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Development of tandem C-H borylation/functionalization procedures for Late Stage Functionalization of Compounds

Tesi di laurea sperimentale

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1 Introduction

1.1 C-H bond activation

The vast majority of organic compounds and materials are derived from non renewable sources as natural gas or petroleum. The major constituents of these feedstocks are hydrocarbons. These molecules are constituted by strong and localized C-C and C-H bonds, so that the molecules have no empty orbitals of low energy or filled orbitals of high energy, that could readily participate in a chemical reaction. This feature is the reason of their chemical inertness and very few processes to convert hydrocarbons into more valuable compounds exist.

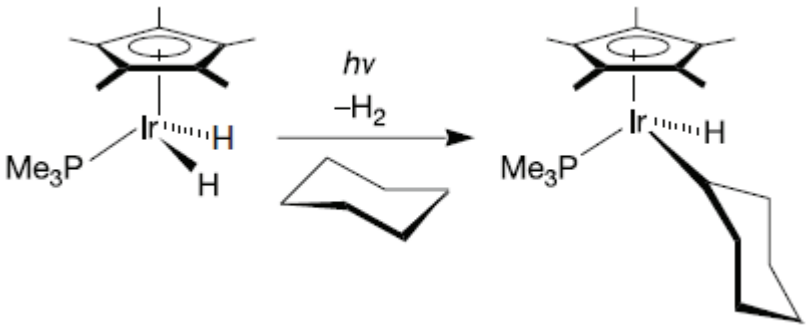
Nowadays hydrocarbons are mainly used in combustion reactions, to exploit their energy content. On industrial scale cracking and thermal dehydrogenation convert alkanes to valuable olefins, but these processes require high temperatures and are energy intensive. Alkanes can also react by exposure to highly reactive species such as superacids or free radicals. However these species are usually demanding and expensive to make, and offer little control over product selectivity. Milder and better-controlled direct conversions of alkanes into olefins and other higher value chemicals, may thus offer large economic benefits.

To reach this goal, the strong C-H bond of hydrocarbons (bond dissociation energy: 105 kcal/mol for $H\text{-}CH_3$), must be activated somehow. The activation consists in the increase of the reactivity of the C-H bond toward a reagent. As a consequence, the bond is capable of splitting to produce two particles in place of the single initial species. The main result of activation of a C-H bond is the replacement of a strong C-H bond, with a weaker, more functionalized bond[1].

The activation of unsaturated species like olefins or arenes, can be induced by the interactions of π-orbitals with empty orbitals of a transition metal centre. Saturated molecules don´t have this possibility, so that activation of aliphatic C-H bonds at transition-metal centres, would not be a good strategy for catalytic alkane conversion. However, during the 1970s, examples[2] of interaction between a metal centre and an alkane C-H bond suggested that this difficulty might have been overestimated. The chemists suggested that C-H activation might take place yielding a thermodynamically

unstable and thus undetectable organometallic product. In 1982, two groups[3,4] independently demonstrated intermolecular alkane activation (figure 1).

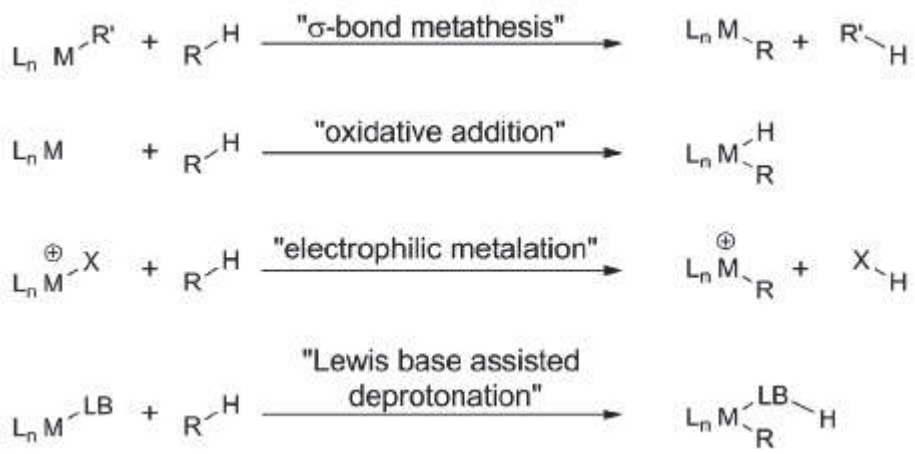
Figure 1 – Intermolecular alkane activation.



Despite these accomplishments, the development of practical alkane conversion poses further challenges[5]. One is activity, as only reactions proceeding at an adequate rate will be useful. Second problem is selectivity, arising from the relative reactivity of different C-H bonds (terminally functionalized alkanes are the most desirable products). Finally, thermodynamics presents a hurdle to an overall alkane conversion. Transformations such as dehydrogenation or carbonylation, are thermodynamically uphill near room temperature.

The nature of C-H bond metalation[5] varies depending on the substrate, the solvent and the transition metal, but four main mechanisms are identified: σ-bond metathesis for metals from group 3 of the periodic table (Sc, lanthanides and actinides); oxidative addition typical of electron-rich, low-valent complexes of the late transition metal (Re, Fe, Ru, Os, Rh, Ir, Pt); electrophilic metalation with a late or post transition metal; Lewis base assisted deprotonation (scheme 1).

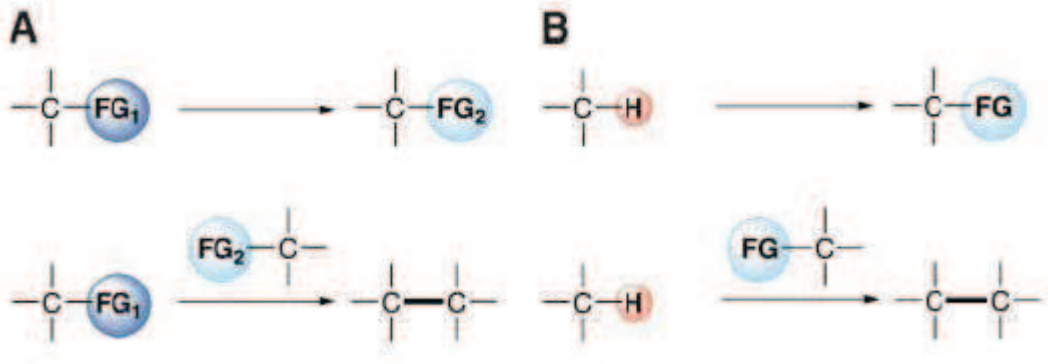
Scheme 1 - Main mechanisms in C-H bond metalation.



