatives and subsequently treating them with aqueous acid, diols, or KHF_2 in order to obtain the corresponding boronic acid, cyclic boronate ester, or potassium trifluoroborate.[5] This approach suffers from regioselectivity issues due to the facile 1,3-metallotropic shift of many allylic organometallic reagents (Scheme 1B). A milder, more contemporary approach involves Tsuji−Trost-type displacement reactions of allylic alcohols and their derivatives with boron-based pro-nucleophiles.[6] One proven advantage of this type of approach is the general trend for the substrate to form the less substituted linear *E*-allylboronate. While the Miyaura group's borylation of allylic acetates demonstrated the feasibility of this chemistry as well as its inherent stereochemical biases,[6] electrophile dimerization at the cost of product formation left room for improvement (Scheme 2A). The Morken group has overcome this limitation in a report on the nickel- or palladium-catalyzed borylation of allylic acetates or chlorides (respectively) using robust conditions and commercially available reagents (Scheme 2B).[7]

Our group has developed robust approaches toward utilizing allylic alcohols for the one-pot synthesis of allylboronates. In 2006, we demonstrated the facile synthesis of allylic boronic acids in this manner through palladium−pincer complex catalysis.[8] Due to the sensitive nature of allylic boronic acids, these compounds were isolated as the corresponding potassium trifluoroborate salts. Soon after, this transformation was extended to isolable pinacol boronic esters using a commercially available catalyst.[9] Complementary studies into the analogous silylation reaction using $Pd(BF_4)_2(MeCN)_4$ and extension of this protocol to allylboronic esters further simplified the methodology, allowing access to allylboronates via direct coupling with B_2pin_2.[10] This work later provided insight into some of the reaction's mechanistic curiosities.[11] The isolation of highly reactive yet configurationally stable allylic boronic acids was finally realized in 2012 via catalysis with the "naked" Pd(0) source, the H_2PdCl_4 precatalyst, and a carefully optimized isolation protocol (Scheme 2C).[12]

Recently, a transition-metal-free approach toward linear allylboronic esters has been described by the Fernández

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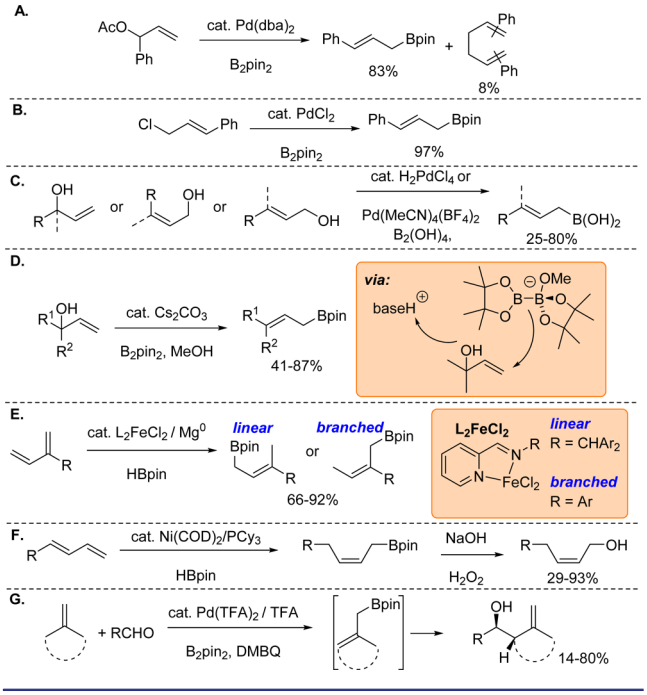
Scheme 2



group in collaboration with our lab.[13] This work takes advantage of the quaternization of diboron reagents and their appreciable increase in reactivity in the presence of suitable bases. Tertiary allylic alcohols react with B_2pin_2 and catalytic Cs_2CO_3 under mild conditions to provide the rearranged linear boronates in moderate to good yields (Scheme 2D).

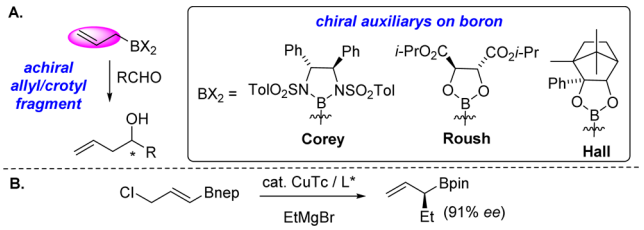
Another useful approach toward achiral allylboronates is the regioselective 1,4-hydroboration of 1,3-dienes. As outlined by the Ritter group, barriers to synthetically useful implementation of this chemistry include chemoselectivity (1,2- vs 1,4-hydroboration), regioselectivity (linear vs branched products), and the resultant olefin stereochemistry (*E* vs *Z*).[14] The Ritter group was able to surmount these obstacles using an iminopyridine-ligated iron catalyst for the hydroboration of 2-substituted dienes with pinacolborane (Scheme 2E). Notably, this transformation was highly divergent, depending on the structure of the substituent on the imino portion of the ligand. A complementary method was later introduced by the Morken group, wherein terminal dienes could be similarly hydroborated via nickel catalysis in a highly stereoselective fashion; the products were oxidized *in situ* to the corresponding allylic alcohol for isolation (Scheme 2F).[15] The methodology was later extended to include chiral 5-siloxy-1,3-dienes, providing densely functionalized allylboronates in a highly diastereoselective fashion.[16] Both methodologies provide *Z*-allylboronates, a result of the metallocyclic intermediates in the proposed catalytic cycles.

Allylic C−H activation is one of the least explored approaches toward linear allylic boronates. The allylic borylation of simple cycloalkenes via Ru[17] or Ir[18] catalysis providing allylic boronates has been demonstrated. The analogous acyclic or exocyclic reactions are less explored due to mechanistic complications involving counterproductive β-hydride elimination, competitively leading to the undesired olefinic boronates.[19] Our group hypothesized that this pitfall could be avoided by using a different catalytic manifold, oxidative palladium catalysis. Palladium readily forms η^3-allyl complexes from olefins under oxidative conditions. By coupling this ability with facile reductive elimination of the palladium-coordinated boronate group, allylboronates were prepared from exocyclic olefins.[20] These reactions were incorporated into a tandem "one-pot" borylation−allylboration reaction (Scheme 2G). The Gong group[21] further developed this process by extending the synthetic scope of the reaction to acyclic alkenes.

Another interesting approach is the synthesis of allylboronates via Pd-catalyzed carbocyclization−borylation cascade reactions. The Bäckvall group[22] and the Cardenas group[23] demonstrated the synthetic value of this approach by developing new methodologies toward the synthesis of fairly complex cyclic allylboronates.

Utilization of a chiral diol/diamine on the boron atom (chiral auxiliary)[24] of an otherwise achiral allylboronate was previously the cutting edge for stereoselective allylations (typically of aldehydes) (Scheme 3A). In the past decade, the use of chiral

Scheme 3



secondary α-branched allylic boronates has supplanted this approach. An illustrative methodology toward this class of compounds was demonstrated by the Hall group, wherein a BINOL-based phosphoramidite-ligated Cu(I) complex catalyzed the asymmetric S_N2' reaction of 3-chloropropenylboronate with alkyl Grignard reagents (Scheme 3B).[25] The same group also disclosed a complementary iridium-catalyzed allylic displacement reaction of the analogous carbonates using malonate-based nucleophiles.[26]

The Ito and Sawamura group has also exploited the ability of chiral Cu(I) complexes to promote asymmetric S_N2' reactions for the synthesis of chiral allylboronates. This allowed for easily accessible, linear allylic carbonates to be used as feedstock for these boron-bearing reagents. In 2007, they first reported this reaction by utilizing *Z*-allylic carbonates with catalytic Cu(O*t*-Bu) and a chiral bidentate phosphine ligand with B_2pin_2.[27] Soon after, the reaction was extended to racemic cyclopentenyl allylic ethers via an unusual enantioconvergent manifold.[28] Linear *Z*-allylic acetals also proved to be suitable substrates for this reaction,[29] in this case yielding *E*-γ-alkoxy allylboronates. While this chemistry has provided densely functionalized chiral allylboronates in good yields and enantioselectivity, its general implementation is hindered by the requisite that the starting material must be of *Z*-geometry. In 2010, the Hoveyda group overcame this limitation by utilizing a bidentate Cu-NHC catalyst.[30] This chemistry demonstrated exceptional scope where both *E*- and Z-allylic carbonates were equally tolerated, leading to enantiomeric products. Also, γ-disubstituted allylic carbonates have demonstrated themselves as suitable substrates, allowing access to isolable tertiary allylic boronates for the first time (Scheme 4A). Not long after, the McQuade group reported an interesting *stereoconvergent* approach toward α-branched allylic boronates (Scheme 4B).[31] Therein, either *E*/*Z* isomer of a γ-substituted allylic nitroaryl ether provided the

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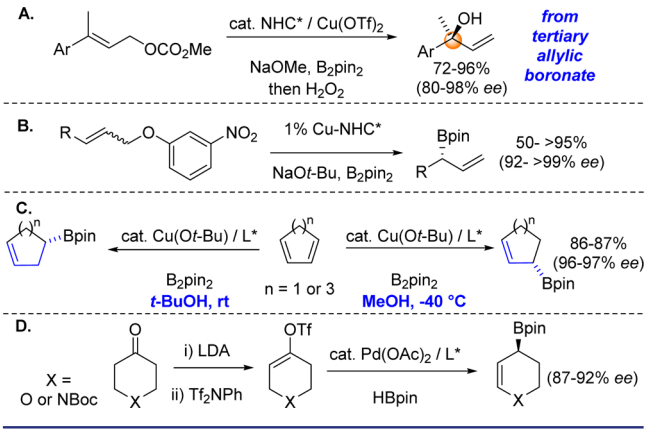
Scheme 4

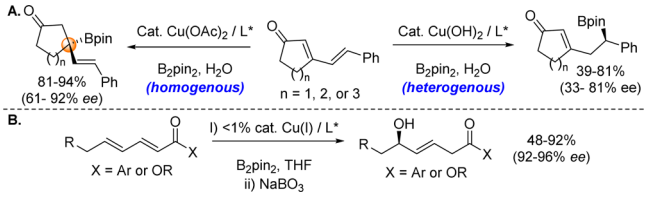


same enantiomer of the chiral allylboronate product. Again, the catalyst system is a chiral Cu(I)-NHC complex and its loading is impressively low. The reaction's utility lies in its ability to provide highly enantioenriched products via asymmetric catalysis from stereoisomeric mixtures of allylic ethers (mixtures often obtained from the ubiquitous olefin metathesis reaction[32]).

