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Functional group directed C–H borylation†

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The direct borylation of hydrocarbons *via* C–H activation has reached an impressive level of sophistication and efficiency, emerging as a fundamental tool in synthesis because of the versatility offered by organoboron compounds. As a remarkable particularity, the catalytic systems originally developed for these reactions are relatively insensitive to directing effects, and the regioselectivity of the borylations is typically governed by steric factors. Likely stimulated by the great synthetic potential of the expected functionalised organoboranes, however, many groups have recently focused on the development of complementary strategies for *directed*, site-selective borylation reactions where a directing group controls the course of the reaction. In this tutorial review, the different strategies and findings related to the development of these directed borylation reactions *via* C(sp^2)–H or C(sp^3)–H activation will be summarized and discussed.

Key learning points
(1) Transition-metal catalysis
(2) C–H bond activation
(3) Directing groups
(4) Ligand design
(5) Atom economy

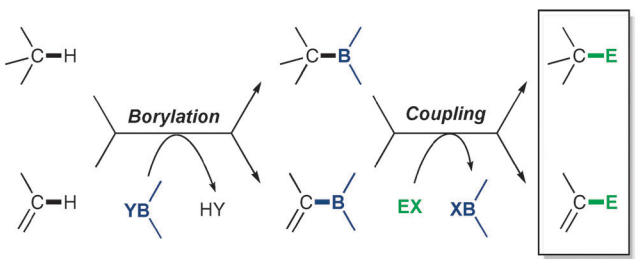
1. Introduction

Direct CH activation/functionalization of hydrocarbons has evolved as one of the most fundamental tools in modern synthetic chemistry, because it enables atom-economic, straightforward routes to achieve functionalised value-added products and intermediates. One of the most efficient reactions in this field is the direct borylation of hydrocarbons including arenes, alkenes and alkanes, which, in combination with cross-coupling methodologies, represents a powerful methodology for the functionalization of raw materials (Scheme 1).[1]

Until recently, the regioselectivity in most of the catalytic processes developed for the borylation of alkanes and arenes was mainly governed by steric factors,[2] and this circumstance has been exploited by using the direct borylation as a complementary tool to the well established directed *ortho* metalation (DoM) methodologies.[3]

It is clear, however, that much of the interest in the direct borylation of hydrocarbons relies on the advantages that organoboron compounds offer over more basic (or more toxic) aryl/alkyl metals, not only because of their higher versatility in cross-coupling applications, but also because of the specific transformations developed for organoboranes, including oxidation, halogenation, amination, etherification (known as the Chan–Lam–Evans[4] reaction), *etc.*[5] In fact, the synthesis of borylated products has been accomplished in an indirect way *via* a directed metalation/borylation (transmetalation) sequence.[6]

As a consequence, the development of site-selective directed borylations (Scheme 2) provides a very attractive alternative to the directed *ortho* metalation (DoM) methodologies, not in terms of complementarity but because of the distinct synthetic potential



Scheme 1 Functionalization of hydrocarbons *via* direct borylation/cross-coupling strategies.

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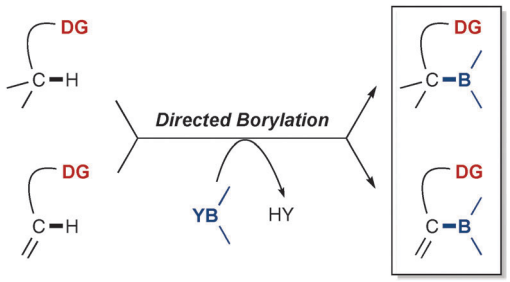
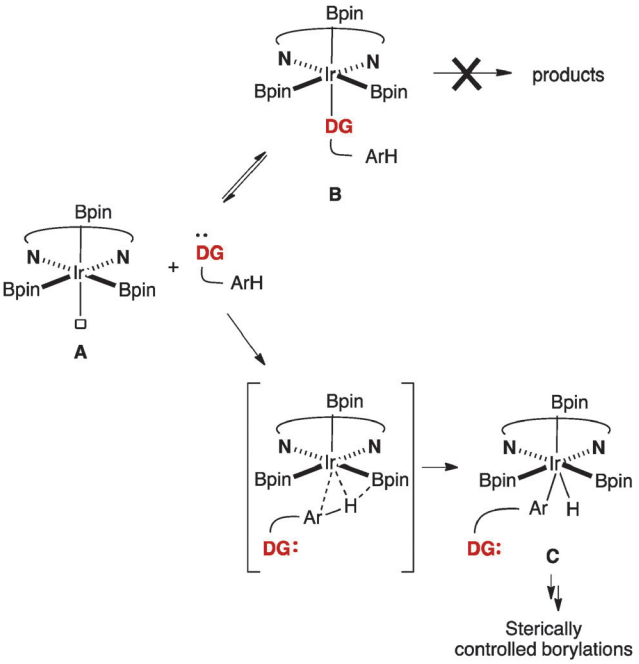
† Dedicated to Professor Ernesto Carmona on the occasion of his 65th birthday.



Scheme 2 Functionalization of hydrocarbons *via* direct borylation/cross-coupling strategies.

(much broader functional group compatibility, tolerance to oxygen, protic media, *etc.*) of organoboranes. An additional advantage of these methods is that cryogenic cooling can be avoided, eventually reducing energy costs in large scale reactions. Consequently, the development of methods and strategies toward this goal has received considerable attention in the last few years. The aim of this review is to offer an overview of the recent advances in this field. Indirect approaches based on transmetalation of boron will not be discussed herein.



Scheme 3 Analysis of regioselectivity in Ir-catalysed borylations.

2. Directed borylations *via* C(sp^2)–H activation

As is the case in many other catalytic C–H functionalizations, the directed borylation *via* C–H activation was first developed in

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R. Fernández

Rosario Fernández studied chemistry at the University of Seville and received both her BS degree (1980) and her PhD degree (1985) under the supervision of Prof. Antonio Gómez Sánchez. She was a NATO postdoctoral fellow at the University of Paris-Sud (Orsay, France) in the laboratory of Prof. Serge David from 1986 to 1987. In 1987 she returned to the University of Seville, where she was promoted to Associate Professor. In 2008 she became a Full Prof. at the same University. Her current research interests include asymmetric synthesis and enantioselective catalysis, in both aspects, asymmetric metal catalysis and organocatalysis.

J. M. Lassaletta

José María Lassaletta received his BS and his PhD in 1990 under the supervision of Prof. Gómez-Guillén at the University of Seville. After a postdoctoral stage in the 'Instituto de la Grasa y sus Derivados' (CSIC, Seville) he joined the group of Professor Richard R. Schmidt (U. Konstanz, Germany). In 1995 he moved to the Instituto de Investigaciones Químicas (CSIC, Seville), where he was promoted to Tenured Scientist in 1996, Research Scientist in 2005 and Research Professor in 2009. He is currently interested in the development of synthetic methodologies, cross-coupling and C–H activation strategies, and ligand design, with emphasis on hydrazones and N-heterocyclic carbenes, and asymmetric organocatalysis.

arenes and heteroarenes. The different approaches have been classified by the transition metal used.

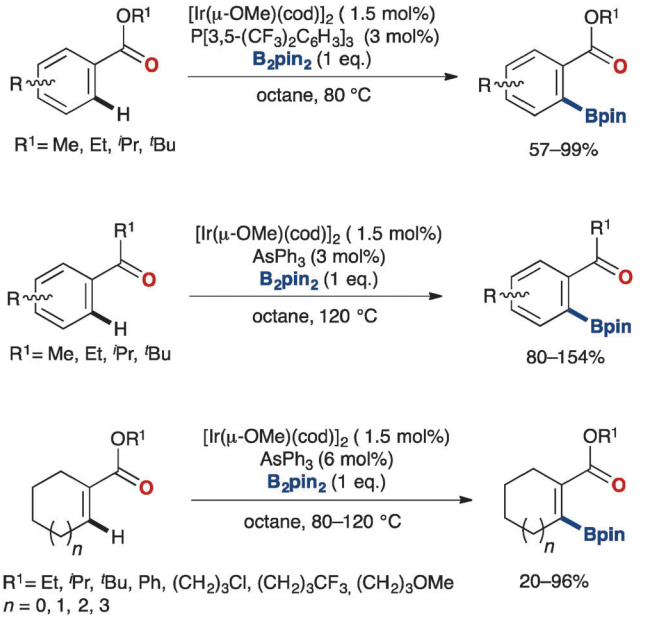
2.1. Ir-catalysed borylations

It has been demonstrated that direct borylation catalysed by the 1 : 2 $[Ir(\mu\text{-}X)(cod)]_2$/dtbpy (X = Cl, OMe) system takes place through a $[Ir(dtbpy)(Bpin)_3]$ $16e^-$ catalytically active species **A**.[7,8] The lack of sensitivity of this process towards any directing effects by basic functionalities in the substrate can be arguably attributed to the lack of additional vacant coordination sites in the complex **B** formed upon coordination of directing functionalities. In this scenario, the reaction can only proceed *via* intermediate **C**, and steric factors represent the main contribution to regioselectivity (Scheme 3).