1.2 C-H bond activation in organic chemistry

Over the decades, developments in organic chemistry enabled the production of a vast number of compounds. Chemists usually prepare molecular structure by the interconversion of functional groups, which are moieties exhibiting relatively high chemical reactivity (figure 2). The reactive sites are typically incorporated in the molecules by means of multiple transformations, which are often wasteful in time and money.

Figure 2 - A: traditional approach to organic synthesis by means of functional group (FG); B: synthesis by means of C-H bond functionalization.

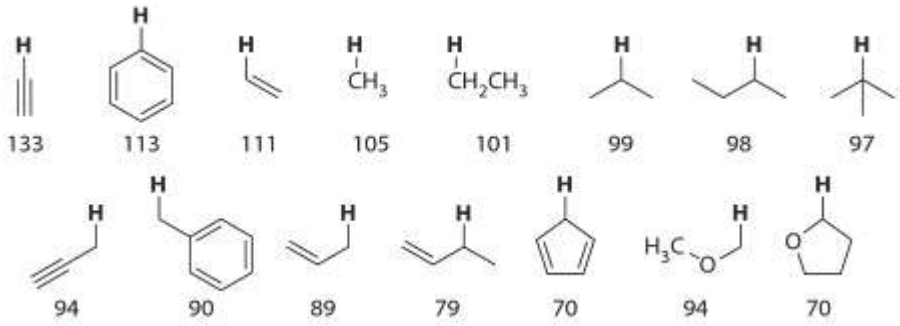


In this context the direct transformation of C-H bonds, would be an efficient and useful tool in organic synthesis. In the last 15 years, the C-H bond activation followed by functionalization has emerged has a revolutionary trend in organic field. This rush has

led to the development of a wide range of reactions aimed at directly installing new C-C or C-X bonds.

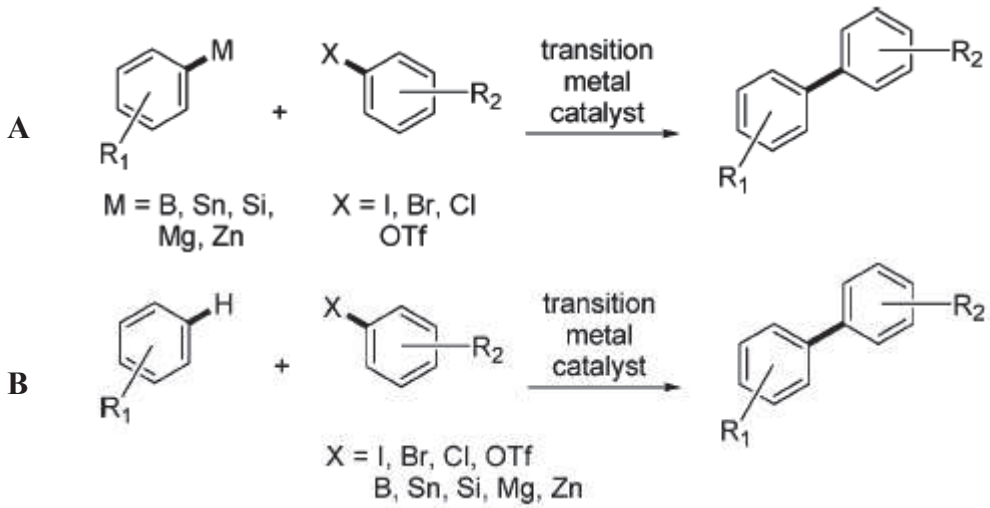
Chemists encountered two main problems in studying the C-H bond functionalization. First, the reactivity: the strength of C-H bond (figure 3), leads to a large kinetic barrier associated with the C-H bond cleavage. Second, the regioselctivity: most molecules contain different types of C-H bond and the selective functionalization of a specific C-H bond is still a challenge. To obtain products with a predictable regioselectivity, a number of approaches have been used: the use of substrates containing activated or weaker C-H bonds (e.g. benzylic or allylic systems); the use of coordinating ligands within a substrate as a directing group; carrying out intramolecular reaction via favourable five- or six-membered transition states; the use of transition metal catalysts/ligand to control the stereoselectivity.

Figure 3 – Bond dissociation energies of C-H bond (kcal/mol).



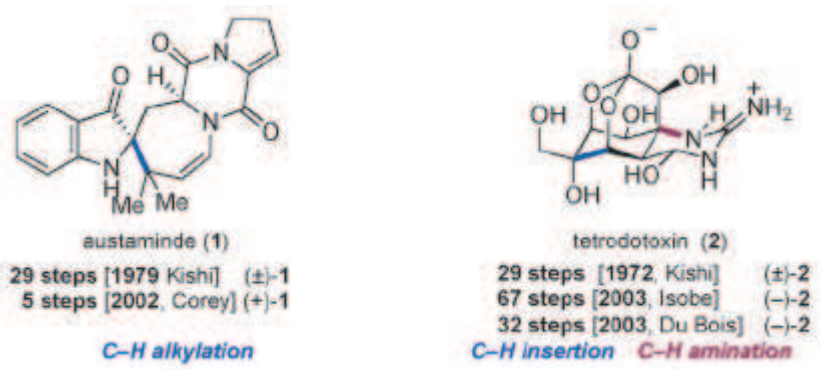
Undeniably, the direct transformation of C-H bonds provides shortcuts compared with classical organic synthesis, thus rendering synthetic routes more straightforward and atom-economical. A prime example is the synthesis of the biaryl structural motif, which is a common feature in pharmaceutical and biological compounds. To date, biaryl moieties are mostly obtained by Suzuki-Miyaura, Mizoroki-Heck, Negishi and Stille coupling reactions. Typically these reactions involve the coupling of an aryl halide with an organometallic reagent. The preparation of the preactivated aryl substrate often requires several steps, which can be time consuming and economically inefficient. An alternative to this approach is to consider the C-H bond activation. In this case, only one coupling reagent is preactivated, while the other reagent is a simple unactivated aryl substrate, resulting in the elimination of the activation steps for one of the arylic substrates (figure 4).

Figure 4 - Biaryl synthesis. A: cross coupling reactions; B: C-H bond activation.