The asymmetric hydroboration of 1,3-dienes is another approach toward (homo)allylic boronates. In 2010, the Ito group reported the first catalytic version of this reaction, again via Cu(I) catalysis.[33] While the scope of the reaction is limited to cyclic dienes, the regioisomeric preferences (allylic vs homoallylic boronates) are governed mainly by temperature. 1,3-cyclohexadiene was only reliable at forming the homoallylic boronate, but both cyclopentadiene and 1,3-cycloheptadiene could be regiodivergently hydroborated via modulation of the temperature and additives (Scheme 4C). In 2011, Hall's group demonstrated that chiral, differentially substituted 1,1-diboryl compounds could be enantioselectively cross-coupled with olefinic halides, providing another means of accessing chiral α-substituted allylboronates.[34] The efficient synthesis of chiral *heterocyclic* allylic boronates has also been demonstrated and exploited by the same group.[35] More recent work within the group has granted access to chiral allylboronates within six-membered heterocycles.[36] These compounds are derived from cyclic ketones via a simple two-step sequence, the latter of which is an interesting Masuda-type[37] palladium-catalyzed asymmetric borylation reaction with HBpin (Scheme 4D).

In 2013, a report from the Kobayashi group demonstrated Cu(II)-catalyzed asymmetric conjugate addition reactions of $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds with B_2pin_2 for the preparation of highly functionalized chiral secondary (or tertiary) allylboronates.[38] While acyclic substrates (both ketones and esters) provided the β-addition products exclusively in good enantioselectivity, cyclic substrates demonstrated regiodivergent behavior (Scheme 5A). It was found that

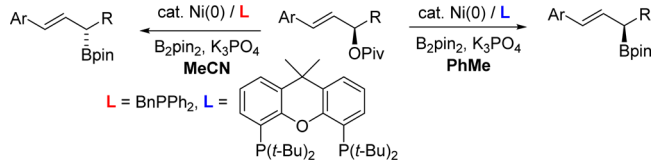
Scheme 5



when $Cu(OH)_2$ was used, a heterogeneous catalyst system formed, favoring δ-addition and, after a thermodynamically driven isomerization process, an alkylboronate. A complementary system favoring 1,6-addition for acyclic substrates was disclosed by the Lam group in 2014 (Scheme 5B).[39] In this reaction a chiral Cu(I) catalyst used at extremely low (up to 0.005%) catalyst loadings under mild conditions. While the δ-addition products in the Kobayashi group's aqueous system isomerized to provide alkylboronates, these conditions allow for the isolation of the non-isomerized and isolable chiral secondary allylic boronates.

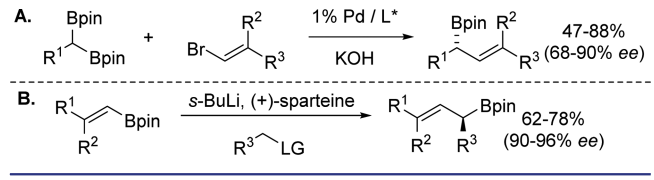
Very recently, the Watson group reported a stereospecific yet enantiodivergent approach toward α-stereogenic γ-aryl allylic boronates.[40] Easily accessible (via Corey–Bakshi–Shibata (CBS) Reduction[41]) γ-aryl allylpivalates can be borylated without transposition/isomerization of the double bond under nickel catalysis. Interestingly, the reaction can be guided into a stereodivergent or stereoretentive pathway, mainly via the influence of solvent. While non-coordinating solvents favor a closed seven-membered TS and retention of configuration, an open transition state and stereoinversion are operative in acetonitrile. In this way both enantiomers of this valuable class of chiral α-substituted allylboronates are easily accessible from one chiral starting material (Scheme 6).

Scheme 6



One of the most difficult to access yet synthetically important classes of allylboronates comprises differentially γ-disubstituted chiral secondary allylic boronates. The importance of these compounds lies in their ability to form quaternary stereocenters. In 2014, the Aggarwal group[42] and the Morken group[43] disclosed two distinct approaches toward this class of compounds. Extension of the Morken group's previously disclosed enantiotopic group-selective cross-coupling of geminal bis(boronates) with aryl halides[44] to olefinic halides allowed access to these densely functionalized reagents. The reaction demonstrates an impressive substrate scope at low catalyst loading (Scheme 7A). In a complementary fashion, the

Scheme 7



Aggarwal group demonstrated that an asymmetric homologation of alkenylboronates was an alternative entry point into this important compound class (Scheme 7B), a follow-up on similar studies within the group geared toward less densely functionalized crotylboronates.[45] The same group also reported a conceptually distinct yet mechanistically similar reaction wherein a vinylogous carbene surrogate was inserted into the C–B bond of an enantioenriched tertiary *alkyl*boronate.[46]

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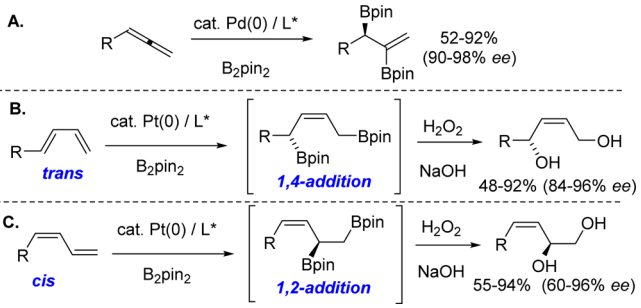
Various approaches toward the asymmetric synthesis of allylboronates via diboration reactions have been investigated by the Morken group. Therein, 1,2- or 1,4-diboration of allenes or 1,3-dienes can provide chiral allylboronates bearing an additional boryl group in a variety of useful topologies. The initial disclosure of a palladium-catalyzed asymmetric 1,2-diboration of prochiral α-allenes to α-branched allylic boronates allowed access to a novel class of differentially functionalized chiral diboryl compounds (Scheme 8A).[47] Further optimization

Scheme 8

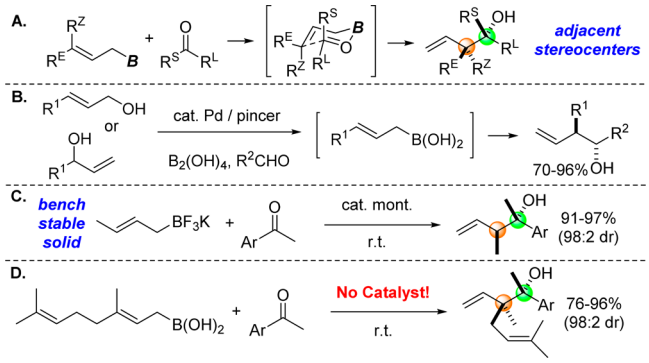


of the reaction and a detailed mechanistic inquiry,[48] including both computational and experimental techniques, revealed that oxidative addition of B_2pin_2 to Pd(0) was the rate-determining step. Notably, this pathway is rarely invoked in palladium-catalyzed borylation reactions with diboron reagents.[49] A similar reaction of *trans*-1,3-dienes soon followed via platinum catalysis to provide chiral 1,4-diboryl compounds.[50] Improvements of this chemistry through ligand modification soon allowed for a broader substrate scope and higher enantioselectivities (Scheme 8B).[50,51] In an attempt at flipping the selectivity of this diboration reaction from 1,4- to 1,2-addition, they found that simply changing the geometry of the diene starting material (*trans* to *cis*) provided entry into this new class of reagents with good enantioselectivity (Scheme 8C).[52]

The allylboration of carbonyl compounds via allylboronates is a field that has experienced dramatic growth, especially following the Hoffman group's realization of the high stereoselectivity of this process when crotylboronates are utilized.[53] The ability to utilize more densely functionalized allylboronates and electrophiles, often in an asymmetric fashion, has allowed for the synthesis of optically enriched tertiary and even quaternary homoallylic alcohols and amines. Generally, the diastereoselectivity of the reactions employing achiral crotylboronates with carbonyls is a product of the "closed" Zimmerman–Traxler (ZT) transition state (TS), wherein the smaller group (R^S) occupies the axial position (Scheme 9A).[54]