In order to enable directing group effects in these reactions, different strategies based on catalyst or substrate modification have been recently developed, affording attractive site-selective borylation methodologies for the synthesis of *ortho*-substituted arylboronic esters and related borylated compounds. Three types of approaches have been designed, with strategies comprising:

2.1.1. Chelate-directed borylations. The first strategy consists of the development of borylation procedures enabled by initial coordination of a basic functionality (the more classical type of directing groups) to the Ir catalyst. In this case, modification of the ligand is the key to facilitate the generation of an additional vacant coordination site in the catalyst–substrate complex. Ishiyama, Miyaura *et al.* developed a catalytic system based on the use of $[Ir(\mu\text{-}OMe)(cod)]_2$ as the iridium source, and an electron-poor phosphine such as $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ as the ligand, which was able to catalyse the site-selective borylation of several substrates containing oxygen-based directing groups. This method was first applied to the *ortho*-regioselective borylation of benzoates (Scheme 4).[9] Using B_2pin_2 as the reagent, these reactions take place in octane at 80 °C for 16 h, leading to the corresponding products in high yields and with complete regioselectivity, although a considerable excess of arene (5 eq.) is needed to avoid partial *ortho,ortho′*-diborylations. The reactions tolerate the use of methyl, ethyl, isopropyl and *tert*-butyl esters as directing groups, while being suitable for substrates possessing electron-donating or electron-withdrawing functional groups. The methodology has also been extended to the borylation of aryl ketones such as acetophenone, but a modest 56% yield of the *ortho*-borylated product was attained in this case.[10] The substitution of the phosphine ligand by $AsPh_3$, however, increases the catalyst activity, so yields higher than 100% based on the B_2pin_2 reagent were observed.‡ The reactions take place at 120 °C for 16 h, with a broad family of ketones containing different functional groups, to give the corresponding *ortho*-borylated products in high GC yields. A drop in the yield of *ca.* 50% was observed after bulb-to-bulb distillation. The catalytic system 2 : 1 $AsPh_3$–$[Ir(\mu\text{-}OMe)(cod)]_2$ also works for the borylation

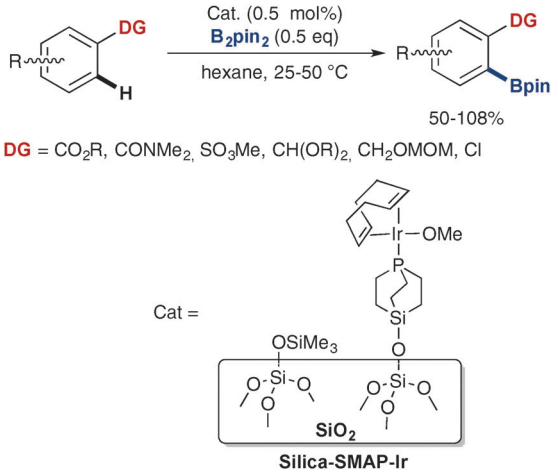
‡ Yields higher than 100% are calculated on B_2pin_2 (limiting reagent) and indicate that the catalyst can also use the HBpin generated in the initial reaction as a boron source after all the B_2pin_2 is consumed.



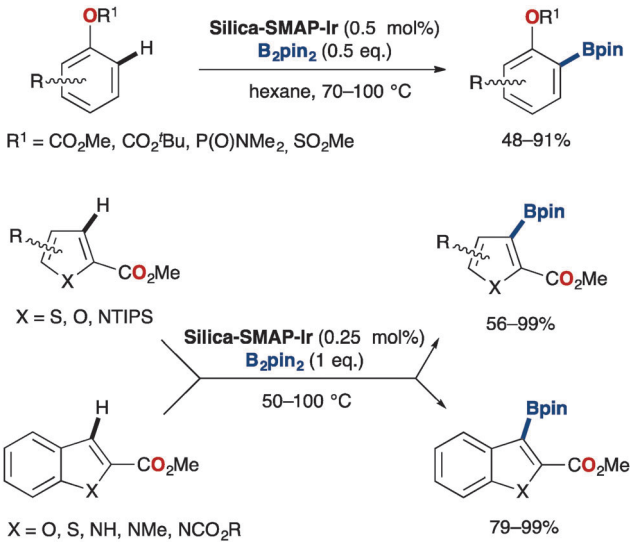
Scheme 4 Oxygen-directed Ir-catalysed borylations.

of C–H bonds of non-aromatic systems such as the vinylic β position of α,β-unsaturated esters.[11] Thus, 1-cycloalkenecarboxylates can be borylated at the sp^2 carbon with total regioselectivity affording the corresponding borylated products in moderate to excellent 20–96% yields. This borylation reaction is compatible with the presence of different groups in the ester moiety. It is noteworthy that the phenyl group, which should be borylated under the Ir-catalysed borylation conditions, remains unmodified after the reaction.

A different approach toward directed, site-selective borylations was recently reported by Sawamura *et al.*[12] In this case, a solid-supported monophosphine–Ir system, Silica-SMAP–Ir, was used as a suitable catalyst for the directed *ortho*-borylation of functionalised arenes in a very efficient manner. This reaction is successful with a range of functionalised arenes with different oxygenated directing groups, such as benzoates, benzamides, arylsulfonates, benzyl acetals, benzyl methoxymethylethers, leading to the corresponding borylated products with complete *ortho*-regioselectivity and good to excellent yields (based on B_2pin_2 using a 2 : 1 substrate-B_2pin_2 ratio) in most cases (Scheme 5). It is noteworthy that even the chlorine atom of aryl chlorides can behave as a directing group, though the *ortho*/*para* selectivity (92 : 8 for the unsubstituted chlorobenzene) is not perfect in this case. Immobilization of the phosphine ligand in the silica support proved to be essential, as the analogue borylation performed in homogeneous media using $[Ir(\mu\text{-}OMe)(cod)]_2$ and monomeric Ph-SMAP (0.5 mol% Ir, 1 : 1 or 1 : 2 Ir/P) afforded only trace conversion at 25 °C. No reaction was observed with other phosphines such as 4-CF_3-Ph-SMAP, PPh_3, $P(tBu)_3$, PCy_3, and PMe_3 (using 1 : 1 or 1 : 2 Ir/P ratios) under the same reaction conditions. Presumably, the supported catalyst assists the formation of 14-electron intermediates necessary for the successive coordination/CH activation of the substrate. Unfortunately, this heterogeneous catalyst cannot be recovered for recycling.



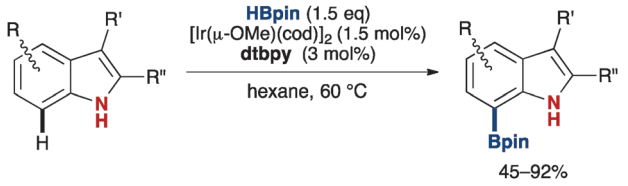
Scheme 5 Oxygen-directed borylations with Ir-supported catalysts.



Scheme 6 Oxygen-directed borylations with Ir-supported catalysts.

This methodology was further extended to phenol derivatives bearing oxygenated protecting/directing groups such as carbamates, carbonates, phosphorodiamides and sulfonates[13] (Scheme 6). All these groups provide complete *ortho*-regioselectivity in the borylation reaction with B_2pin_2, but moderate to good yields are achieved only with carbamates. Finally, the method has also been applied for the site-selective borylation of heteroarenes including thiophene, pyrrole, furan, benzothiophene, benzofuran, and indole derivatives, using in all cases the 2-methoxycarbonyl directing group. In the case of thiophenes and furans, however, minor amounts of regioisomers resulting from the borylation at position 5 were also observed.[14]

With the exception of carbazole, borylation takes place in the heterocycle at the vicinal position to the directing group. Interestingly, in the case of 2-methoxycarbonylindoles, the borylation at position 3 provides a complementary regioselectivity to the previously reported method[15] where the borylation takes place at the 7-position (*vide infra*).



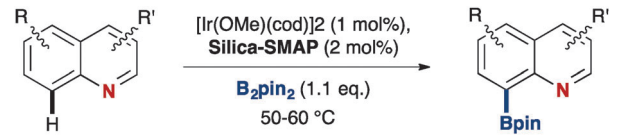
Scheme 7 Selective borylation of 2-substituted indoles.

The methodologies described above provide satisfactory solutions for the directed borylation of a wide range of arenes, heteroarenes and alkenes, but are limited to oxygenated directing groups, and do not work when nitrogen-based directing groups are used. An early report by Maleczka, Smith and co-workers on the borylation of 2-substituted indoles, appears to be an exception.[15] Using the $[Ir(\mu\text{-OMe})(cod)]_2$/dtbpy catalytic system, these compounds yield selective borylation at the 7-position, which, as mentioned above, is complementary to the selectivity achieved with silica-supported SMAP–Ir.[14] Although the mechanism remains unclear, control experiments and labelling studies performed so far support a mechanism where *N*-chelation to the iridium center (or the boron atom of a boryl ligand) directs the borylation (Scheme 7). The observed selectivity is also consistent with an alternative mechanism involving H-bonding of the NH proton to an O atom of the boryl ligands in the catalyst (*vide infra*), but a similar regioselectivity observed for benzofuran suggests that such an interaction is not a requisite.

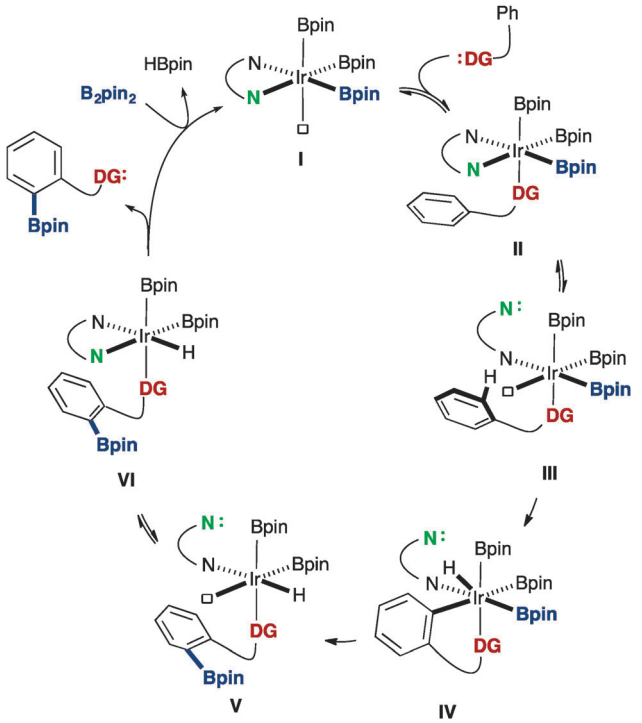
As a second exception, Steel, Marder, Sawamura and co-workers have recently reported on the C(8)-selective borylation of quinolines using the previously mentioned Silica-SMAP–Ir system (Scheme 8).[16]

The development of a more general approach for the nitrogen-directed Ir-catalyzed arene *ortho*-borylations was recently reported by us.[17] We envisaged that replacement of the dtbpy ligand in complex **B** (Scheme 2) by a hemilabile *N*,*N* ligand should facilitate the temporary generation of a coordinatively unsaturated intermediate **III** from the established catalytic species **I** *via* complex **II**. This complex **III** is preorganized for the intramolecular activation of C(*ortho*)–H bonds (→**IV**), from which reductive elimination (→**V**) and re-coordination of the hemilabile ligand (→**VI**) lead to the product and regenerate the catalyst **I** after reaction with B_2pin_2 (Scheme 9).