Even more alluring is that this new approach enables previously unachievable synthetic disconnections. For this reason C-H functionalization strategies have been incorporated into the synthesis of complex natural products and biologically active molecules. For example, the synthesis of racemic austamide (**1**), by Hutchinson and Kishi[6] in 1979 was completed in 29 steps, whereas that of (+)-**1** in 2002 by Baran and Corey[7] based on C-H alkylation took only 5 steps (figure 5). Another striking comparison is a 67-steps synthesis of (-)-tetrodotoxin (**2**) published by Isobe and co-workers[8] in 2003, versus the 32-steps synthesis by Hinman and Du Bois[9] that made use of a C-H insertion and amination methods (figure 5).

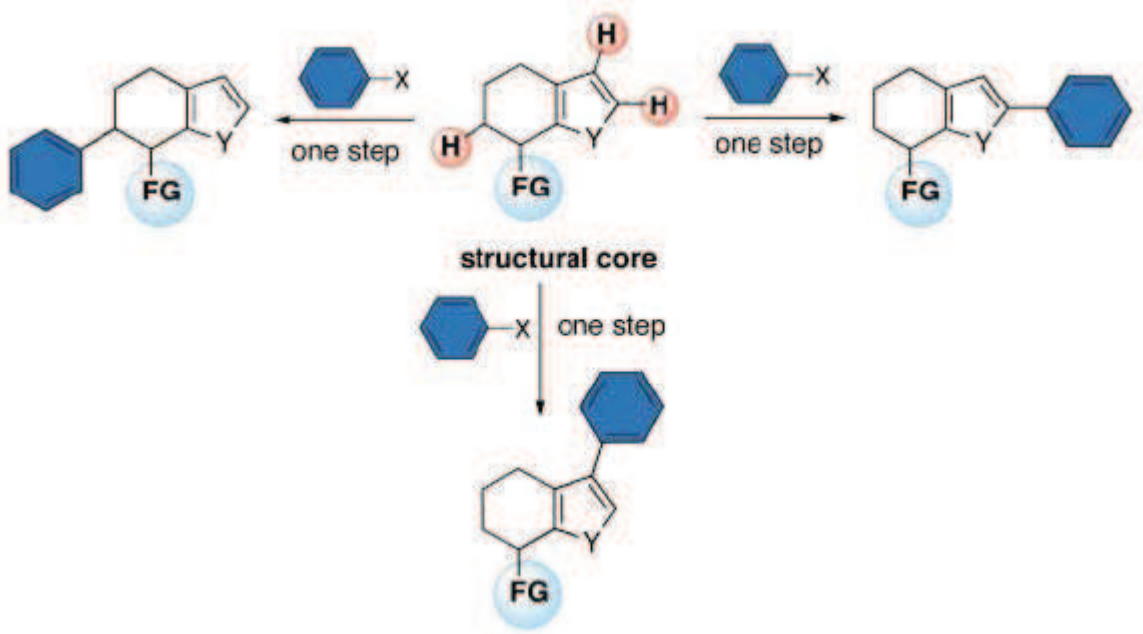
Figure 5 – Examples in the evolution of the synthesis of biologically active compounds with the advent of C-H functionalization.



In many organic fields, the search for optimal compound imposes an optimization of target molecules that show interesting characteristics. The enhancement of the properties is accomplished by the modification of the chemical structure of the molecule, provided

that the basic scaffold must not be modified. Since it´s impossible to know in advance which substituent would increase most the properties of the target molecule, a wide range of related analogues should be synthesized and tested. In this context, chemists use a synthetic strategy called "late stage functionalization": this approach enables the insertion of functional group in the final steps of the synthesis of a compound. Owing to the omnipresence of C-H bonds in all kinds of organic molecules, the ability to transform selectively, efficiently and in a predictable manner a specific C-H bond opens the door for the almost unlimited exploitation of this strategy for the late stage modification of various compounds[10] (figure 6). This approach surpasses de novo synthesis strategies not only by shortcutting the laborious and time-consuming preparations of each analogue, but also giving the opportunity to install functional groups that could be incompatible with standard synthetic sequences.

Figure 6 – Late stage functionalization by means of C-H bond activation.

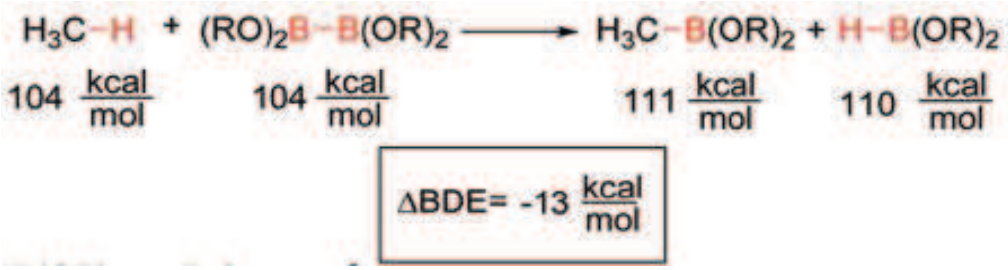


1.3 C-H activation for the constructions of C-B bond

Organoboron compounds are very useful in organic synthesis, not only because they are very versatile in cross-coupling reactions but also because a wide range of transformation of boronate molecules has been developed (oxidation, halogenation, amination and etherification).

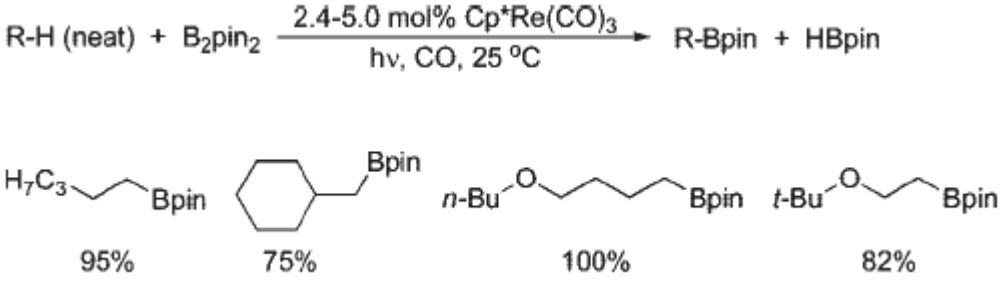
For these reasons the direct transformation of C-H bonds to C-B bonds in alkanes, alkenes and arenes, has made great progresses. In the last twenty years, this reaction has developed from stoichiometric reactions of transition metal-boryl complexes to metal-catalyzed system leading to organoboron compounds in high yield and high selectivity.
The conversion of C-H bonds to C-B bonds is both thermodynamically and kinetically favourable (figure 7). On the basis of calculated bond energies, the reaction at a primary C-H bond of methane or a higher alkane with $B_2(OR)_4$, is thermodynamically downhill[11].