Some important hurdles outside of asymmetric synthesis that have been surmounted within this period include achieving high levels of diastereoselectivity and extending the scope of electrophiles from aldehydes to ketones. In 2006, our group reported a novel borylation–allylboration multi-component reaction (MCR) between allylic alcohols, aldehydes, and tetrahydroxydiboron (Scheme 9B).[55] It was found that, following a stereoconvergent borylation reaction of linear/branched allylic alcohols, an extremely diastereoselective allylboration could be realized under ambient conditions. The high degree of diastereoselectivity observed in this reaction is a result of the allylic boronic acid's configurational stability, coupled with its closed ZT TS. This selectivity was later

Scheme 9



exploited in further applications: (1) use of stable acetals as (otherwise sensitive) aldehyde surrogates,[56] (2) utilization of aldehydes/acetals bearing a vinyl group for a tandem borylation–allylboration ring-closing metathesis (RCM) reaction for the synthesis of cyclic (homo)allylic alcohols,[57] and (3) regiodivergent synthesis of linear or branched homoallylic alcohols via the previously established borylation–allylboration cascade terminated by a solvent-controlled 3,3-sigmatropic rearrangement.[58]

Following the first report of a catalytic asymmetric ketone allylboroation by the Shibasaki group,[59] the Kobayashi group provided another inroad to ketone allylboration utilizing In(I) catalysis.[60] While the reaction could be performed under surprisingly mild conditions, it was limited to the simple allylBpin reagent and thus products bearing only one stereocenter. In 2009, the Batey group demonstrated the first robust crotylboration of ketones (9C).[61] Practical conditions employing bench-stable potassium organotrifluoroborates and montmorillonite K10 clay catalyst lend this methodology utility. Our own group has made significant progress in this area through the use of *allylboronic acids* (Scheme 2C).[12] These compounds undergo a highly diastereoselective allylboration of ketones, even with γ,γ-disubstituted allylboronates, providing homoallylic alcohols bearing adjacent quaternary stereocenters (9D).[12] Even more sensitive ketones, such as conjugated enynes, halomethyl ketones, and α-keto esters/acids, could also be efficiently allylated in a predictable fashion with high diastereoselectivity.[62]

Unfortunately, diastereoselective allylboration reactions utilizing chiral α-substituted allylBpin reagents have long suffered from poor selectivity.[63] This poor selectivity is a result of steric clashes introduced by the α-substituent in the ZT TS. If it is oriented in the equatorial position, then it clashes with the bulky Bpin group. But if it is oriented in the axial position, then it suffers from 1,3-diaxial interactions (Scheme 10A).[25] The use of Lewis acids to modify the geometry of these TSs, and thus the stereoselectivity, has been studied by the groups of Hall[64] and later Roush.[65] The Aggarwal group has disclosed two different and divergent methodologies for overcoming this issue with aldehydes, providing densely functionalized homoallylic alcohols in high yields with almost complete diastereo- and enantioselectivity. The first method relies on transforming chiral α-substituted crotylBpin reagents into their corresponding *borinic* esters via sequential treatment with *n*-BuLi and TFAA.[66] These observable intermediates have a less sterically encumbered environment around boron and thus avoid clashes between the equatorial α-substituent at the TS (Scheme 10B). In this case, almost complete *E*-selectivity is observed.

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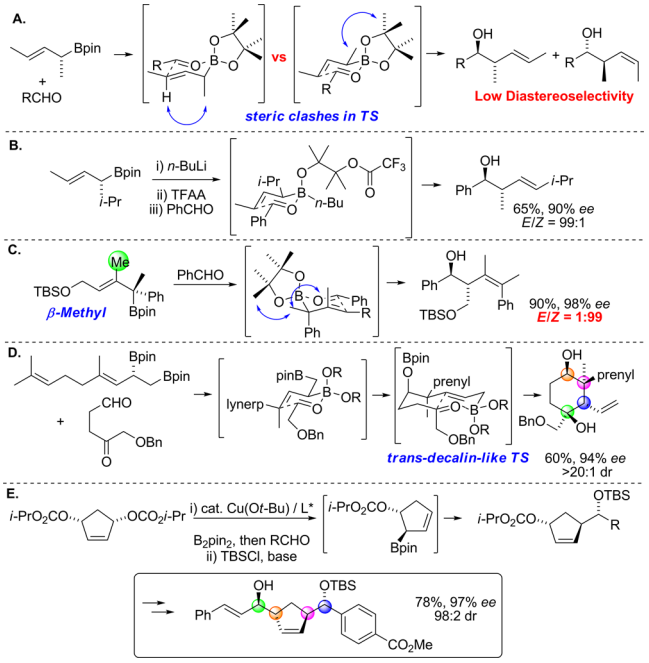
Scheme 10



Extension of these *borinic* ester intermediates to the allylboration of ketones and imines was soon after disclosed (this will be discussed in more detail later in the Perspective),[42] as well as the development of a highly selective tandem allyboration−Prins cyclization for the synthesis of highly substituted tetrahydropyrans.[67] The other approach involves utilization of chiral α-disubstituted allylBpin reagents bearing a methyl group (or other substituent) at the β-position (Scheme 10C).[68] But here, the larger aryl group prefers the axial position of the ZT TS in order to avoid steric clashes between both the bulky Bpin and adjacent methyl groups. Thus, the facial bias is flipped and the *Z*-isomer is formed, again in almost complete diastereoselectivity. Notably, this methodology allows access to enantioenriched homoallylic alcohols bearing adjacent stereocenters and a tetrasubstituted olefin.

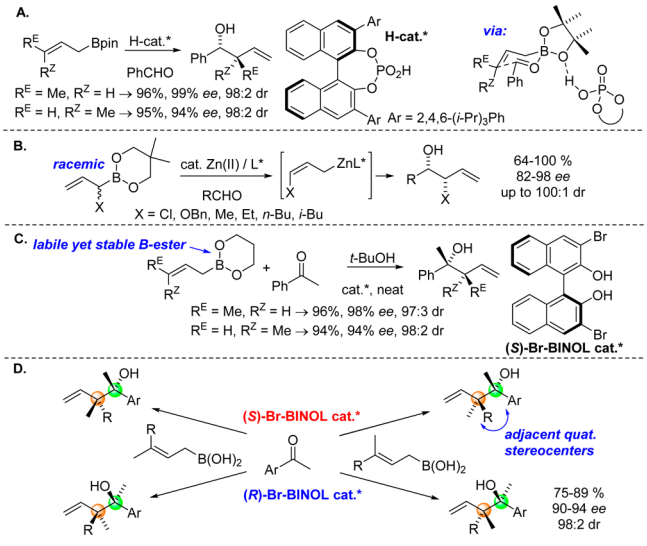
Another notable asymmetric reaction of chiral α-substituted allylboronates comes from the Morken group. Application of their previously disclosed enantioselective 1,2-diboration reaction[52] toward a tandem diboration−allylation−allylation reaction of dicarbonyls with dienes provided six-membered carbocycles bearing *four* adjacent stereocenters with good selectivity (Scheme 10D).[69] While the diastereoselectivity of the initial allylation could be worrisome (as per the above discussion), the use of *Z*- or γ-disubstituted reagents forces the bulky α-boronomethyl substituent into the equatorial position in order to avoid unfavorable 1,3-diaxial interactions.[70] The diastereoselectivity of the second allylation is governed by balancing the favorability of having the newly formed OBpin group in the axial position[71] with placing the remaining groups in equatorial positions about the *trans*-decalin TS. Presumably, due to the closely tethered nature of the second carbonyl and the newly formed allylBpin fragment, even ketones can be utilized for the final allylation step, allowing for the synthesis of up to two quaternary centers.

Another desymmetrization-type tandem borylation−allylboration reaction has been disclosed by the Ito and Sawamura group.[72] Similar to the Morken group's approach, the chirality was introduced during the borylation step and transferred to the final product via a highly diastereoselective allylboration. In this case, achiral *meso*-2-alkene-1,4-diol derivatives are subjected to the same group's previously disclosed Cu(I)-catalyzed asymmetric borylation chemistry,[27] providing sensitive (non-isolable) cyclic allylboronates bearing two adjacent stereocenters. These compounds are reacted *in situ* with various aldehydes to provide homoallylic alcohols bearing (at least) three stereocenters (Scheme 10E). Because the resultant products are also allylic carbonates, they could be subjected to another borylation−allylboration reaction (after silyl protection of the homoallylic alcohol), providing complex diols bearing four stereocenters.

Some recent examples of asymmetric diastereoselective allylboration reactions in total synthesis are also noteworthy. One is the Hall group's application of their tandem borylation−isomerization−allylboration sequence, coupling cyclic enol triflates with aldehydes[36a] toward the stereodivergent synthesis of all four isomers of the antimalarial drug mefloquine.[73] This study provided valuable results to the medical community, as it demonstrated the higher potency of the non-commercial and less synthetically accessible *threo*-isomer. Another example is the Batey group's diastereoselective allylboration of a chiral *N*-protected α-amino aldehyde toward the synthesis of depsipeptides kitastatin and respirantin.[74] In this study, potassium prenyltrifluoroborate demonstrated clean reactivity under the group's previously described crotylboration conditions[61] despite further substitution at the γ-position.