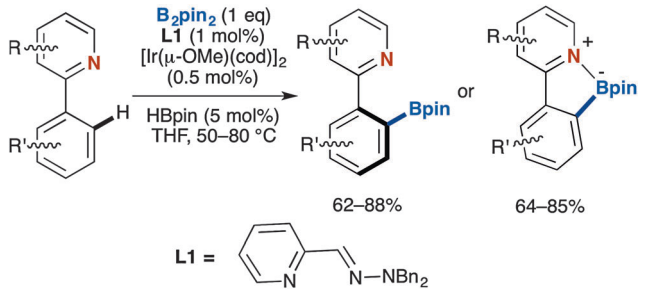
In particular, picolinaldehyde *N*,*N*-dibenzylhydrazone **L1** combined with $[Ir(\mu\text{-OMe})(cod)]_2$ proved to be a very efficient ligand for the borylation of 1-naphthylisoquinolines and 2-arylpyridines with B_2pin_2 under mild conditions. Two types of products were observed, depending on the steric hindrance around the biaryl axis. Thus, X-ray diffraction and NMR data for hindered products revealed no internal N–B interactions, and



Scheme 8 Selective borylation of quinolines.



Scheme 9 Envisaged mechanism using hemilabile *N,N*-ligands.



Scheme 10 Directed borylation of arylpyridines/isoquinolines.

the (hetero)aromatic rings arrange in a perpendicular fashion. On the other hand, less hindered products present intramolecular N–B bonds in planar structures (Scheme 10).

This methodology has been applied to the preparation of BAI (borylated aryl isoquinolines) dyes as a new class of fluorophores with potential as ion-triggered molecular switches (Fig. 1).[18] After introduction of an additional 4-methylpiperazin-1-yl group, these compounds also appear as interesting platforms for the design of multi-level logic switches as a consequence of the observed *off–on–off* ternary and quaternary responses to orthogonal protonation.[19]

The reaction has also been extended to the site-selective *ortho*-borylation of aromatic *N,N*-dimethylhydrazones (Scheme 11, method **A**).[17] The reaction proceeds efficiently for derivatives carrying electron-withdrawing or donating substituents at any position of the aromatic ring, and allowed clean monoborylations of C-6 unsubstituted substrates. In order to increase the activity of the catalyst, the original picoline dibenzylhydrazone ligand **L1** was

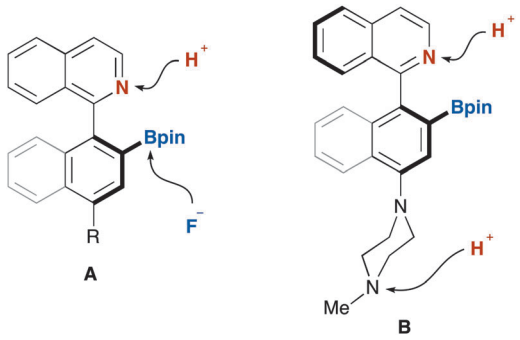


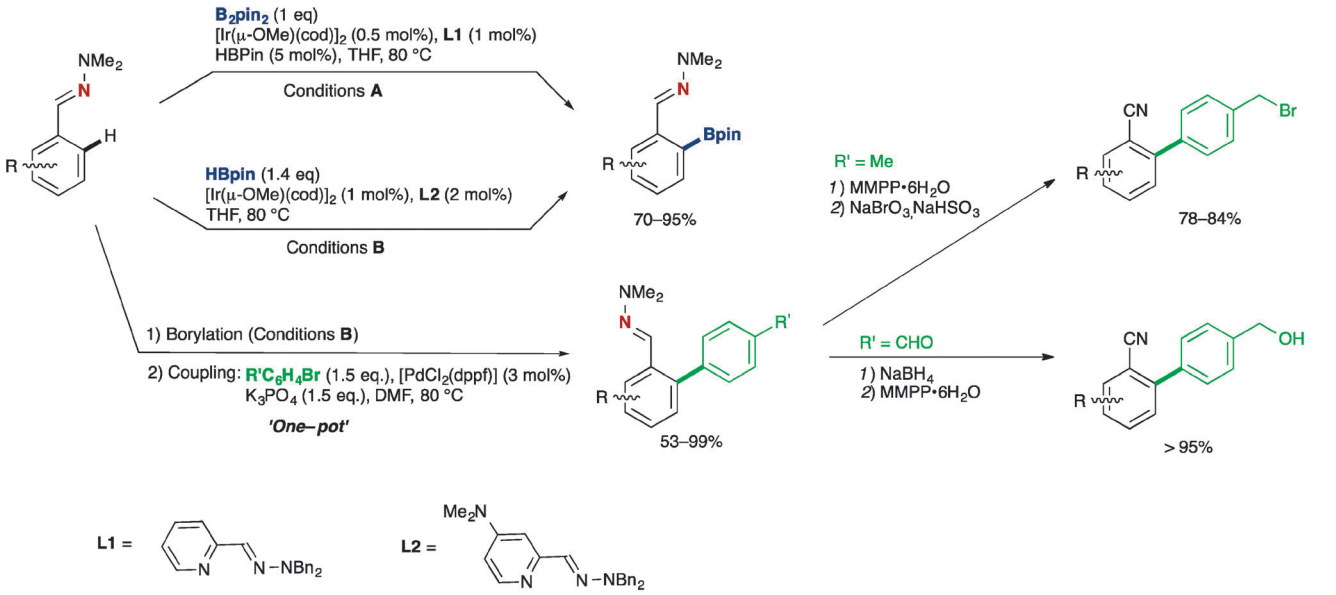
Fig. 1 Borylated aryl isoquinoline (BAI) dyes.

modified by the introduction of electron-donating groups (NMe_2, ^{t}Bu) at the 4-position of the pyridine ring. The use of the best DMAP/hydrazone ligand **L2** allowed using cheaper and more 'atom-economic' HBpin as the boron source in the same site-selective borylations (method **B**).[20] The reaction crudes can be used in Suzuki–Miyaura couplings without any further purification, and the resulting biphenyl derivatives can be transformed into valuable intermediates for the synthesis of modified Sartan-type drugs upon high yielding, 'one-pot' functional group transformations.

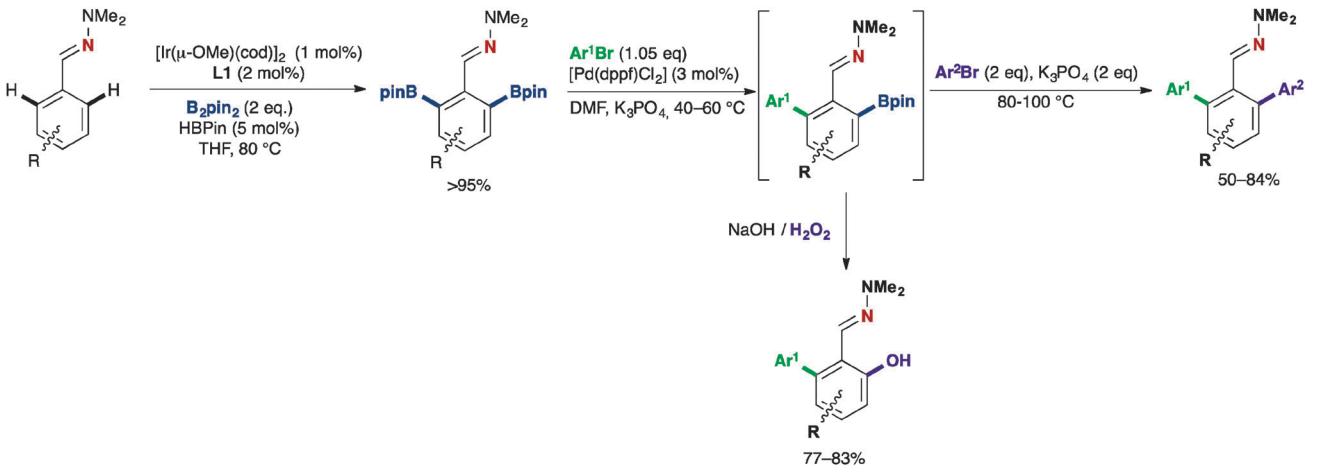
NMR and X-ray data for monoborylated *N,N*-dimethylhydrazones indicated the absence of N–B interactions in these products,[17,20] a fact that can be attributed to the significant NMe_2/Me(pinacol) steric repulsion. Therefore, the hydrazone N(sp^2) atom remains available to achieve a second directed borylation. Consequently, aromatic *N,N*-dimethylhydrazones can be *ortho,ortho′*-diborylated in nearly quantitative yields (Scheme 12).[21] These products proved to be useful synthetic intermediates that can be unsymmetrically functionalised by introduction of two different electrophiles.

In a related context, Clark *et al.*[22] have recently reported the nitrogen-directed *ortho*-C–H borylation of benzylic amines using the picolylamine ligand–[Ir(μ-OMe)(cod)]$_2$ (2 : 1) system as the catalyst (Scheme 13). The original idea was to use bifunctional ligands containing N–H bonds that could be used to direct C–H borylation through hydrogen bonding to the directing group (Lewis base) in the substrate, but during the study they observed that the *N,N*-dimethylated ligand (lacking N–H bonds) afforded the corresponding *ortho*-borylated product with equal regioselectivity and higher yield. In accordance with this result, the origin of the *ortho*-regioselectivity seems to lie in the hemilability of the ligand,[17] instead of a hydrogen bonding directing effect as it was originally proposed.