Figure 7 – Thermodynamics of methane borylation with $B_2(OR)_4$.



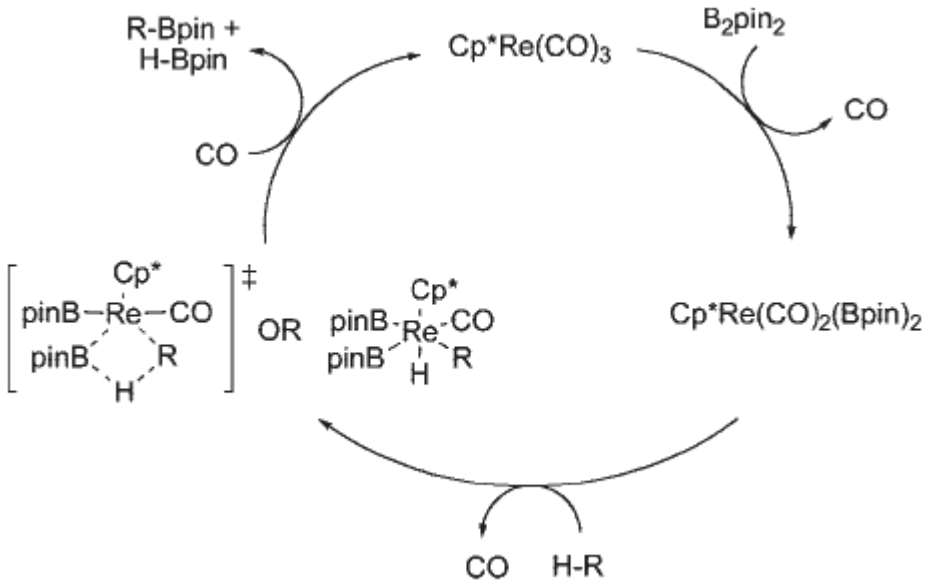
One of the most difficult problems in C-H bond activation is the selective functionalization of primary C-H bond in alkanes. Primary C-H bonds are stronger than secondary or tertiary ones, thus reactions like halogenation or autoxidation occur at the internal position of alkanes.
In 1999 Hartwig and co-workers[12] reported a reaction between alkanes and bis(pinacolato)diboron (B_2Pin_2) to form an alkylboronate ester. The transformation was catalyzed by the metal complex $Cp^*Re(CO)_3$, stabilized by 2 atm of CO. The reaction occurred with perfect regioselectivity leading to functionalized product at primary C-H bond. In addition to alkenes, alkyl ethers underwent borylation at the least sterically hindered terminal methyl groups in moderate to excellent yields (scheme 2).

Scheme 2 – Cp*Re-catalyzed borylation of alkanes.



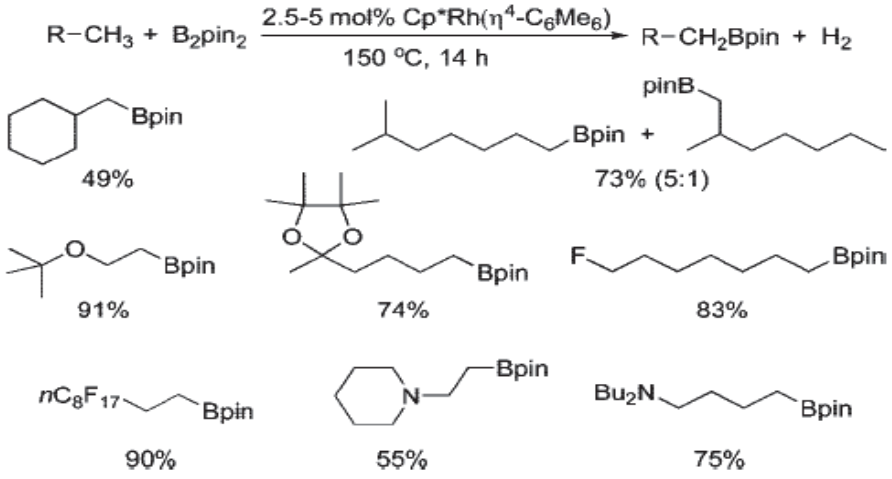
After a series of experiments, a mechanism for the borylation reaction (scheme 3), was proposed. After the photochemical dissociation of CO, B_2Pin_2 undergoes oxidative addition to form the intermediate $Cp^*Re(CO)_2(Bpin)_2$. Following the dissociation of another molecule of carbon monoxide, the resulting unsaturated bisboryl complex reacts with alkane, leading after reductive elimination to the observed alkylboronate ester product.

Scheme 3 – Proposed mechanism for Cp*Re-catalyzed alkane borylation.



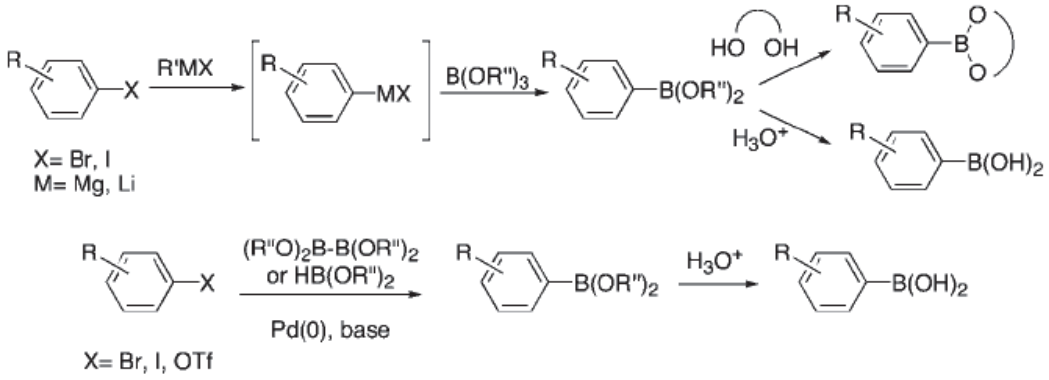
In 2000, Chen and Hartwig[13] tested a series of Cp^*ML_2 complexes that catalyze the borylation of alkene under thermal conditions. $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ was found to be the best complex, as the hexamethylbenzene ligand was resistant to C-H bond functionalization, and the reaction of octane with B_2Pin_2 catalyzed by 5 mol% of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ provided high yield (88%) of octylBpin. This complex also catalyzes the borylation of terminal methyl groups in alkanes, alkyl ethers, tertiary amines and partially fluorinated alkanes (scheme 4). When a molecule includes a heteroatom, the C-H bond α to the heteroatom is activated toward cleavage by many metal complexes[14]. However, this property of heteroatom did not override the preference of the catalyst for the functionalization of the least hindered of the primary C-H bond.