The catalytic asymmetric addition of γ-substituted *achiral* allylboronates to carbonyls can be thought of as the pinnacle approach toward densely functionalized chiral homoallylic alcohols. The ability to combine two achiral starting materials in an atom-economical fashion, such that two adjacent stereocenters are formed in one step, is highly desirable. Following previous reports of chiral Brønsted acid-catalyzed asymmetric allylboration reactions by Hall's group,[75] the Antilla group presented the first chiral phosphoric acid-catalyzed asymmetric addition of allylBpin reagents to aldehydes in 2010.[76] This reaction also demonstrated its ability to fare equally well for both *E*- and *Z*-crotylboronates (Scheme 11A). The transformation is suggested to proceed via protonation of one of the oxygen atoms of the Bpin group (as opposed to the

Scheme 11



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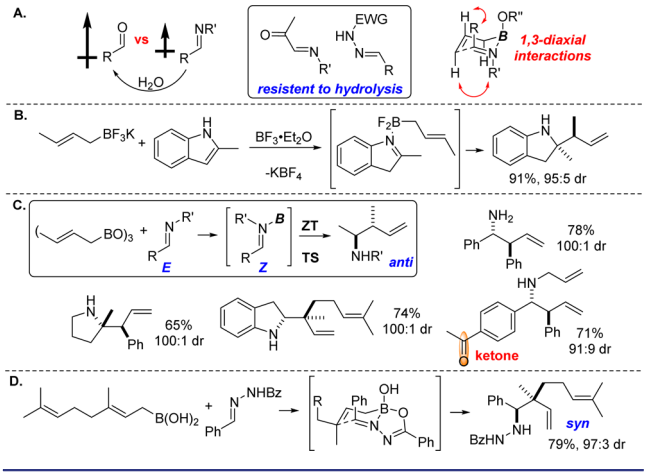
carbonyl), as originally proposed by the Hall group.[75a] The exact geometry of the catalyst in the stereoinduction step has been investigated computationally by the Houk group[77] and the groups of Goodman and Pellegrinet.[78] The utility of this reaction has been thoroughly explored by the Fustero group[79] toward more complex products, including (1) relay allylation−RCM reactions for the synthesis of cyclic benzo-fused homoallylic alcohols;[80] (2) utilization of *E*-γ-silyl-allylBpin reagents for the synthesis of chiral allylic silanes;[81] and (3) use of aldehydes bearing tethered alkynes providing chiral ene-yne products, primed for various transition-metal-catalyzed cyclization reactions.[82]

Another important advance within this realm is that of formal α-allylation reactions pioneered by the Kobayashi group.[83] Initial studies on the surprisingly diastereoconvergent reaction of racemic α-subsituted allylBpin reagents with aldehydes under zinc catalysis to form almost exclusively the *syn*-α-addition products[83a] led the group to develop an asymmetric version (Scheme 11B).[83c] Presumably, γ-addition to a chiral phenanthridine-ligated Zn(II) complex provides a linear (*Z*)-allyl zincate, which undergoes a highly enantioselective allylation reaction with aldehydes. The process is tolerant of a wide range of α-substituents, such as chloro, benzyloxy, and primary alkyl groups, and can be run under mild aqueous conditions. The catalytic asymmetric allylboration of ketones presents additional challenges due to their decreased reactivity relative to aldehydes. For example, the allylboration of aldehydes with pinacol boronates generally proceeds cleanly at −78 °C, while the analogous uncatalyzed reaction with ketones will not, even at ambient (or elevated) temperatures. In this vein, the Schaus group has made important advances over the past decade via organocatalysis employing BINOL derivitives.[84] It was found that employing 3,3′-disubstituted BINOL derivatives as catalysts with labile boronic esters (such as 1,3-propanediol) allowed for even the crotylboration of ketones (Scheme 11C).[84a] The reactions were conducted neat in the presence of *t*-BuOH, which was shown to dramatically increase the rate of the reaction via aiding in catalyst turnover. Computational studies into the stereoinduction of the BINOL-catalyzed allylboration reactions have been undertaken by the groups of Goodman and Pellegrinet.[85]

Utilizing γ-disubstituted allylboronates with ketones under catalytic asymmetric conditions allows for the synthesis of adjacent quaternary stereocenters. Due to severe congestion, this is a difficult topology to access via catalytic synthesis. Building on the Schaus group's results, our group was able to utilize a similar platform to access these densely functionalized homoallylic alcohols for the first time catalytically.[86] Key to our success was the employment of the more reactive and highly privileged allylic *boronic acids* (Scheme 2C). Terpene-derived γ-disubstituted allylboronic acids reacted with a variety of ketones under mild conditions in high diastereo- and enantioselectivities. Importantly, the approach was highly stereodivergent, depending on the *E*/*Z* geometry of the allyl fragment and the enantiomer of the catalyst (Scheme 11D).

The allylboration of imines has also been explored for the synthesis of homoallylic amines. In general, the reaction is thought to be less favorable due to the decreased polarization of the C−N double bond relative to its oxo-analogues. Also, due to the preference of imines to exist in an *E*-geometry, they are expected to have higher activation barriers due to having unfavorable 1,3-diaxial interactions in the ZT TS[87] (Scheme 12A). Another potential difficulty with regard to the allylation

Scheme 12



of simple imines is their facile hydrolysis, which is potentially catalyzed by the organoboronate itself.[88] One approach toward overcoming this issue is the use of hydrazones as the imine component.[83b,89] Another is the use of an electron-withdrawing group adjacent to the imino functionality, thus providing amino acid derivatives.[90]

One important development in regard to the allylboration of imines is the γ-selective allylation at the 2-position of indoles. Originally developed by the Bubnov group via utilization of pyrophoric triallylborane,[91] this chemistry was made bench-friendly by the Batey group in 2013, using highly robust potassium allyltrifluoroborates.[92] The reaction was shown to fare well with both *E*- and *Z*-crotylboronates as well as various substitutions on the indole skeleton, including the 2-position, leading to adjacent stereocenters (Scheme 12B). The reaction is thought to proceed via Lewis acid-mediated abstraction of a fluoride to generate a highly electrophilic allylic boron difluoride intermediate. This species is thought to form a Lewis acid−base adduct with the 3*H*-indole imine tautomer of the indole and undergo allylboration through a chairlike TS.

Our group has made some significant progress toward diastereoselective imine allylboration reactions as well. In 2014, we found that non-stabilized acyclic imines could be allylated with remarkably high (and unexpected) *anti*-selectivity with γ-substituted allylic boroxines under aprotic conditions.[88] This is the opposite diastereoselectivity as would be expected for an *E*-imine reacting through a ZT TS. Through both computational and experimental studies, it was found that the Lewis acidic boroxine functionality catalyzed a rapid and exergonic *E*-to-*Z* isomerization prior to the C−C bond-forming event. The reaction could be extended to differentially γ-disubstituted boronic acids and various electrophiles, including indoles and cyclic ketimines (Scheme 12C). Interestingly, a substrate containing both a ketone and an *N*-allyl imine moiety preferentially reacted at the *less electrophilic* but *more basic* imine group. Soon after, our group disclosed a complementary reaction wherein acylhydrazones were utilized as imine surrogates, this time providing the *syn*-products.[89a] This flip in stereoselectivity is attributable to a mechanism lacking the *E*-to-*Z* isomerization seen in the previous study. The exact structure of the hydrazine was detrimental to functional reactivity and hints at a "partial esterification" between the reaction partners, providing a bicyclic ZT TS (Scheme 12D). Again, the substrate scope was broad, tolerating alkyl-, aryl-,

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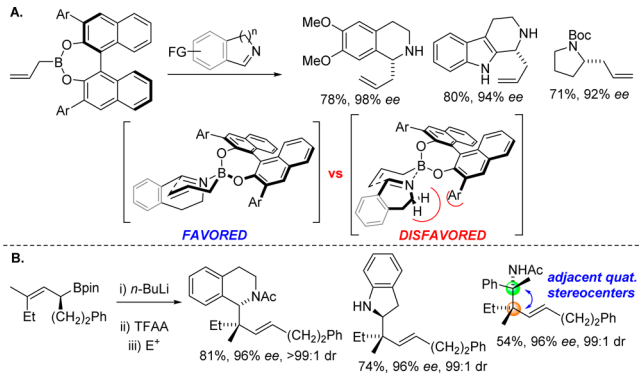
alkenyl-, alkynyl-, and carboxy-substituted hydrazones, as well as one derived from a cyclic ketone.