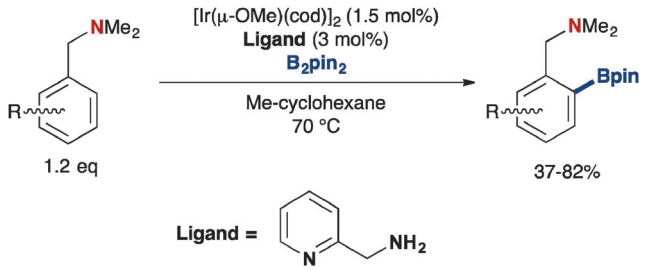
2.1.2. Relay-directed borylations. A second strategy developed by Hartwig and co-workers for the site-selective Ir(III)-catalysed borylation of arenes is based on the use of silanes as traceless directing groups (Scheme 14).[23] Using benzyl dimethylsilanes as substrates, it was envisaged that an initial Si–H/Ir–B σ-bond metathesis between the above mentioned catalytically active species **I** and the substrate would render a silyl bis-boryl Ir complex **II** in which the intramolecular activation of the *ortho* CH bonds takes place preferentially to afford intermediate **III** which after reductive elimination (→**IV**) and



Scheme 11 Directed borylation of aromatic *N*,*N*-dimethylhydrazones.



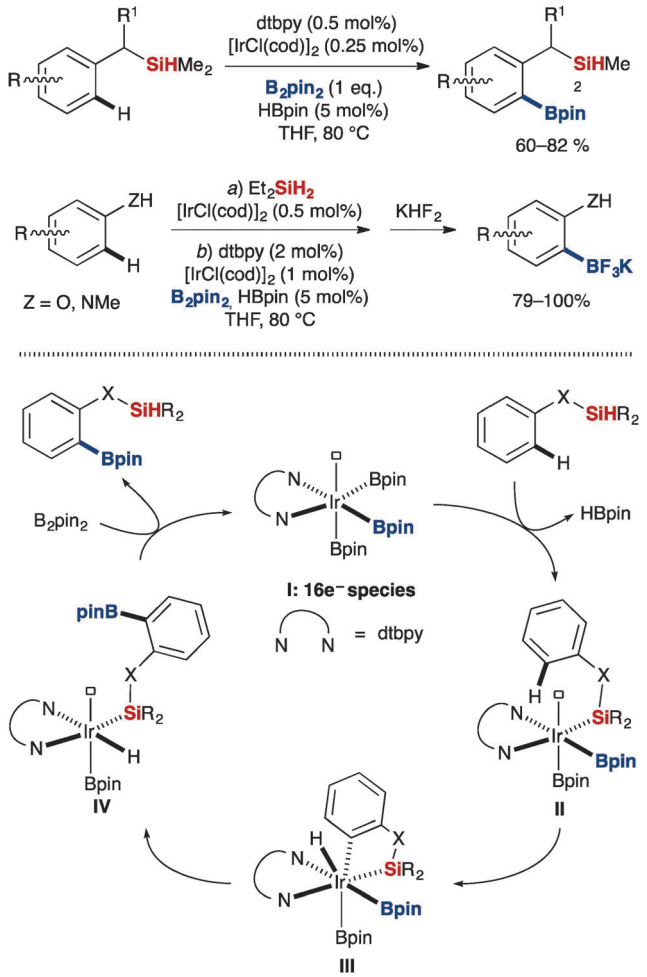
Scheme 12 Hydrazone-directed *ortho,ortho'*-diborylations and sequential disymmetric functionalizations.



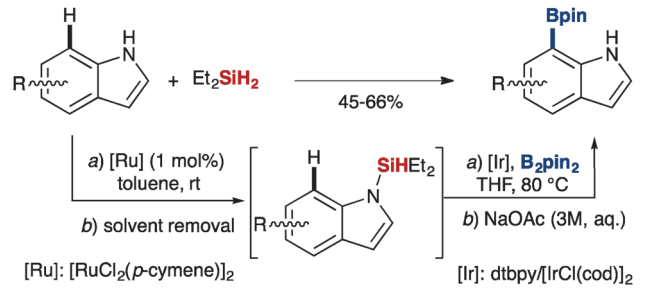
Scheme 13 Ir-catalysed C–H borylation of benzylic amines.

reaction with B_2pin_2 releases the product and regenerates the catalyst. Under optimized conditions, this procedure affords the corresponding *ortho*-borylated products in good to excellent yields; the formation of small amounts of *ortho,ortho'*-diborylated arylboronic esters is observed in some cases. Although benzylsilanes can be easily transformed into valuable intermediates, the methodology has been applied to more interesting substrates, such as silyl ethers and silylamines, formed *in situ* by iridium-catalysed silylation of the corresponding phenols and anilines. This '*one pot*' silylation–borylation procedure affords the corresponding boronic esters in good NMR or GC yields, but protodeborylation products are observed during purification by flash chromatography. Alternatively, the reaction crude mixtures can be treated with KHF_2 to afford *ortho*-trifluoroborylated aryl alcohols in 79–100% yield.

Silyl-directed borylations have also been applied to the regioselective borylation at the 7-position of indoles (Scheme 15)[24] which are borylated at the most reactive 2-position by direct borylation.[25] In contrast to the previously mentioned methods based on chelating effects,[14,15] this procedure tolerates the use of 2-unsubstituted substrates. The Ru-catalysed N-silylation followed by Ir-catalysed borylation affords the corresponding 7-borylated indoles with complete regioselectivity in moderate yields.

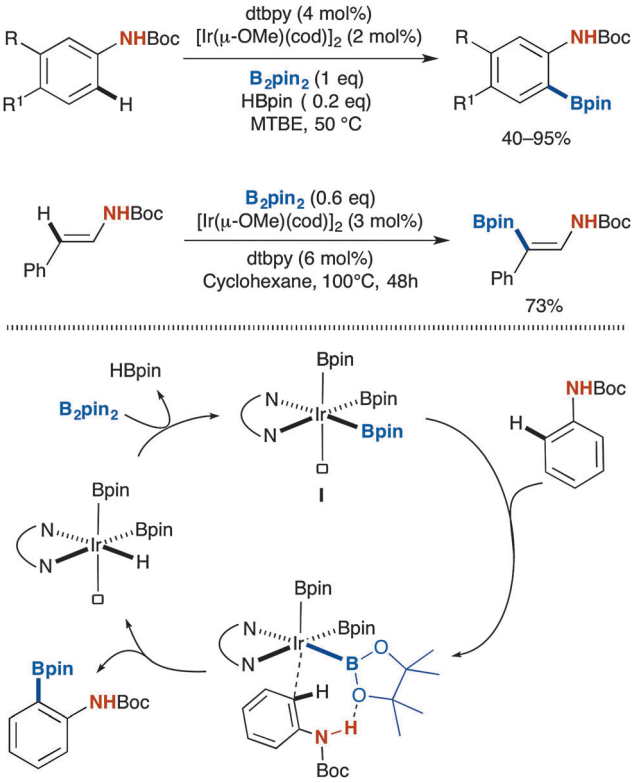


Scheme 14 Silicon-directed *ortho*-borylations of arenes and the proposed catalytic cycle.



Scheme 15 Silicon-directed borylations of indoles.

2.1.3. Outer sphere H-bond-directed borylations. Outer sphere direction is a concept that refers to the recognition of a functionality in the substrate by a ligand on the catalyst. Based on this idea, Smith, Maleczka, Singleton *et al.*[26] explored the directing effect of acidic NH groups in monoprotected anilines, finding out that Boc protecting groups provide a significant *ortho* selectivity in the borylations performed with B_2pin_2 as the reagent and the unmodified [Ir(μ-OMe)(cod)]$_2$–dtbpy catalytic system. Control experiments and computational studies support an *outer sphere* mechanism initiated by the

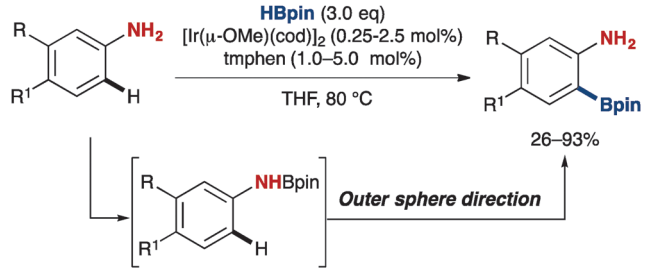


Scheme 16 Outer-sphere directed borylation of Boc-protected anilines and enamines.

formation of a (Boc)NH–O(Bpin) hydrogen bond between the NH group of the substrate and the basic oxygen atom of one of the catalyst boryl groups (Scheme 16).

The efficiency of the NH bond interaction increases with the basicity of the pinacolate oxygen atom in the catalytically active species **I**, which can be increased with more electron-rich dipyridyl ligands. Accordingly, an enhancement of the *ortho*-selectivity was observed when donating groups (NMe_2, OMe, *t*Bu) were installed in the 4,4′positions of the bipyridine ligands. This borylation reaction was shown to be compatible with the presence of different electron donating and electron withdrawing groups, but a complete *ortho*-regioselective C–H borylation was only observed in *para*-monosubstituted substrates. With *meta*-substituted derivatives, a mixture of borylated products at 5 and 6-positions was obtained. This methodology was also extended to the borylation of a Boc-protected enamine, which under similar conditions afforded the product borylated at the β-position in 73% yield and with complete regioselectivity.