Scheme 4 – Scope of Cp*Rh(η^4-C_6Me_6) catalyzed borylation of aliphatic substrates.



Arylboronates are widely used in synthesis[15] and most of them are prepared from aryl halides (scheme 5). As a consequence, the range of arylboronates available depends on the availability of the substituted aryl halides. The development of methods for the direct transformation of C-H bonds to C-B bonds, reduces steps in arylboronate synthesis and provides access to isomers of arylboronates that would be difficult to access otherwise.

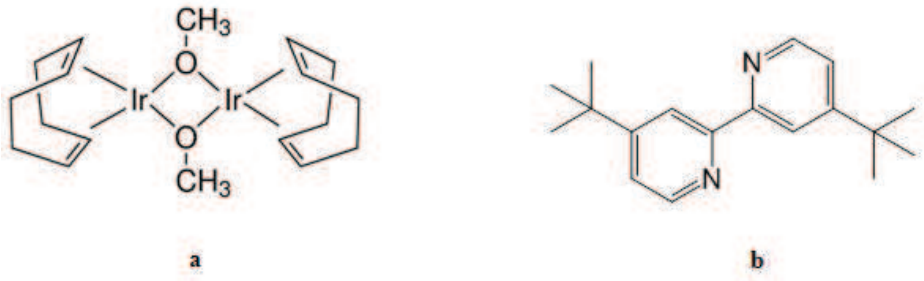
Scheme 5 – Common synthesis of arylboronate esters and acids.



The first arene borylation reactions[16,17] were accomplished using Cp*Rh and Cp*Ir complexes as catalysts. Later, Smith and co-workers[18] obtained good results with a combination of (Ind)Ir(COD) (Ind: indenyl; COD: cyclooctadiene) and phosphine ligands. However a big breakthrough was in 2002, when Ishiyama, Miyaura, Hartwig and co-workers[19] reported the borylation of arenes catalyzed by iridium complexes of bipyridine (bpy). An optimization of the catalyst[20] was conducted and $[Ir(COD)(OMe)]_2$ (figure 8a), was found to be the best Iridium(I) precursor. Different substitued bipyridine

were tested as ligand. Due to steric effects the best pattern was found for 4,4´-disubstituted-2,2´-bipyridine[20]. Using this pattern, electronic effects of the bipyridine ligand on borylation were tested. When bpy contained electro-donating group such as NMe_2, OMe or *t*Bu the borylation reaction occurred in high yield; on the other hand with electron-withdrawing group such as Cl and NO_2, no product was observed. After these experiments the best ligand was found to be 4,4′-Di-*tert*-butyl-2,2′-dipyridyl[20] (dtbpy) (figure 8b).

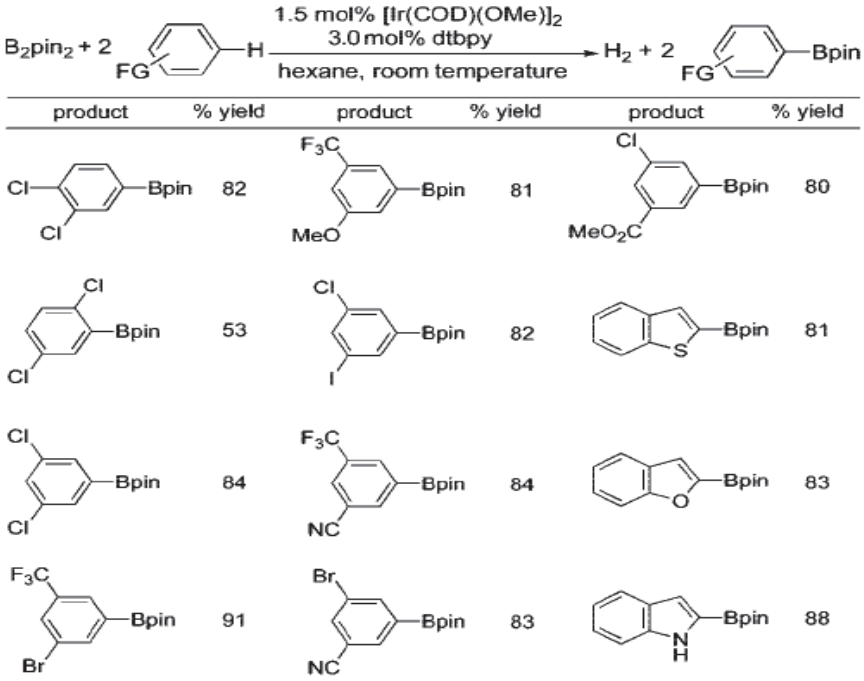
Figure 8 – a: $[Ir(COD)(Ome)]_2$; b: 4,4′-Di-*tert*-butyl-2,2′-dipyridyl.



a b

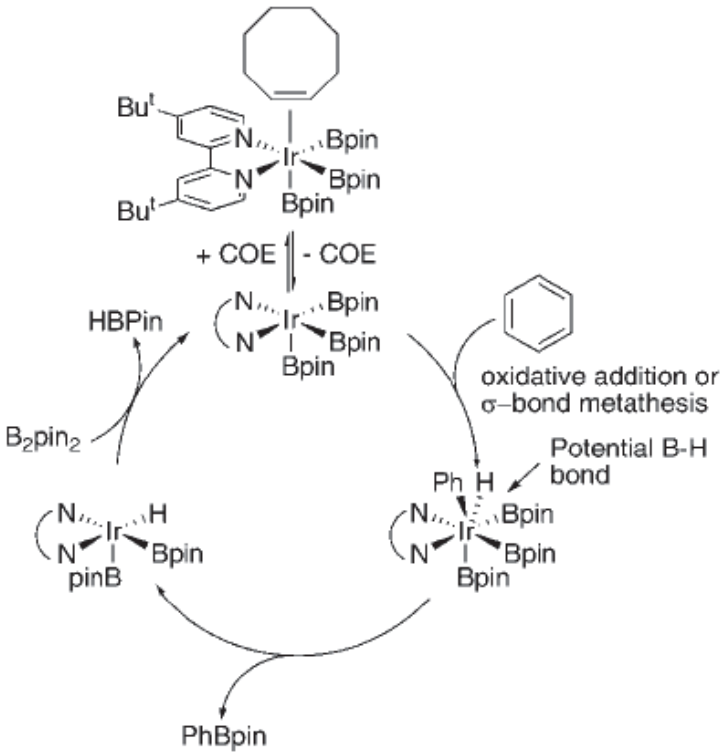
A variety of arenes reacted with B_2pin_2 at room temperature to form arylboronate esters with the $[Ir(COD)(OMe)]_2$ (OMe: methoxy) and dtbpy system[20] (table 1). A number of functional group was tolerated and also heteroaromatic molecules reacted. The regioselectivity of the reactions catalyzed by dtbpy-ligated iridium was controlled by steric effects.