Use of enantioenriched α-substituted allylboronates or achiral allylboronates esterified with a chiral diol (chiral auxiliary) are the two general approaches for achieving enantioinduction in allylboration reactions with imines via chirality transfer. The latter approach was demonstrated by the Chong group using 3,3′-subsituted BINOL esterified allylboronates (Scheme 13A).[93] While these reagents had been

Scheme 13

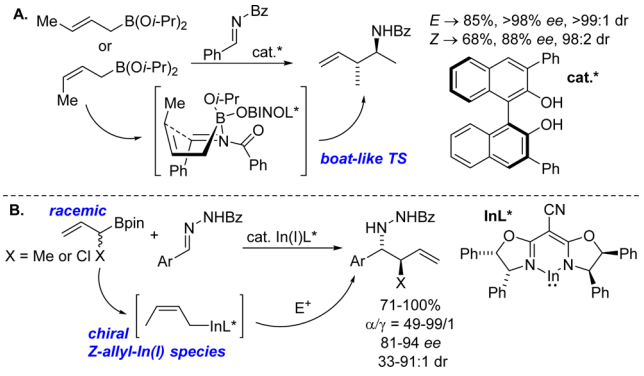


used within the same group for the enantioselective allylboration of aldehydes and even ketones,[94] they had not yet been extended to imines. Cyclic imines are a suitable proving ground for such a reaction, as the hydrolysis is less problematic due to entropy considerations and the imine is locked into the more reactive *Z*-conformation. The electrophiles' scope is generally limited to various five- and six-membered cyclic imines and provides rapid access to some biologically relevant alkaloids.[95]

As previously discussed, the Aggarwal group's utilization of *borinic* ester intermediates in asymmetric allylboration reactions of chiral α-substituted allylboron reagents has demonstrated great utility, despite its lack of functional group tolerance.[42] The impressive reactivity of these compounds provides high diastereo- and enantioselectivity with both aldehydes and ketones, but also with imines, indoles, and even ketimines (Scheme 13B).[42] Because the allylboronate starting materials are also differentially γ-disubstituted, the products with ketimines bear adjacent quaternary stereocenters. The chemistry has the added advantage of being fully stereodivergent with respect to these centers by changing the *E*/*Z* geometry of the allylboronate and the absolute configuration at its α-stereocenter.

In 2007, the Schaus group was the first to introduce a catalytic asymmetric crotylboration of imines utilizing achiral allylboronates.[96] Building on the group's previous success with BINOL catalysis for the corresponding crotylboration of ketones,[84b] they found that highly reactive acylimines were a useful class of electrophiles for such a reaction. Due to the high propensity for hydrolysis of both acylimines and acyclic allylboronic esters, the reaction requires stringently dry conditions and molecular sieves. While crotylboration was possible, both the *E*- and *Z*-isomers provided the same *anti*-addition product. This surprising outcome was ascribed to the *Z*-crotylboronate reacting through a boatlike TS in order to avoid unfavorable 1,3-diaxial intereactions in the typical ZT TS (Scheme 14A).

Scheme 14



An early (2006) and as of yet unrivaled catalytic asymmetric formal allylboration of *ketimines* was reported by the Shibasaki group.[97] While in this study the only nucleophile surveyed was the simple allylBpin reagent, and thus the products contain only one stereocenter, the reaction is novel. The reaction is guided by Cu(I) catalysis, utilizing chiral bidentate phosphine ligands. *In situ* formation of chiral allyl-Cu(I) species was observed spectroscopically, and their addition to *N*-benzyl keto-imines provided homoallylic amines with high enantioselectivity. Transmetalation from bench-stable allylic Bpin reagents to more reactive chiral metal complexes of In(I),[89b] Zn(II),[83b] and Cu(I)[98] has provided important advances in the catalytic asymmetric allyboration of imines with γ-substituted reagents.

In 2008, the Kobayashi group presented a Zn(II)-catalyzed formal α-allylboration reaction of racemic secondary allylBpin reagents with hydrazano esters, providing optically enriched allylglycine derivatives.[83b] In this case a chiral diamine ligand was employed in an aqueous acetone solution under mild conditions, providing the *anti* isomer in excellent regio- and diastereoselectivities and good enantioselectivities. The mechanism of the reaction is presumed to follow two sequential γ-additions. The first proceeds from B to Zn, forming a chiral *Z*-allylzinc reagent. This zincate then undergoes an allylation reaction through a ZT TS, similar to the group's analogous observations with aldehydes.[83a,c] In 2010, the same group reported a similar reaction with a broader substrate scope and higher enantioselectivities, this time catalyzed by an In(I) complex ligated with chiral semicorrin ligands.[89b] In that case, benzoyl hydrazones derived from simple aromatic aldehydes bearing a variety of functional groups could be utilized. Also, both racemic α-methyl- and α-chloro-allylBpin reagents underwent the reaction to provide the *anti*-α-addition products in excellent regio-, diastereo-, and enantioselectivities (Scheme 14B).

The Hoveyda group has also reported a Cu(I)-catalyzed asymmetric allylboration of aldimines between allylBpin reagents and phosphinoylimines.[98] "In-house"-synthesized C_1-symmetric chiral NHC ligands gave the products high enantiomeric purity, even with β-substituted allylboronates. Crotylboronates, however, furnished products with low stereoselectivity, a result of plausible π-allylcopper intermediates, also evidenced by deuterium isotope labeling of allylBpin.

The same group later presented a completely distinct and organocatalytic approach toward the allylboration of phosphinoylimines as well as other electrophiles, which to a large extent has overcome this limitation.[99] This new approach combines the themes of stereoinduction via chiral diols on the boron atom[84,86,93] with the formal α-addition reactions

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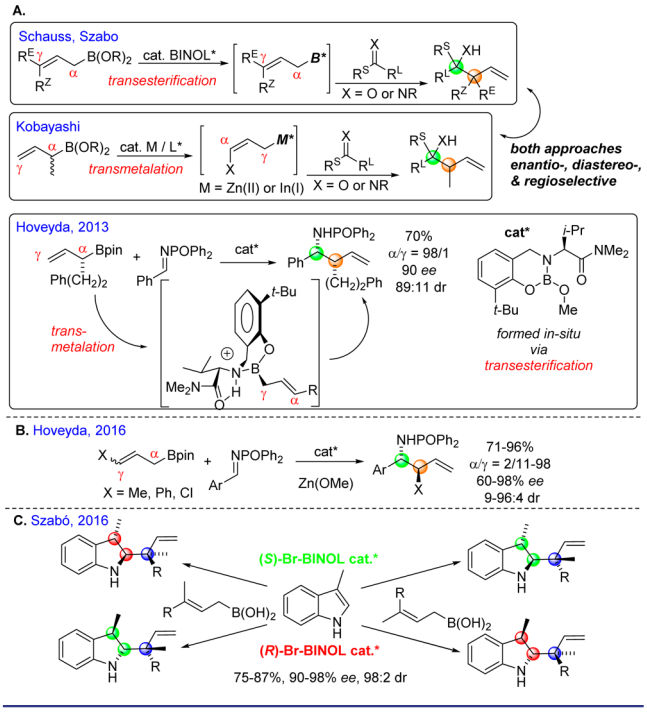
mediated by an intermediate transmetalation step, wherein a *Z*-crotylmetalate is formed.[83b,c,89b] The novelty of this innovation hinged on this transmetalation being from boron to boron, that is, from an achiral allylic Bpin reagent to a chiral allylboron intermediate (Scheme 15A). The initial disclosue demonstrated

Scheme 15



the ability of allylBpin as well as its β-substituted analogues to react with a large scope of phosphinoylimines, including (hetero)aryl-, alkenyl-, alkynyl-, and alkyl-, with high enantioselectivity. Notably, chiral α-substituted allylBpin reagents reacted stereodivergently with inversion at the α-carbon atom, a result of the initial γ-selective transmetalation to the chiral boron species.

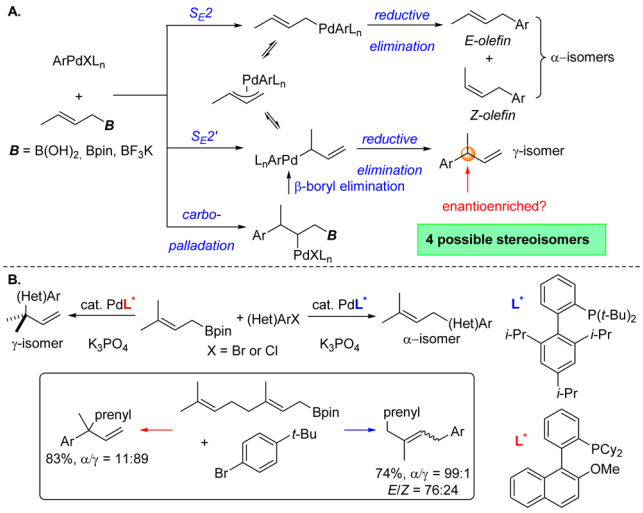
As previously stated in this Perspective and noted by the Hoveyda group, the ability to apply asymmetric catalysis with achiral γ-substituted allylboronates to furnish an optically enriched homoallylic amine (or alcohol) with adjacent stereocenters is highly desirable. In 2016, the Hoveyda group achieved this feat by slightly modifiying this organocatalytic approach with Lewis acidic Zn(II) additives.[99b] This mediated an intramolecular 1,3-borotropic shift between the previously proposed transmetalation and allylboration steps. The net result, when using either an *E*- or *Z*-γ-substituted allylboronate is a highly enantioselective (*anti*)-γ-addition product (Scheme 15B).

Recently, the same group reported that, under slight modifications, this approach could also be extended to the catalytic asymmetric allylboration of various fluoroketones.[99a] This is a difficult task due to the relative size (for example, methyl vs trifluoromethyl) and unique electrostatic properties of highly fluorinated organic moieties. Yet its importance is obvious due to the importance of chirality in biological systems coupled with the ever-increasing proportion of fluorinated compounds in the agrochemical[100] and pharmaceutical[101] industries.

Our own group recently disclosed a catalytic asymmetric allylboration of imines utilizing differentially γ-disubstituted allylboronates (Scheme 15C).[102] Cyclic imines and indoles were prenylated under mild conditions, generating products with adjacent stereocenters and pharmaceutically relevant architectures, such as indolines and tetrahydroisoquinolines. The reaction is fully stereodivergent in the same manner as our previous report with ketones (Scheme 11D).[86] Notably, allylation of 3-methylindole led to a suite of products bearing *three adjacent stereocenters*, one of which being quaternary.