The strategy failed for the *ortho*-selective borylation of free anilines, presumably due to the poor acidity of the free amino group. Very recently, however, it has been demonstrated by the same authors that Bpin can be used as a traceless directing group for the *ortho* borylation of a variety of anilines, using in this case 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) as the ligand and HBpin (2–3 equiv.) as the protecting group and the borylating reagent.[27] In these reactions, the NBpin directing group can be installed and removed *in situ*, and the products



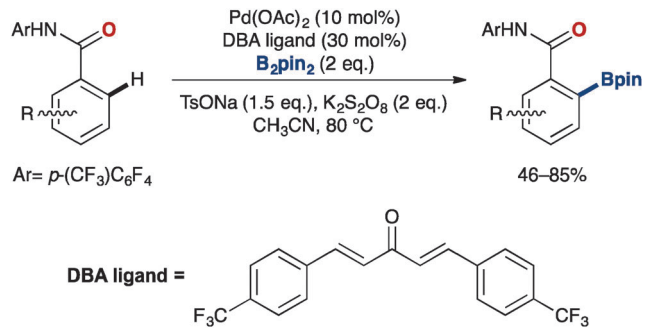
Scheme 17 Outer-sphere directed borylation of free anilines.

were isolated in better yields compared with those observed by using the NBoc protecting group. This is remarkable considering that a much lower catalyst loading (typically eight times lower) was used in these cases. As in the previous case, the reaction tolerates substitution by electron donating and electron-withdrawing groups, but the scope of the method is again limited to *para*-substituted substrates (Scheme 17).

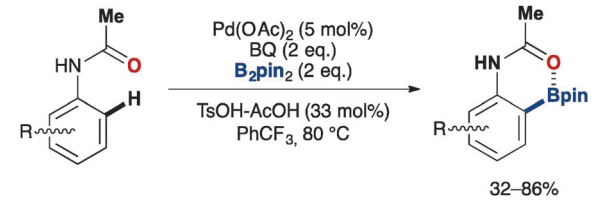
2.2. Pd-catalysed borylations

Palladium-based catalysts have not been extensively used in C–H borylation due to the fact that the obtained product (*i.e.* a boronic ester) is susceptible to decomposition *via* transmetalation with the Pd(II) species. Recently, however, Yu *et al.*[28] reported the Pd-catalysed oxidative borylation of *N*-arylbenzamides with a diboron reagent *via* a Pd(II)/Pd(0) manifold. Their strategy was based on the use of a weak base (*e.g.* TsONa) that can promote the transmetalation of the Bpin fragment from the B_2pin_2 to the metal center, without activating the generated aryl boronic ester. After an extensive screening of conditions, they found that the ideal catalytic system consists of 1 : 3 $Pd(OAc)_2$/dba as the catalyst, TsONa (1.5 eq.) as the base and $K_2S_2O_8$ (2 eq.) as the oxidant (Scheme 18). Under these conditions, a wide family of benzamides carrying the highly efficient auxiliary group –CONHAr [Ar = $(4\text{-}CF_3)C_6F_4$] have been regioselectively borylated to afford the *ortho*-borylated benzamides in 46–85% yield. The formation of small amounts (5–18%) of *ortho,ortho′*-diborylated products was observed in some cases. In addition, borylated benzamides can be efficiently transformed into interesting synthetic intermediates by hydroxylation, cyanation, amination and halogenation of the Bpin group.

A second example of Pd-catalysed directed *ortho*-borylation has been recently reported by Fu *et al.*[29] In this case, the



Scheme 18 Pd-catalysed oxidative *ortho*-C–H borylation of benzamides.

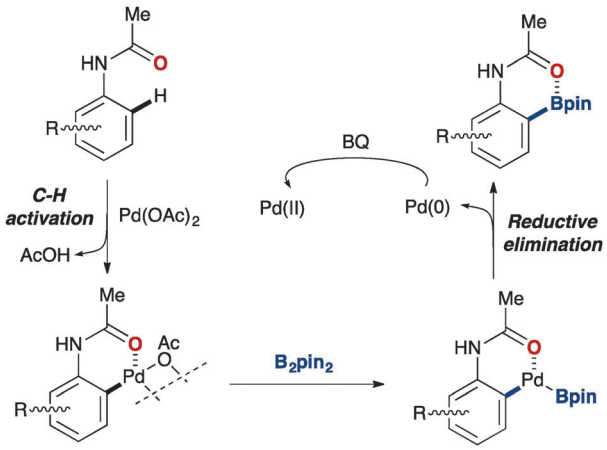


Scheme 19 Palladium-catalysed monoselective C–H borylation of acetanilides under acidic conditions.

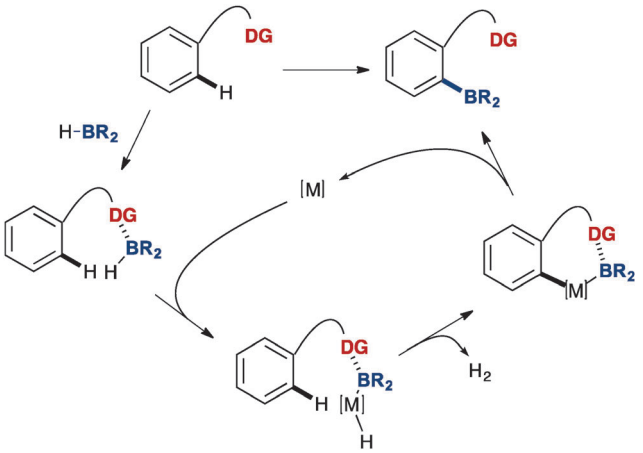
reaction is carried out under acidic conditions to avoid the decomposition of the borylated product. A complete regioselectivity for the *ortho*-borylation of acetanilides was achieved under mild conditions, employing $Pd(OAc)_2$ as the catalyst, benzoquinone as the oxidant and without the need of an inert atmosphere (Scheme 19). A wide family of acetanilides with donating and withdrawing groups were used to afford the *ortho*-borylated products in moderate to good yields. The boron fragment adopts a tetrahedral coordination due to the formation of an internal CO–B bond, which makes the acetyl directing group unavailable for further directed *ortho′*-borylation.

A substantial intermolecular isotopic effect was observed when the borylation reaction was performed using a stoichiometric amount of a palladacycle pre-generated from acetanilide. According to the collected data, a plausible mechanism (Scheme 20) was proposed involving the C–H activation by the Pd(II) center as the rate-determining step, followed by transmetalation of Bpin to Pd and formation of the product by reductive elimination. Finally, Pd(0) is re-oxidized to Pd(II) by BQ to close the catalytic cycle. A similar mechanism was proposed by Yu *et al.*,[28] but in this case a stronger oxidant ($K_2S_2O_8$) was used and an alternative catalytic cycle involving Pd(II)/Pd(IV) cannot be disregarded.

In the Pd-catalysed methodologies previously mentioned, as well as in the chelate-directed Ir-catalysed borylations, the directing group acts as a Lewis base, which coordinates to the metal centre thus driving the C–H bond (usually in the *ortho* position) to the proximity of the metal centre and therefore



Scheme 20 Proposed mechanism for Pd-catalysed C–H borylation.



Scheme 21 Lewis base–borane interaction strategy for directed *ortho*-borylation.

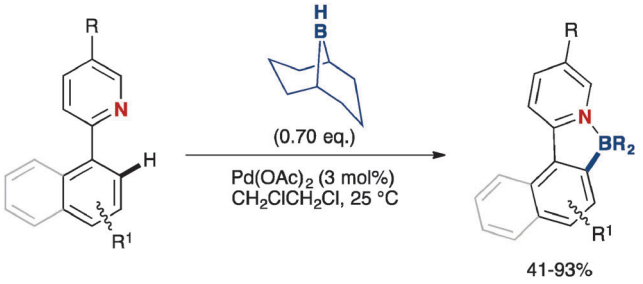
triggering the C–H activation. Kuninobu, Takai *et al.*[30] have very recently introduced a new strategy for the Pd-catalysed *ortho*-selective C–H borylation of 2-arylpyridines. In this case the electron pair of the directing group (Lewis base) is coordinated to a Lewis acidic boron reagent, which also bears a hydrogen atom. This interaction generates a species which is then activated by oxidative addition of a transition metal to the B–H bond. The reaction then proceeds from the resulting intermediate after successive oxidation by an external reagent and reductive elimination to afford the product and regenerate the catalyst (Scheme 21).

Initial experiments performed to explore the application of this new strategy failed when pinacolborane was used as the boron source, but use of a more Lewis acidic reagent such as 9-borabicyclo[3.3.1]nonane (9-BBN) in the presence of $Pd(OAc)_2$ as the catalyst allowed the selective borylation of a series of 2-arylpyridines under mild conditions (Scheme 22). Remarkably, directed borylation in the absence of catalysts also takes place for some substrates *via* a free-radical process at 135 °C, albeit in lower yields.