Table 1 – Arene borylation with B_2Pin_2 catalyzed by $[Ir(COD)(OMe)]_2$ and dtbpy.



On the basis of data obtained from NMR spectroscopy of catalytic system, isolation of intermediates and kinetic data, Hartwig and co-workers proposed the mechanism[19,21] shown in scheme 6 for the borylation of arenes catalyzed by dtbpy-ligated complexes of iridium (in the experiments $[Ir(COE)_2Cl]_2$, COE: cyclooctene, was used as metal precursor). Since the reaction is inhibited by adding COE, the first step is the reversibly dissociation of COE from the stable tris boryl complex. The resulting 16 electrons complex, which is the real active form of the catalyst, coordinates the arene and then the oxidative addition of the aryl C-H bond occurs to form an iridium(V) intermediate. The cleavage of the aryl C-H bond is the turnover-limiting step in the formation of the arylboronate ester. Reductive elimination of Ph-Bpin, followed by oxidative addition of B_2Pin_2 would then regenerate the active iridium trisboryl complex.

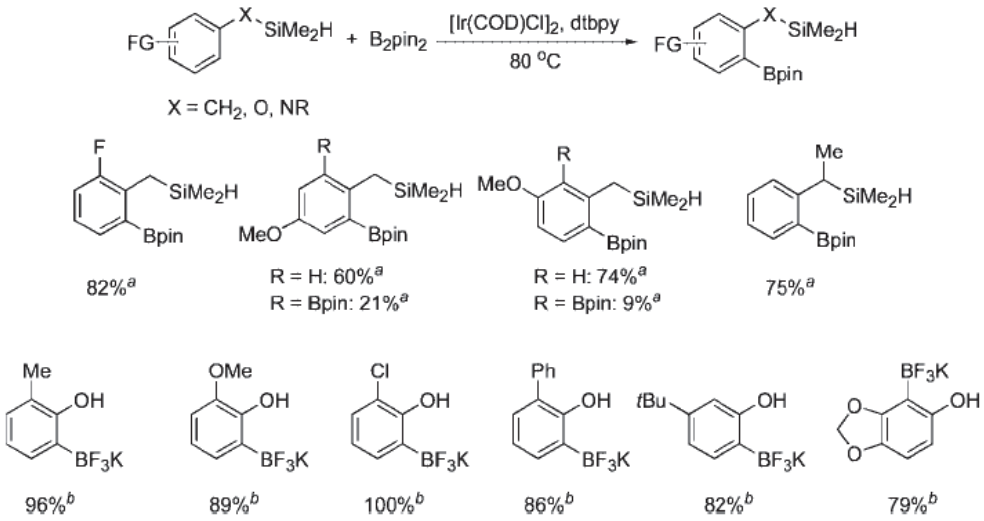
Scheme 6 – Proposed mechanism for the iridium-catalyzed borylation of arenes.



The regioselectivity controlled by steric effects, complements the regioselectivity of most other types of arene functionalization. Nevertheless a method to accomplish different regioisomers would be a valuable tool. In 2008 Hartwig and co-workers[22] described the selective *ortho*-borylation of arenes catalyzed by the combination of $[Ir(COD)Cl]_2$ and dtbpy (scheme 7). In this method, the borylation of arenes was directed to the *ortho*

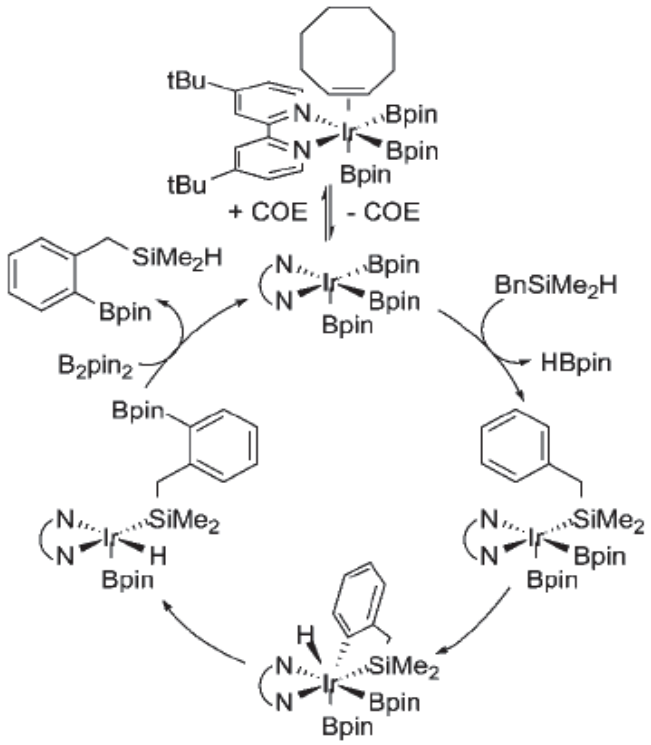
position by a dialkyl hydrosilyl group. This method provides a mild alternative to *ortho*-metalation methods based on alkyl lithium or magnesium reagents[23].

Scheme 7 – *ortho*-directed arene borylation observed with benzylic dimethylsilanes as substrates.



The mechanism envisioned for this *ortho*-borylation is shown in scheme 8. Following the COE dissociation, the elimination of Hbpin leads to a bisboryl silyl species. Then this intermediate will cleave the aryl C-H bond in the *ortho* position. C-B bond formation and further reductive elimination of the silane would release the functionalized product.