Cross-coupling reactions of substituted allylboronates with various electrophiles for the formation of C−C bonds in a "traceless" manner are another important and developing area for the synthesis of complex molecules. As previously stated, transferring an allyl group to an electrophile in a stereospecific fashion is difficult due to regio-, diastereo-, and enantioselectivity issues. These issues are further complicated when the electrophile is a transition metal complex, due to the different possible transmetalation pathways and binding modes in which the allyl group can participate. For example, the Pd(0)-catalyzed cross-coupling of an aryl halide with an *E*-crotyl boronate can provide up to four stereoisomers (Scheme 16A).

Scheme 16



After oxidative addition of Pd(0)L_n with ArX to form the electrophilic ArPd(II)XL_n species, transmetalation can occur through three possible pathways: S_E2, S_E2', and carbopalladation, followed by β-boryl elimination to form σ-allylpalladium intermediates. The latter two result in forming the C−Pd σ bond at the γ-carbon, while the former provides its regioisomer (α-carbon bond formation). Reductive elimination from these intermediates will provide the corresponding "branched" or "linear" products. Due to the potential for these organometallic intermediates to form π-allyl species, equilibration prior to reductive elimination can provide a regioisomeric product mixture as well as scrambling of the *E*/*Z* geometry of the olefins in the linear isomers. Not only this, but when the branched isomer is obtained, then a stereocenter is formed (and thus two enantiomers). The product mixture becomes potentially more complex when other electrophiles are used, such as allylic halides or diazo compounds.

Studies into controlling the regiochemistry of this reaction were disclosed independently by the Miyaura group[103] and our own.[104] The Miyaura group[103] found that *E*-γ-substituted allylBF_3K reagents formed the branched isomer preferentially with aryl bromides when bisphosphine ligands with a large bite

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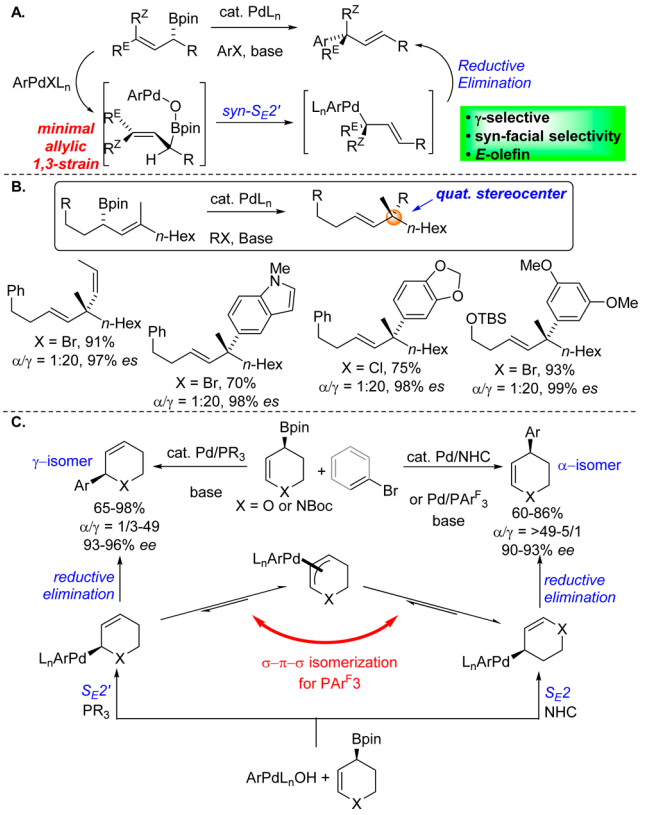
angle were utilized. An asymmetric variant of this reaction was disclosed by the same group immediately afterward, using a similar but chiral ferrocene-based ligand.[105] These reactions are presumed to proceed via an S_E2' transmetalation followed by a rapid reductive elimination, avoiding π-allyl intermediates and providing high regioselectivity. This mechanism was later supported by computational studies.[106] Therein it was found not only is the S_E2' transmetalation operative but that it proceeds with a cationic arylpalladium complex through an open TS.

In a separate study, our group demonstrated the feasibility of the relatively cheap and commonly used $Pd(PPh_3)_4$ catalyst to facilitate the cross-coupling of iodoarenes with *in situ*-generated allylboronic acids following the same regiochemical bias.[104] The reaction proceeds under mild conditions and allows for the use of complex allylic alcohol or vinyl cyclopropane boronic acid precursors for the synthesis of more-complex products. Again, π-allyl intermediates were ruled out via some experimental mechanistic studies. In this case, a carbopalladation−β-boryl elimination transmetalation pathway was proposed to account for the high regioselectivity of the process with such a seemingly unbiased ligand (PPh_3).

More recently, the Organ group introduced the first α-selective allylation reaction using the extremely bulky NHC catalyst, Pd-PEPPSI-IPent.[107] The reaction works with the bench-stable and soluble prenylBpin reagent, a γ-dimethyl-allylboronate. Aryl bromides and chlorides as well as a suite of nitrogenous heteroaromatics couple smoothly under the protocol. Mechanistic inquiries hinted at an S_E2-type transmetalation. When differentially γ-disubstituted allylboronates such as geranylBpin were utilized, some scrambling of the resultant olefin geometry was observed, thus hinting at (at least to some extent) π-allyl complex formation.

In 2013, the Buchwald group introduced a regiodivergent cross-coupling approach allowing for the synthesis of either the linear or branched isomers via changing the electronic/steric nature of the phosphine ligand for the Pd catalyst (Scheme 16B).[108] Both systems utilize the group's typical dialkylbiaryl-phosphine ligands, yet seemingly slight modifications in catalyst architecture have a dramatic effect on the regioselectivity of the process. Again, a variety of (hetero)aryl bromides/chlorides could be coupled with high efficiency at low catalyst loading. As in the Organ group's study,[107] olefinic scrambling was observed when differentially γ-disubstituted reagents were utilized. While there have been a few reports on the catalytic asymmetric cross-couplings of achiral crotylboronates toward the synthesis of optically enriched allylic aromatics,[105,106] the enantio-selectivities are limited as well as the substrate scope. Chirality transfer cross-coupling reactions of chiral α-substituted allyl-boronates are another means of generating these products. Initial studies into the regioselectivity of such a reaction were disclosed by the Crudden group.[109] Reactions of racemic allylboronates substituted once at both the α- and γ-positions generally provided products with bond formation at the γ-carbon when using triphenylphosphine as a ligand and a silver oxide additive. A more in-depth study into this reaction and its potential in asymmetric chemistry was soon after presented in a collaborative effort between the Crudden group and the Aggarwal group (Scheme 17A).[110] In this case a broader range of highly enantioenriched allylboronates demonstrated a high level of chirality transfer. Important insights into the factors governing stereoselectivity were also uncovered. The mechansim of the reaction is thought to proceed through an

Scheme 17



S_E2'-type transmetalation whose facial selectivity is *syn*. This preference is guided by minimizing allylic strain after the commonly inferred Pd−O−B linkage[111] formed between the boronate and the aryl Pd(II) complex in Suzuki couplings. Rapid reductive elimination then provides the product, bearing an *E*-alkene adjacent to the newly formed stereocenter. Interestingly, π-allyl intermediates and formation of the α-isomer are minimal unless there is an aryl substituent at the γ-position. In that case, the $\sigma-\pi-\sigma$ isomerization process is driven by the formation of a more conjugated styrene.

A recent advance in this chemistry comes from the Morken group, allowing for the ability to synthesize quaternary stereocenters by employing a similar manifold to chiral γ-*disubstituted* secondary allylic boronates.[112] Exploitation of the group's recently disclosed ability to synthesize this privileged class of nucleophile[43] toward this end provided products with high stereoselectivities (Scheme 17B). In this case, the Buchwald ligand RuPhos was utilized at low catalyst loading without the need for a silver additive. The reaction has a broad substrate scope, and the stereochemistry of the resultant product can be switched by changing the *E*/*Z* geometry of the starting material.

Hall's group has applied the Buchwald group's concept of ligand-controlled regiodivergent cross-coupling[108] to their previously discussed chiral heterocyclic allylboronates[73] (Scheme 4D) for the synthesis of 2- and 4-substituted dihydropyrans and dehydropiperidines (Scheme 17C).[113] Because either enantiomer of the starting material is accessible by choice of ligand during the borylation step, the complete stereo-/regiochemical tetrad of products is accessible. The enantioselectivity is nearly perfect, a result of the high facial selectivity during transmetalation, as previously observed,[110] coupled with the conformational rigidity of the cyclic substrate.