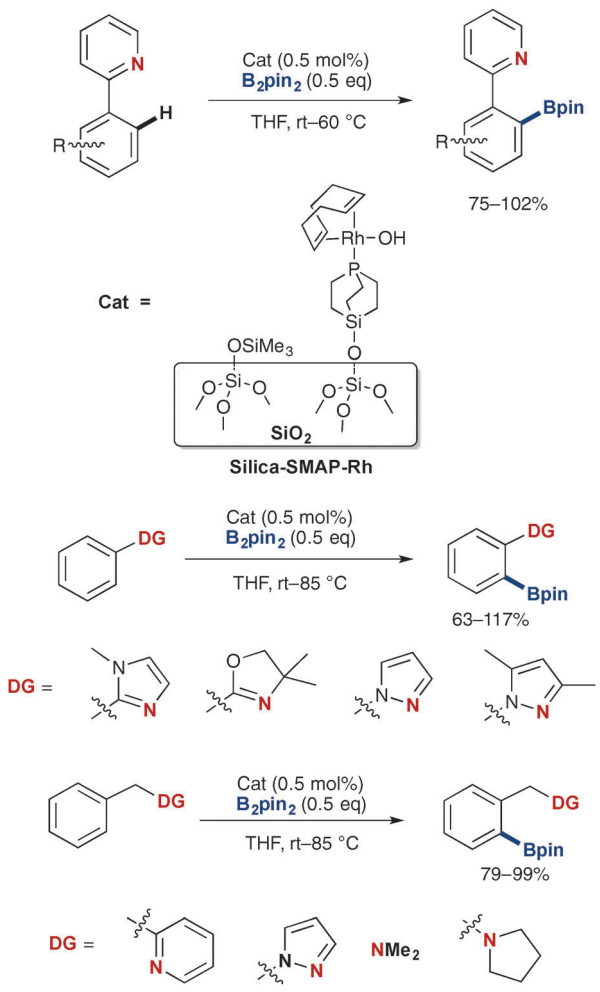
2.3. Rh-catalysed borylations

Rh-based catalysts have been typically used in the direct borylation of C–H bonds,[31,32] but their use has not been widely extended because harsh conditions are required compared with Ir–dtbpy systems. Recently, Sawamura *et al.*[33] described the first example of nitrogen directed C–H borylations that involve a silica-supported rhodium catalyst (P/Rh 1 : 1) containing their silica-SMAP supported phosphine as the ligand.[12] Different homogenous catalysts bearing phosphines or dtbpy as ligands were also tested, but no reaction or low conversions were observed. The silica-SMAP–Rh catalyst has allowed achievement of *ortho*-selective C–H borylations of a wide range of arenes containing different sp^2 nitrogen-based directing groups such as pyridine, imidazole, oxazoline and pyrazole, or sp^3 nitrogen-based directing groups such as NMe_2, pyrrolidine and 1,3-dimethyl-imidazolidine, affording the corresponding borylated products in 63–117% yields (Scheme 23). 0.5 equivalents of the borylating agent (B_2pin_2) are needed to avoid the formation of the 2,6-diborylated by-products, which are observed in 4–13% yield depending on the substrate.

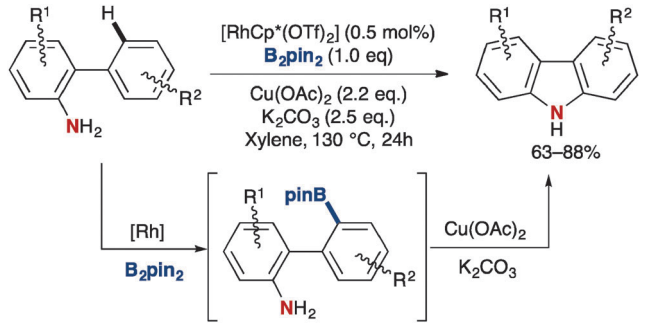
A second example of directed Rh-catalysed C–H borylation has been recently published, and it also involves a nitrogen-containing functionality as the directing group. In this case, Chen, Yan *et al.*[34] described a C–H borylation–amination procedure for the synthesis of N–H carbazoles employing a NH_2 group directed C–H borylation as the key reaction. The complex [RhCp*$(OTf)_2$] proved to be the most active catalyst for



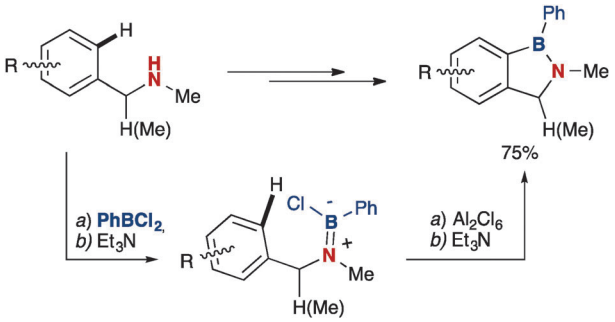
Scheme 22 Pd-catalysed C–H borylation of 2-arylpyridines.



Scheme 23 Rh-catalysed nitrogen directed *ortho*-C–H borylation.



Scheme 24 *'One pot'* borylation–amination procedure for the synthesis of carbazoles.



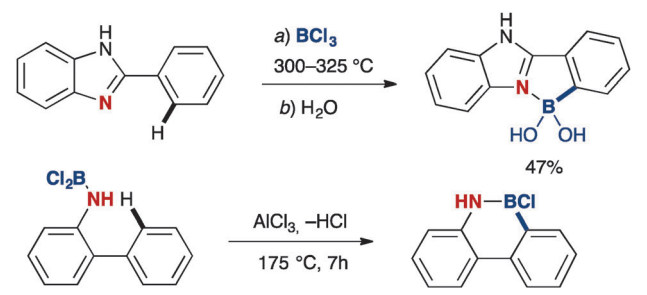
Scheme 26 Early examples of metal-free directed borylations.

the borylation step after a screening of several Rh- and Ir-based complexes, although low yields of borylated products were observed in all cases. The efficiency of the methodology could be improved when a $[Cu(OAc)_2]$ oxidant was used, although low conversions (*ca.* 30%) were still observed, likely due to the ability of the borylated product to trap the catalytic rhodium species. Taking these observations together and considering that $Cu(OAc)_2$ can play a dual role both as an oxidant to convert Rh(I) back to Rh(III), and as the catalyst for C–N bond formation, a *'one pot'* borylation–amination was developed, provided that K_2CO_3 is added as a required base for the coupling step (Scheme 24). Following this new methodology a broad family of NH carbazoles was obtained in good to excellent 63–88% yield.

2.4. Miscellaneous metal-free directed borylations

Borylation reactions can take place without any catalyst *via* electrophilic aromatic borylation, although harsh conditions and the presence of a strong Lewis acid are usually required. Early reports of the nitrogen-directed metal-free borylation of arenes can be found in the literature (Scheme 25).[35–37] Despite achieving very good levels of regioselectivity, however, harsh conditions were needed and the substrate scope was very limited.

In 2000, Nagy *et al.*[38] reported on the Lewis acid-catalysed intramolecular borylation of benzylaminochloroboranes for the synthesis of benzazaborole derivatives (Scheme 26). The authors found experimental evidence supporting an electrophilic substitution mechanism involving cationic complexes as reactive intermediates.

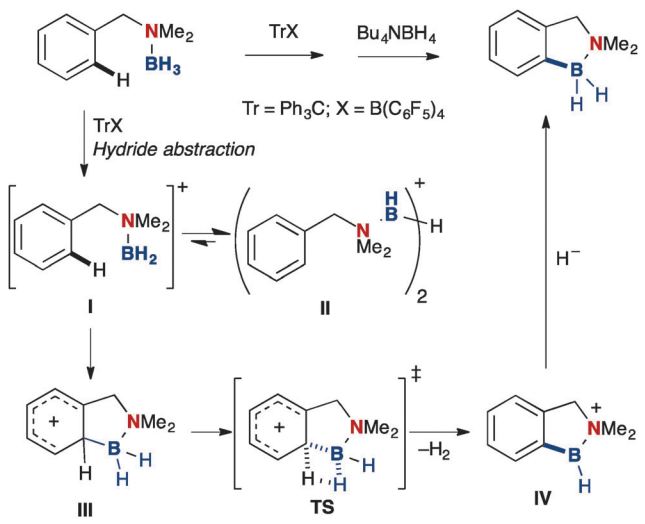


Scheme 25 Early examples of metal-free directed borylations.

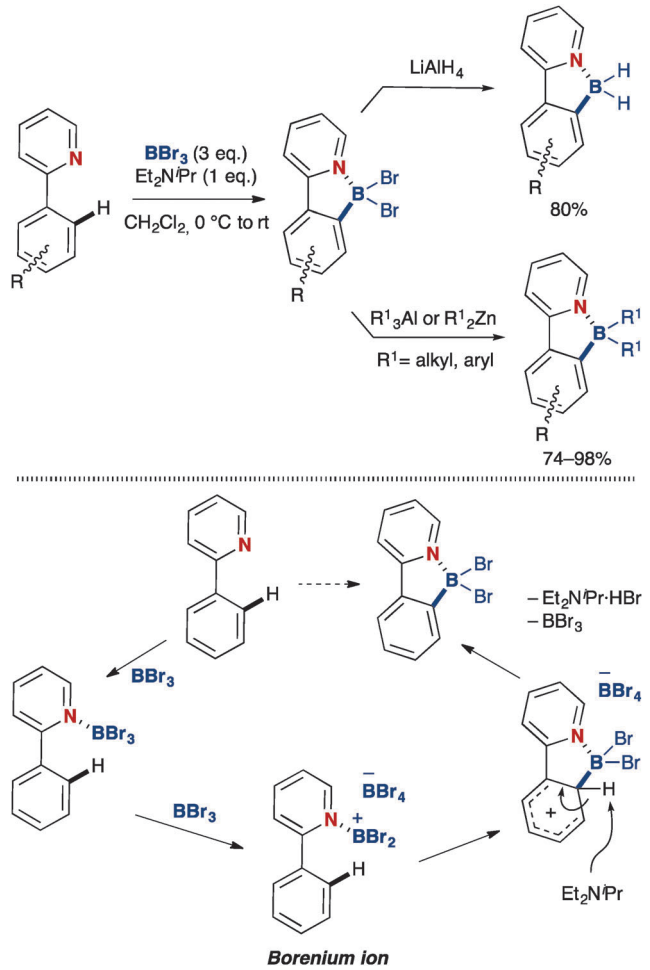
More recently, the mechanism of the nitrogen-directed aromatic borylation of tertiary benzyl amines has been studied in detail by Harvey, Vedejs and co-workers.[39] Treatment of the corresponding amine–borane complex with trityl salts affords borenium cations **I** which react with a second molecule of the starting complex to form hydrogen-bridged boron cations **II**, which behave as an *in situ* source of superelectrophilic borenium species. Computational studies indicate that the rate-determining step can be described as a C–H insertion at the stage of the intermediate borenium π-complex (not shown) or the corresponding Wheland intermediate **III** that is transformed into the stabilized ''bora-benzylic'' boron cation **IV** through a dehydrogenation step *via* transition state **TS** (Scheme 27). Very recently, it has been shown that this type of intramolecular borylation from amine-boranes can also be performed with catalytic amounts of Tf_2NH.[40]

Recently, Murakami *et al.*[41] described an optimized metal-free methodology for the borylation of 2-arylpyridines using BBr_3 (3 eq.) as the borylating agent and Et_2N^iPr (1 eq.) as the base. The borylation reactions take place at room temperature affording the *ortho*-BBr_2 products in high yields (Scheme 28).