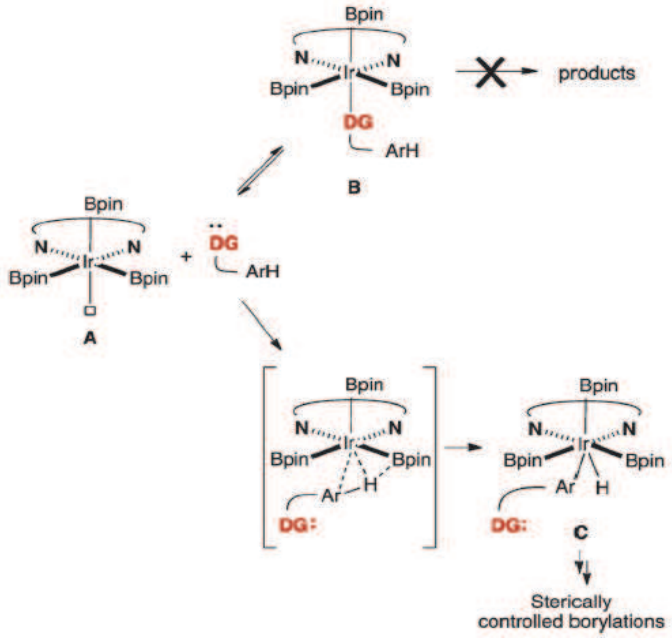
Scheme 8 – Proposed mechanism for hydrosilyl-directed *ortho*-borylation of alkylarenes.



In 2009 Sawamura and co-workers[24] reported the reaction of methyl benzoates with B_2Pin_2, catalyzed by the combination of $[Ir(COD)(OMe)]_2$ and the silica-supported monodentate, electron-rich, and compact phosphine ligand SMAP (a silica-supported phosphine ligand). Excellent regioselectivity, under mild condition was observed, resulting in *ortho*-directed borylation of the substrates. Moreover reactions of arenes containing CO_2Et, CO_2tBu, $CONMe_2$, SO_3Me, $CH(O(CH_2)_3O)$ led to the *ortho*-borylated product, showing the efficacy of these substituent as directing group. In 2011 Sawamura and co-workers[25], using again silica-supported phosphine ligand, described a different method for *ortho*-borylation of arenes. The catalyst was $[Rh(OH)(COD)]_2$ and the arenes contain different nitrogen-based directing group such as pyridine and pyrazole.

A more general approach for the iridium-catalyzed *ortho*-borylation of arenes was reported by Ros and co-workers[26] in 2011. As shown earlier, the direct borylation of arene with the iridium/dtbpy system, takes place through a $[Ir(dtbpy)(Bpin)_3]$ 16 electrons catalytically active species **A** (scheme 9).

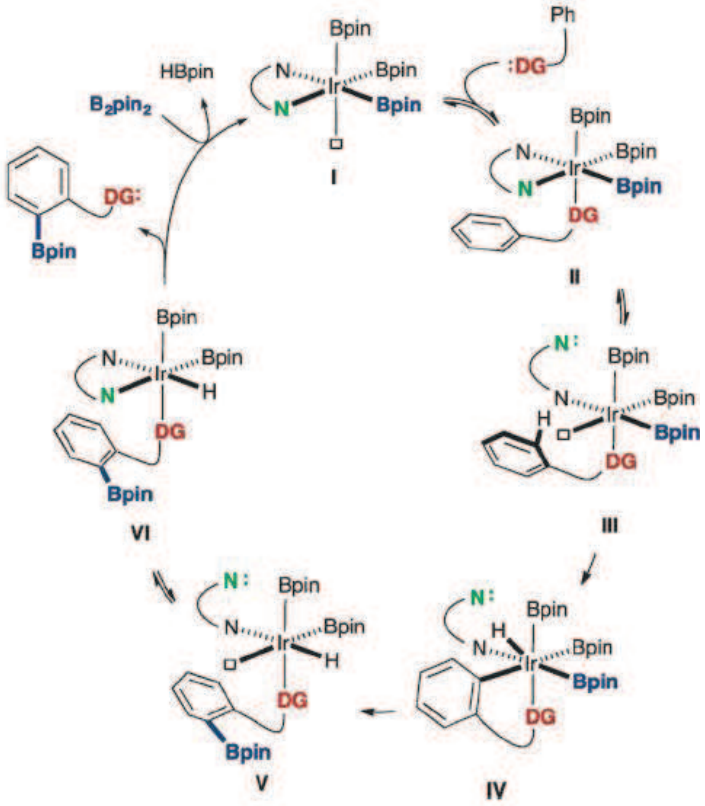
Scheme 9 – Analysis of regioselectivity in Ir-catalyzed borylations.



The lack of sensitivity of this process towards any directing group in the substrate, can be attributed to the lack of additional vacant coordination sites in complex **B**. In this scenario, the reaction can only proceed via intermediate **C**, and steric factors represent the main contribution to regioselectivity. As a consequence, if vacant coordination site can be generated in the metal complex, a new reaction pathway could be created. As an

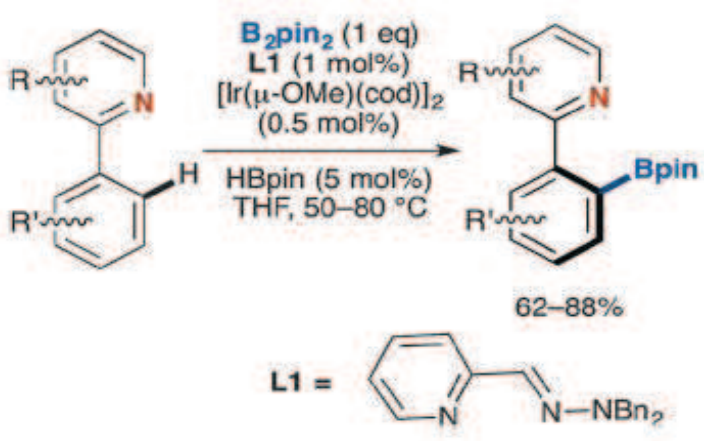
example, when the dtbpy ligand is replaced by a hemilabile N,N ligand (scheme 10), the properties of this latter ligand should facilitate the temporary generation of a coordinatively unsaturated intermediate **III** from the established catalytic species **I**, via complex **II**. This complex **III** undergoes oxidative addition of the *ortho* C-H bond of the arene, followed by reductive elimination and recoordination of the hemilabile ligand, leading to product and to regenerate catalyst **I**.