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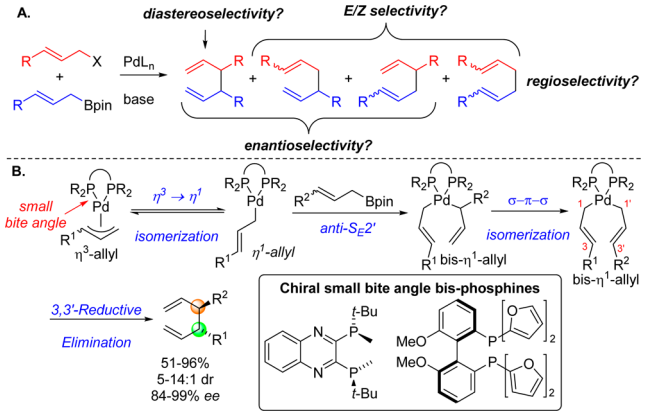
The regioselectivity is guided by similar principles to the acyclic systems discussed above. As in the Organ group's studies,[107] the bulky NHC ligand favors an S_E2 transmetalation followed by rapid reductive elimination to form the α-product, while using the Buchwald ligand (Xphos with Cy groups on P atom[108]) provided the γ-product. Interestingly, when an electron-deficient phosphine ($(4\text{-}CF_3Ph)_3P$) was employed, the α-product was favored. This was attributed to an S_E2' transmetalation, as is commonly invoked for phosphines,[103−106] followed by $\sigma-\pi-\sigma$ isomerization and then reductive elimination from the α-carbon-bound σ-allyl-Pd intermediate. The equilibrium favoring the α-isomer is due to increased conjugation between the olefin and the heteroatom, similar to the conjugation-driven processes observed by the Crudden and Aggarwal groups.[110] Soon after, the Hall group disclosed an extension of this chemistry to optically enriched ethoxy-dihydropyranyl boronates for the synthesis of more highly functionalized dihydropyrans.[114]

The cross-coupling of substituted allylmetal reagents with allylic electrophiles is a desirable reaction because it has the potential to provide functionalized 1,5-dienes, synthetically useful intermediates. As discussed earlier, the intermediacy of the allylPd(II) species can provide complex product mixtures due to the various intermediates, elementary steps, and equilibria accessible to such systems. These issues are aggravated when *both* of the coupling partners are substituted allylic reagents. Consider the reaction between an α-substituted allylboronate and an α- or γ-substituted allylic electrophile, wherein the product mixture can contain up to four different regioisomers. Of course the issue is more complex, as within each subset of stereoisomers one must consider the enantio- and diasteroselectivity and the E/Z-geometry of the products (Scheme 18A).

Scheme 18

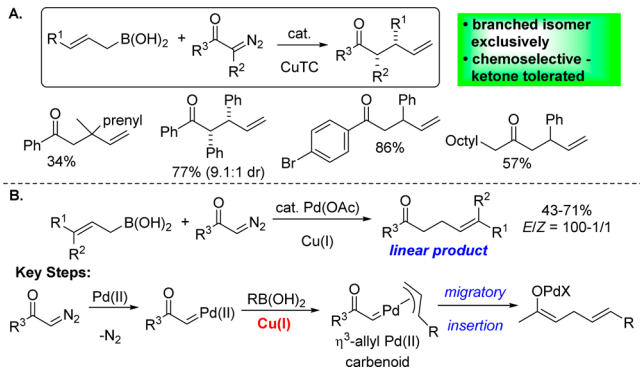


Despite this daunting task, the Morken group has undertaken the challenge.[115] In their initial publication, cross-coupling reactions between allylBpin (or their β-substituted analogues) and either linear or branched allylic carbonates provided 1,5-dienes bearing a stereocenter and two terminal olefins in good regio- and enantioselectivity.[115e] Later it was found that the reaction could be extended to γ-substituted allylBpin reagents, providing compounds bearing adjacent tertiary stereocenters.[115c] In that case the reaction proved quite robust, and even allylic chlorides demonstrated themselves as useful electrophiles. The reaction is thought to proceed via oxidative addition of the allylic electrophile to a Pd(0) catalyst ligated with a chiral *small bite angle*-type ligand (Scheme 18B).[116] In this case the ligand enviornment is thought to provide a bis-η^1-allyl complex after transmetalation/isomerization, wherein the substiuents on the allyl groups are now at the 3- and 3′-positions and of *trans*-geometry. The small bite angle of the ligand encourages a large bite angle between the organic substituents with respect to the metal. This geometry makes the inner-sphere 3,3′ reductive elimination favored over the 1,1′.[117] Computational and experimental studies have provided detailed insight into the exact nature of the elementary steps at work in this process, wherein it was found that the transmetalation proceeds through an *anti* (open) S_E2'-type process.[115a] This is in agreement with previous cross-couplings of allylic boronates wherein bidentate phosphine ligands were utilized.[103,105,106] Other important advances from the same group include the ability to use more-substituted allylic electrophiles for the synthesis of quaternary centers,[115f] as well as the utilization of 2-boryl-allylboronates as nucleophiles.[115d]

Other allyl−allyl cross-coupling reactions of allylboronates have been reported as well. The earliest was a report by the Kobayashi group, wherein the issue of regioselectivty was addressed.[118] They found that using catalytic $Pd(PPh_3)_4$ with various substituted allylic carbonates and allylboronates generally provided the linear isomers with opposite regioselectivity to that observed in the Morken group's studies. Also notable is that the Ni(0) analogue of this catalyst provided superior results in some cases where yields were diminsihed by β-hydride elimination. Another more recent report by the Sawamura group showcases the ability of chiral Cu(I) catalysts ligated with novel NHC ligands to mediate the coupling of linear Z-allylic phosphates with allylBpin to provide the branched isomer in high enantioselectivity.[119]

One developing area in the realm of C−C bond-forming reactions is the use of diazo compounds for cross-coupling with organoboronates. For example, the Barluenga group demonstrated the ability of arylboronic acids to couple with non-stabilized diazo intermediates formed *in situ* from tosyl hydrazones in a transition-metal-free process.[120] Also, the Wang group utilized stabilized α-diazocarbonyls as electrophiles in cross-coupling reactions with arylboronates under oxidative conditions.[121] These reports prompted us to wonder whether allylboronates could be utilized as the nucleophilic component in similar processes. Our initial foray into this arena led us to the discovery that α-diazoketones could be coupled with γ-substituted allylboronic acids via Cu(I) catalysis regioselectively to provide *only* the branched product (Scheme 19A).[122]

Scheme 19



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Interestingly, only traces of product were observable under these conditions when the analogous pinacolboronate ester was utilized, underscoring the higher reactivity of boronic acids. Also notable is that when the reaction was done in the absence of a metal carbenoid-generating catalyst,[123] preferential addition to the ketone was observed (followed by hydrolysis of the diazo moiety), while under catalytic conditions this process is apparently less favorable. The substrate scope allows for the use of γ-disubstituted boronic acids (thus providing products bearing quaternary stereocenters) as well as α-substituted electrophiles (thus providing products bearing adjacent stereocenters). Soon after, we disclosed an analogous and complementary Pd(II)-catalyzed reaction providing the *linear* isomer (Scheme 19B).[124] In contrast to the Wang group's studies on Pd(II)-catalyzed cross-couplings between α-diazocarbonyls and organoboronates,[121] our reaction did not require an external oxidant. This is likely due to divergent mechanisms: the Wang group's reaction terminating in a β-hydride elimination, and ours terminating in protonation of a Pd(II) enolate. Cu(I) additives were found to be beneficial in obtaining high yields, and through some preliminary mechanistic experiments we assume these additives aid in transmetalation,[125] not in metal-carbenoid formation. When differentially γ-disubstituted allylboronates were utilized, a mixture of E/Z stereoisomers formed, a result indicative of a π-allyl intermediate in the catalytic cycle.

In summary, in the past decade there has been dramatic progress in the area of allylboronates in stereoselective synthesis. In terms of allylboronate synthesis, highly efficient catalytic methods have been developed for the synthesis of achiral linear allylic boronates in excellent yields and E/Z selectivity. These compounds have demonstrated an impressive ability to undergo highly regio-, diastereo-, and even enantioselective allylboration or cross-coupling reactions to provide important synthetic intermediates. Equally impressive methods have been developed for the synthesis of highly substituted chiral allylic boronates. These compounds have demonstrated their outstanding ability at imparting their asymmetry to products of both allylboration and cross-coupling reactions. Most of the transformations for asymmetric synthesis were carried out using allylboronic esters (typically allylBpin). The boron atom of these reagents is sterically encumbered, making these compounds easy to purify and handle. However, the unprotected $B(OH)_2$ groups of allylboronic acids interact efficiently with chiral auxiliaries (such as BINOL) and thus extend the synthetic space of the catalytic asymmetric transformations.

While many outstanding problems have been solved, there remains room for development. Currently, methods for the preparation of allylboronates bearing heteroatoms or other functional groups directly bonded to the allyl moiety are limited. The application of these (a)chiral reagents in chirality-transfer reactions or asymmetric catalysis toward medicinally relevant motifs would be of great value. Also, specific reaction types in regard to the application of achiral γ-substituted allylboronates (a now simple class of reagents to access) to catalytic asymmetric transformations are still needed. This is important, as the ability to have complete control over the stereochemistry of densely functionalized molecules from achiral starting materials is the pinnacle of asymmetric synthesis.

For instance, while the completely stereodivergent synthesis of homoallylic alcohols bearing adjacent quaternary stereocenters has been achieved (though it is currently limited to aryl ketones), its "aza-analogue" (analogous reaction with ketimines) still remains elusive. Also, while there are reports of catalytic asymmetric Suzuki couplings of these boronates with aryl halides, they are limited to γ-monosubstituted allylboronates. Thus, the ability to form aryl-substituted all-carbon[126] quaternary stereocenters via such an approach would be an important contribution to the community.

Our group's recent studies into the use of diazo compounds as electrophiles in cross-coupling reactions of γ-substituted allylboronic acids has intriguing potential as well. Asymmetric variants of this chemistry would be an important advance in the synthesis of highly functionalized chiral compounds. Also, the Pd(II) or Cu(I) enolates furnished at the back ends of these catalytic cycles appear primed for further bond formation processes.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, 2011.