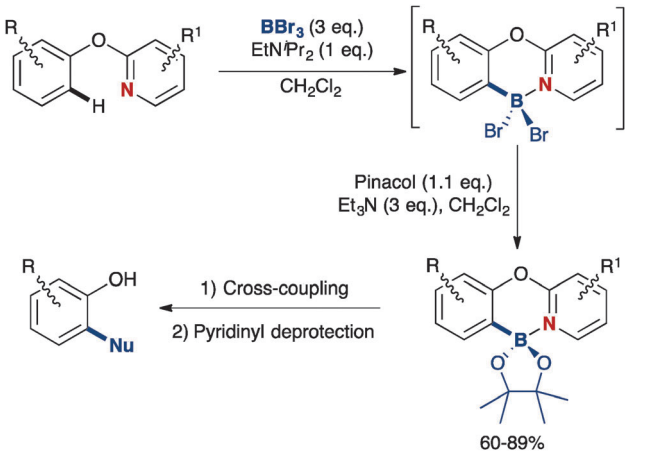
These pyridine–dibromoborane complexes can be easily transformed into pyridine-(dialkyl/diaryl)boranes by treatment with organoaluminum or organozinc reagents or reduced with



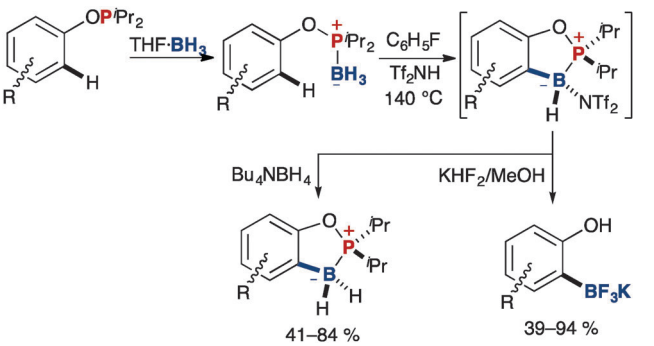
Scheme 27 N-directed borylation *via* borenium intermediates.



Scheme 28 Metal-free *ortho*-borylation of 2-arylpyridines.



Scheme 29 Metal-free pyridyl directed *ortho*-borylation.



Scheme 30 Metal-free phosphorous-directed *ortho*-borylation.

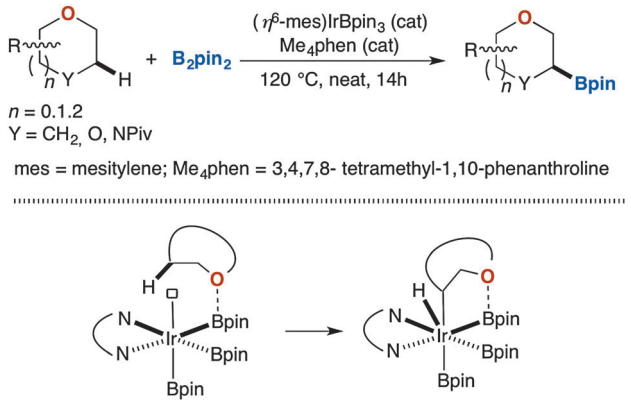
$LiAlH_4$ in Et_2O to afford the corresponding borohydride in 80% yield. Again, the formation of a borenium cation intermediate by attack of BBr_3 on the pyridine–BBr_3 adducts is proposed as the key step in the mechanism. The reaction then proceeds by attack of the cationic boron centre to the neighbouring aromatic ring, followed by rearomatization to furnish the product. An extension of this methodology has been applied to the *ortho*-borylation of phenols using the pyridine moiety as an easy removable directing group. Thus, Fu *et al.*[42] used these metal-free borylation conditions (3 eq. BBr_3/1 eq. EtN^iPr_2) for the borylation of 2-phenoxypyridines (Scheme 29). Additionally, a sequential two-step (borylation + esterification) process was developed to afford easily isolable boronic esters. Ensuing Suzuki cross-coupling or amination (Chan–Lam–Evans) of the boronic ester, followed by pyridyl group deprotection, afforded 2-functionalised phenols in moderate to good overall yields.

The use of tethered borenium cations as potential borylation intermediates has also been recently applied to the P-directed borylation of phenols. Vedejs *et al.*[43] have described a methodology for the synthesis of *ortho*-borylated phenols starting from phosphinite–borane adducts, followed by the treatment with a strong electrophile to abstract a hydride and generate the corresponding borenium cation (Scheme 30). After a screening of electrophiles and conditions, they found that the treatment of adducts with 90 mol% of Tf_2NH in fluorobenzene and heating at 140 °C for 16 h generate a borenium precursor which afforded the expected cyclic phosphinite–borane adducts or trifluoroborate salts by using NH_4BH_4 or KHF_2/MeOH respectively. Although this new methodology has a broad substrate scope, harsh conditions are required in comparison with the Hartwig protocol,[23] which afforded the trifluoroborate salts in higher yields.

3. Directed borylations *via* C(sp^3)–H activation

As in the case of non-directed borylations *via* CH activation, the directed borylation of C(sp^3)–H bonds proved to be a more challenging reaction. Very recently however, several remarkable contributions appeared in this field. In 2012, Hartwig *et al.*[44] reported on the development of an Iridium catalyst for the regioselective borylation of cyclic ethers, which takes places at the β position relative to oxygen (Scheme 31).

Isotope labelling techniques were used to disregard a mechanism *via* activation of the weaker C(α)–H bonds followed by isomerization. Thus the directed C(β)–H activation was proposed to take place through an outer sphere mechanism

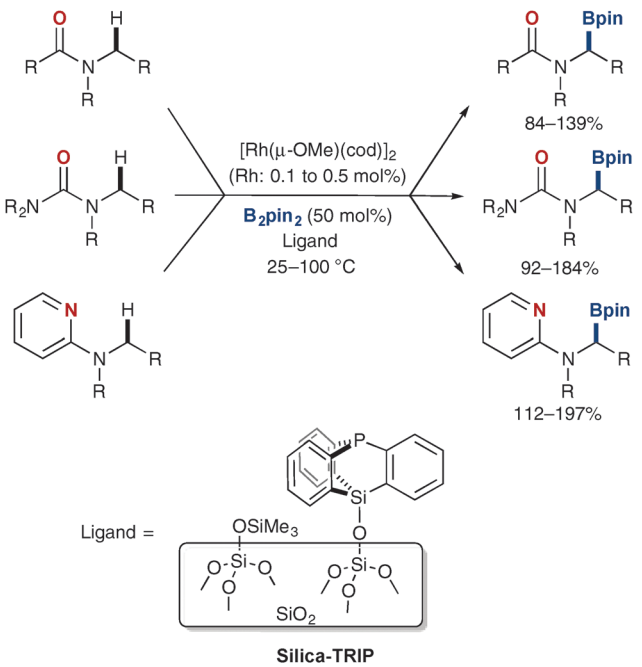


Scheme 31 Site selective β-borylation of cyclic ethers.

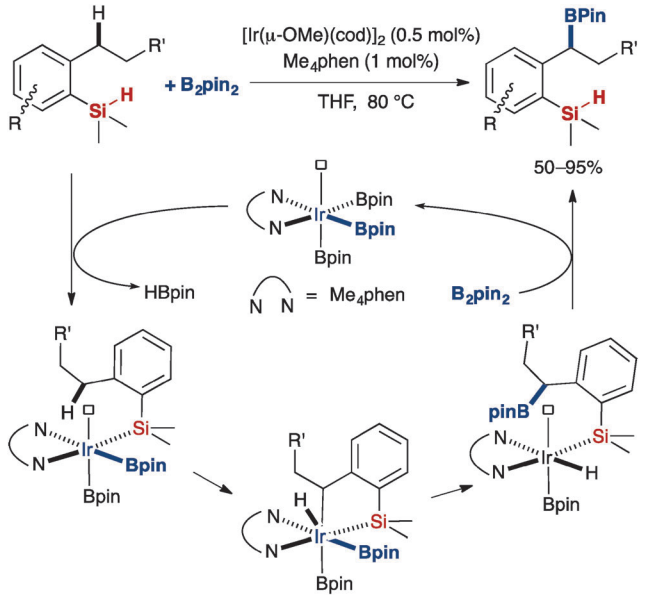
based on the precoordination of the basic oxygen atom to the Lewis–acidic boryl ligands of the catalyst, followed by activation of the nearest C(β)–H bond.

Simultaneously, Sawamura and co-workers reported on the Rh-catalyzed α-borylation of amides, ureas, and 2-aminopyridine derivatives. Using in this case the silica-supported triarylphosphine ligand (Silica-TRIP), the borylation proceeds selectively *via* activation of the C(sp^3)–H bonds adjacent to the N atom (representative examples shown in Scheme 32).[45]

The strategy developed by Hartwig for the silyl-directed borylation of arenes has also been extended to the site-selective monoborylation of secondary C(sp^3)–H benzylic bonds in 2-alkyl dimethylsilylarenes. Best results in this case were observed by using [Ir(μ-OMe)(cod)]$_2$ as the precatalyst and Me_4Phen as the ligand (Scheme 33).[46] As in the case of directed borylation of arenes, a boryl–silyl transligation (*via* Si–H/Ir–B bond metathesis) is proposed as the key step leading to a key



Scheme 32 α-Borylation of amides, ureas and 2-pyridylamines.