(2) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.

(3) Hall, D. G.; Lachance, H. *Allylboration of Carbonyl Compounds*; Wiley: Hoboken, NJ, 2012.

(4) (a) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *2008*, 1647. (b) Kennedy, J. W.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (d) Neeve, E.; Geier, S.; Mkhalid, I.; Westcott, S.; Marder, T. *Chem. Rev.* **2016**, *116*, 9091. (e) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 2004. (f) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (g) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303. (h) Hall, D. G.; Lee, J. C. H.; Ding, J. *Pure Appl. Chem.* **2012**, *84*, 2263. (i) Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397. (j) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (k) Hall, D. G. *Synlett* **2007**, *2007*, 1644. (l) Hall, D. G.; Rybak, T.; Verdelet, T. *Acc. Chem. Res.* **2016**, *49*, 2489.

(5) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

(6) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889.

(7) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416.

(8) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588.

(9) Dutheuil, G.; Selander, N.; Szabó, K.; Aggarwal, V. *Synthesis* **2008**, *2008*, 2293.

(10) Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409.

(11) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc.* **2013**, *135*, 443.

(12) Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 13050.

(13) Miralles, N.; Alam, R.; Szabó, K. J.; Fernández, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 4303.

DOI: 10.1021/jacs.6b10017
J. Am. Chem. Soc. 2017, 139, 2−14

(14) (a) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915. (b) McNeill, E.; Ritter, T. *Acc. Chem. Res.* **2015**, *48*, 2330.
(15) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534.
(16) Ely, R. J.; Yu, Z.; Morken, J. P. *Tetrahedron Lett.* **2015**, *56*, 3402.
(17) Caballero, A.; Sabo-Etienne, S. *Organometallics* **2007**, *26*, 1191.
(18) Olsson, V. J.; Szabo, K. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6891.
(19) Olsson, V. J.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 7715.
(20) Deng, H.-P.; Eriksson, L.; Szabo, K. J. *Chem. Commun.* **2014**, *50*, 9207.
(21) Tao, Z.-L.; Li, X.-H.; Han, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054.
(22) (a) Deng, Y.; Bartholomeyzik, T.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2013**, *52*, 6283. (b) Qiu, Y.; Yang, B.; Zhu, C.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2016**, *55*, 6520.
(23) Martos-Redruejo, A.; Lopez-Duran, R.; Bunuel, E.; Cardenas, D. J. *Chem. Commun.* **2014**, *50*, 10094.
(24) (a) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (d) Brauns, M.; Muller, F.; Gülden, D.; Böse, D.; Frey, W.; Breugst, M.; Pietruszka, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 1548. (e) Böse, D.; Niesobski, P.; Lübcke, M.; Pietruszka, J. *J. Org. Chem.* **2014**, *79*, 4699.
(25) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913.
(26) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, *48*, 3305.
(27) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.
(28) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972.
(29) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515.
(30) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.
(31) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410.
(32) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(33) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226.
(34) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.
(35) (a) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628. (b) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (c) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.
(36) (a) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612. (b) Kim, Y.-R.; Hall, D. G. *Org. Biomol. Chem.* **2016**, *14*, 4739.
(37) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, *2000*, 778.
(38) Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2013**, *49*, 8184.
(39) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 4186.
(40) Zhou, Q.; Srinivas, H. D.; Zhang, S.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 11989.
(41) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.
(42) Chen, J. L. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 10992.
(43) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918.
(44) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.
(45) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025.
(46) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760.
(47) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328.
(48) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.
(49) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713.
(50) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.
(51) Hong, K.; Morken, J. P. *J. Org. Chem.* **2011**, *76*, 9102.
(52) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 521.
(53) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.
(54) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(55) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, *2006*, 4085.
(56) Selander, N.; Szabó, K. J. *Chem. Commun.* **2008**, 3420.
(57) Selander, N.; Szabó, K. J. *Adv. Synth. Catal.* **2008**, *350*, 2045.
(58) Selander, N.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 5695.
(59) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
(60) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909.
(61) Nowrouzi, F.; Thadani, A. N.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2631.
(62) Alam, R.; Raducan, M.; Eriksson, L.; Szabó, K. J. *Org. Lett.* **2013**, *15*, 2546.
(63) Hoffman, R. W.; Weidmann, U. *J. Organomet. Chem.* **1980**, *195*, 137.
(64) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981.
(65) Chen, M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 2706.
(66) Chen, J. L. Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316.
(67) Millán, A.; Smith, J. R.; Chen, J. L. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 2498.
(68) Hesse, M.; Essafi, S.; Watson, C.; Harvey, J.; Hirst, D.; Willis, C.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6145.
(69) Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 2501.
(70) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309.
(71) Baldry, K. W.; Gordon, M. H.; Hafter, R.; Robinson, M. J. T. *Tetrahedron* **1976**, *32*, 2589.
(72) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560.
(73) Ding, J. Y.; Hall, D. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8069.
(74) Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2014**, *16*, 2322.
(75) (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (b) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426.
(76) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.
(77) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1208.
(78) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716.
(79) Barrio, P.; Rodríguez, E.; Fustero, S. *Chem. Rec.* **2016**, *16*, 2046.
(80) Fustero, S.; Rodríguez, E.; Lázaro, R.; Herrera, L.; Catalán, S.; Barrio, P. *Adv. Synth. Catal.* **2013**, *355*, 1058.
(81) Barrio, P.; Rodriguez, E.; Saito, K.; Fustero, S.; Akiyama, T. *Chem. Commun.* **2015**, *51*, 5246.
(82) Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506.
(83) (a) Kobayashi, S.; Endo, T.; Schneider, U.; Ueno, M. *Chem. Commun.* **2010**, *46*, 1260. (b) Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914. (c) Kobayashi, S.; Endo, T.; Ueno, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12262.
(84) (a) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

DOI: 10.1021/jacs.6b10017
J. Am. Chem. Soc. 2017, 139, 2−14

(85) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *Org. Lett.* **2009**, *11*, 37.
(86) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc.* **2015**, *137*, 11262.
(87) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115.
(88) Alam, R.; Das, A.; Huang, G.; Eriksson, L.; Himo, F.; Szabó, K. J. *Chem. Sci.* **2014**, *5*, 2732.
(89) (a) Das, A.; Alam, R.; Eriksson, L.; Szabó, K. J. *Org. Lett.* **2014**, *16*, 3808. (b) Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1838.
(90) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723.
(91) Bubnov, Y. N.; Zhun', I. V.; Klimkina, E. V.; Ignatenko, A. V.; Starikova, Z. A. *Eur. J. Org. Chem.* **2000**, *2000*, 3323.
(92) Nowrouzi, F.; Batey, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 892.
(93) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.
(94) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.
(95) (a) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795. (b) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850.
(96) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.
(97) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(98) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332.
(99) (a) Lee, K.; Silverio, D. L.; Torker, S.; Robbins, D. W.; Haeffner, F.; van der Mei, F. W.; Hoveyda, A. H. *Nat. Chem.* **2016**, *8*, 768. (b) van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4701. (c) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216.
(100) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16.
(101) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.
(102) Alam, R.; Diner, C.; Jonker, S.; Eriksson, L.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 14417.
(103) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704.
(104) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150.
(105) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368.
(106) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152.
(107) Farmer, J. L.; Hunter, H. N.; Organ, M. G. *J. Am. Chem. Soc.* **2012**, *134*, 17470.
(108) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642.
(109) Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. *Chem. Commun.* **2012**, *48*, 1230.
(110) Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L. Y.; Aggarwal, V. K.; Crudden, C. M. *Chem. - Eur. J.* **2013**, *19*, 17698.
(111) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352*, 329.
(112) Potter, B.; Edelstein, E. K.; Morken, J. P. *Org. Lett.* **2016**, *18*, 3286.
(113) Ding, J.; Rybak, T.; Hall, D. G. *Nat. Commun.* **2014**, *5*, 5474.
(114) Rybak, T.; Hall, D. G. *Org. Lett.* **2015**, *17*, 4156.
(115) (a) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092. (b) Ardolino, M. J.; Morken, J. P. *Tetrahedron* **2015**, *71*, 6409. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778. (d) Le, H.; Kyne, R. E.; Brozek, L. A.; Morken, J. P. *Org. Lett.* **2013**, *15*, 1432. (e) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686. (f) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716.
(116) Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, *120*, 8527.
(117) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. - Eur. J.* **2002**, *8*, 3620.
(118) Ferrer Flegeau, E.; Schneider, U.; Kobayashi, S. *Chem. - Eur. J.* **2009**, *15*, 12247.
(119) Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 10816.
(120) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.
(121) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566.
(122) Das, A.; Wang, D.; Belhomme, M.-C.; Szabó, K. J. *Org. Lett.* **2015**, *17*, 4754.
(123) Mondal, S.; Nechab, M.; Campolo, D.; Vanthuyne, N.; Bertrand, M. P. *Adv. Synth. Catal.* **2012**, *354*, 1987.
(124) Belhomme, M.-C.; Wang, D.; Szabó, K. J. *Org. Lett.* **2016**, *18*, 2503.
(125) Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J. *J. Am. Chem. Soc.* **2014**, *136*, 7563.
(126) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682.

DOI: 10.1021/jacs.6b10017
J. Am. Chem. Soc. 2017, 139, 2–14