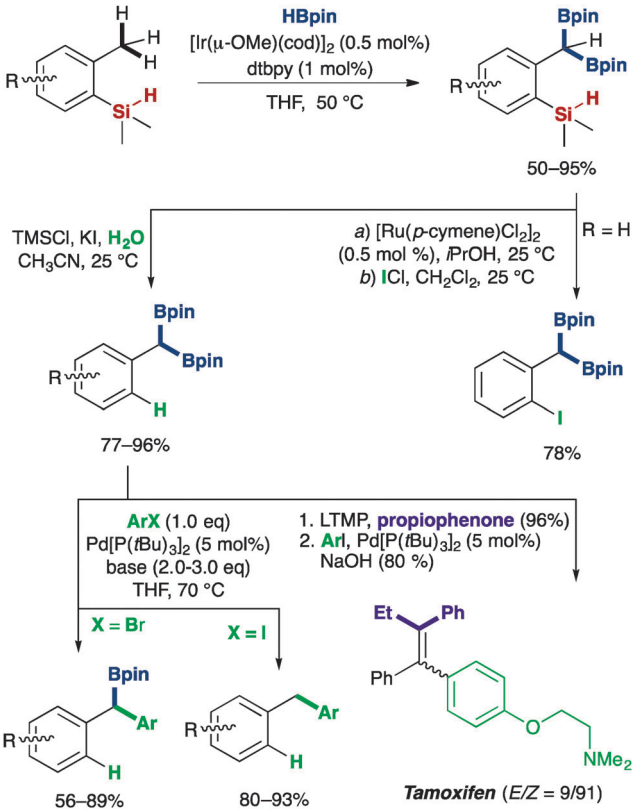
Scheme 33 Silyl-directed borylation of benzylic C(sp^3)–H bonds.

intermediate preorganized for the activation of the neighbour benzylic C–H bond.

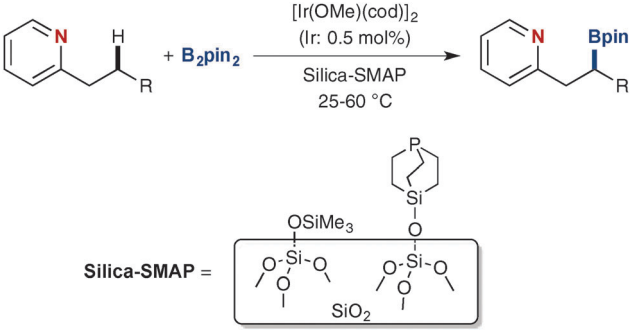
This methodology has also been applied to the diborylation of 2-methyl silylarenes.[47] In this case, the 'classic' [Ir(μ-OMe)(cod)]$_2$–dtbpy catalytic system and 2 equiv. of B_2pin_2 were used to perform the desired diborylation reactions under mild conditions (Scheme 34). The reaction tolerates a variety of functional groups and substitution patterns and the pretty stable 1,1-benzyldiboronate esters were obtained in good yields after purification by chromatography. The synthetic utility of these products was demonstrated by traceless removal of the dimethylhydrosilyl group, and also by its transformation into an aryl iodide using Ru catalysts. Moreover, the diborylmethyl group in the desilylated products was used in chemoselective Suzuki–Miyaura cross-coupling with several aryl bromides to yield the monoarylated products in good yields. Interestingly, the reaction conducted with aryl iodides and NaOH as the base gave diarylmethanes under the same reaction conditions. Finally, the unsubstituted diboronate was transformed into the tetrasubstituted alkenylboronates by treatment with 2,2,6,6-tetramethylpiperidide (LTMP) and reaction with the corresponding ketone. The products were formed with high (*E*) diastereoselectivity when the reaction was conducted at °C, and the propiophenone derivative was converted into (*Z*)-tamoxifen after a Suzuki–Miyaura cross-coupling with the corresponding aryl iodide.

Sawamura and co-workers also reported a nitrogen-directed borylation of 2-alkylpyridines, using in this case the more basic silica-supported trialkylphosphine silica-SMAP (Scheme 35). Under these conditions, the borylation occurs selectively at C–H bonds located γ to the pyridine nitrogen atom.[48]

The use of threefold cross-linked polystyrene–PPh_3 hybrids has also been exploited by Sawamura and co-workers for the Rh-catalysed N-adjacent C(sp^3)–H borylation of ureas and



Scheme 34 Ir-catalysed diborylation of 2-methyl silylarenes.

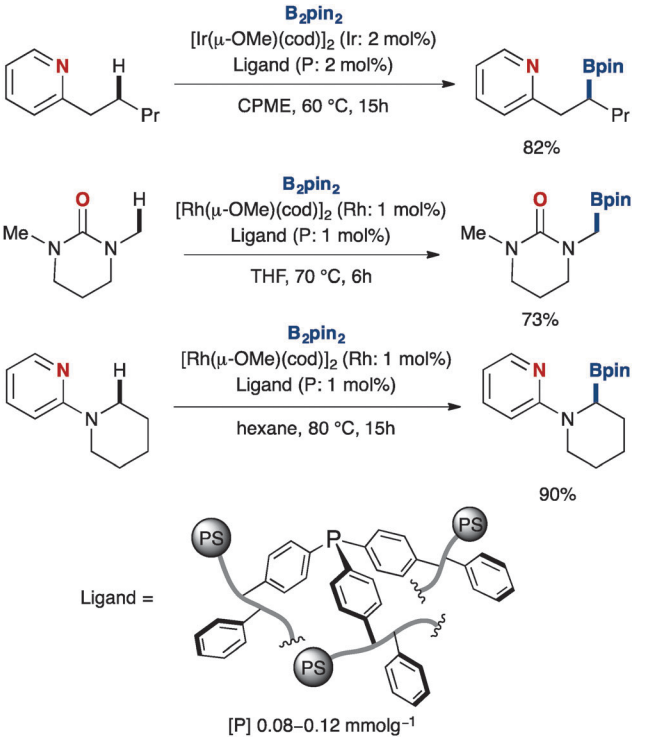


Scheme 35 Site-selective borylation of 2-alkylpyridines.

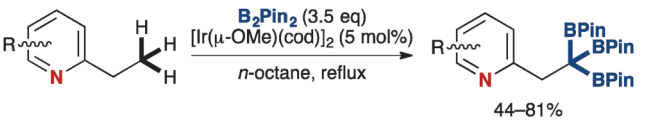
2-aminopyridines as well as for the Ir-catalysed N-directed borylation of 2-alkylpyridines (Scheme 36).[49]

According to the authors, the success achieved in these challenging reactions might be correlated with the mono-P-ligation and to the steric properties of the solid-supported ligand, presumably facilitating the generation of coordination vacancies required for the directing effect to operate.

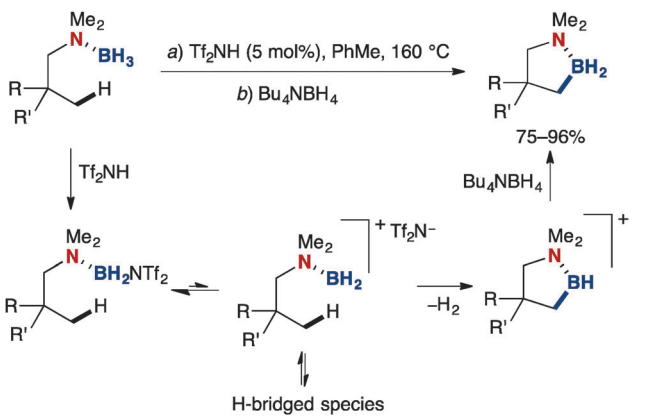
Very recently, Sato and co-workers reported that in the absence of the commonly employed *N*,*N*-ligands, the Ir-catalysed reaction of ethylpyridines and isoquinolines with a large excess of B_2pin_2 (3.5 equiv.) under forcing conditions ([Ir]: 10 mol%, octane, reflux) affords products resulting from triple borylation of the terminal C(sp^3)–H bonds. As a limitation, the reaction proceeds only in good yields for 6-unsubstituted, electron-rich pyridines (Scheme 37).[50]



Scheme 36 Site-selective borylations by catalysts supported on cross-linked polystyrene–PPh_3 hybrids.



Scheme 37 Ir-catalysed triborylation of ethyl pyridines.



Scheme 38 Catalytic electrophilic borylation of tertiary amine–borane complexes.

Finally, catalytic electrophilic C(sp^3)–H intramolecular borylation of tertiary amine–borane complexes has been described by Vedejs and co-workers.[40,51] Using Tf_2NH as the catalyst, the reaction proceeds at elevated temperatures (160 °C) to afford preferentially 5-membered cyclic products (Scheme 38). The proposed mechanism involves activation of the complex and

insertion of highly electrophilic borenium species, although the detailed mechanism is still to be elucidated.

4. Concluding remarks

In just a few years, the directed borylation of functionalised arenes, heteroarenes, alkenes and alkanes *via* C–H activation has emerged as a useful methodology, significantly expanding the potential that the well-established borylation of hydrocarbons had already demonstrated. In the case of directed borylation of arenes, these approaches compete directly with directed *ortho* metalation (DoM) methodologies, but are clearly more appealing for the milder conditions required in the metalation (borylation) procedure (absence of strongly basic conditions), and for the better functional group tolerance of organoboron reagents in further applications, particularly in cross-coupling chemistry but also in applications that exploit the specific reactivity of these compounds. Similar catalysts and strategies have also been developed for the site-selective mono- di- and triborylation of secondary and primary C(sp^3)–H bonds in a variety of derivatives. It is noteworthy that the examples reported to date include not only borylations of relatively weak C–H bonds (α to nitrogen and benzylic) but also borylations of more challenging secondary, unfunctionalised methylenes.

Challenges that remain to be faced in the future include the identification of catalytic systems based on cheaper metals, and the development of chiral catalysts for the asymmetric synthesis of borylated derivatives.

Acknowledgements

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