Scheme 10 – Envisaged mechanism using hemilabile N,N-ligands.



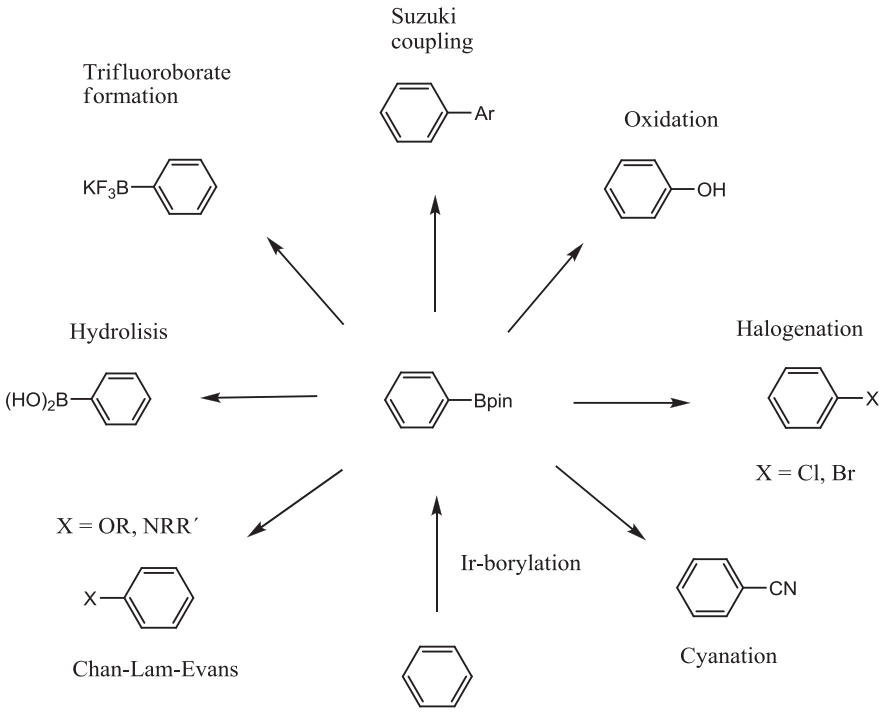
In particular, picolinaldheyde N.N-dibenzylhydrazone **L1** combined with $[Ir(\mu\text{-}OMe)(COD)]_2$ proved to be a very efficient ligand for the borylation of 1-naphtylisoquinolines and 2-arylpyridines with B_2Pin_2 under mild conditions[27] (scheme 11).

Scheme 11 – Directed borylation of arylpyridines/isoquinolines.



To exploit the original regioselectivity of the iridium-catalyzed borylation, a wide range of derivatization of the boronate esters has been developed (scheme 12). The boronate esters product can be used in Suzuki cross-coupling, resulting in biphenyl motifs that are very useful in medicinal chemistry. Other common transformations include oxidation, halogenation, cyanation, Chan-Lam-Evans[28] amination and etherification, hydrolysis and trifluoroborate formation.

Scheme 12 – Derivatization of boronate esters.

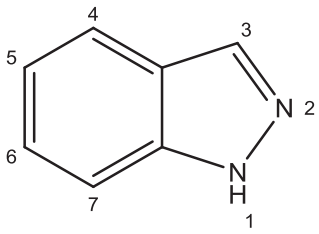


1.4 Indazole and pyrazolopyrimidine

1.4.1 Indazole

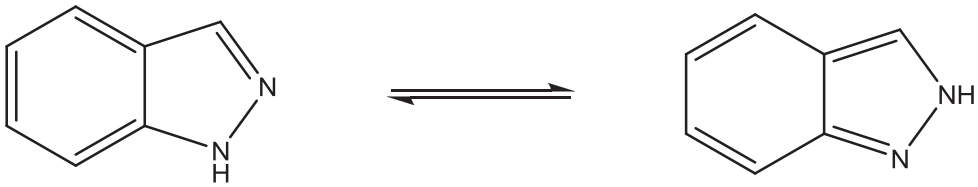
Indazole is a heterocycle molecule in which a pyrazole ring is fused with a benzene ring (figure 9). Indazoles are naturally occurring alkaloids. Indazoles derivatives are pharmacologically important as they form the basic structure of several drug molecules. They possess several activities such as anti-inflammatory, anti-tumor, anti-HIV, anti-platelet and serotonin 5-HT_3 receptor antagonist activities[29].

Figure 9 – Indazole.



Indazole is a ten π-electron aromatic heterocycle system, resembling both pyridine and pyrrole and its reactivity reflects this dual behaviour. The indazole ring has two nitrogen atoms and presents annular tautomerism with regards to the position of the NH hydrogen atom (figure 10). Due to the difference in energy between the tautomers, the 1H-tautomer (**1**) predominates in the gas phase, solution and solid state and its derivatives are usually thermodynamically more stable then the corresponding 2H-form (**2**).

Figure 10 – Annular tautomerism of indazole.

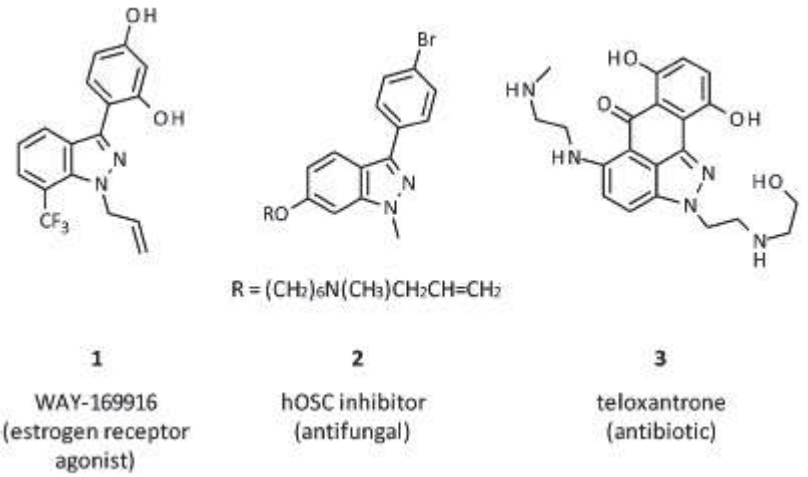


1 **2**

An important class of indazoles are the 3-aryl-1H-indazoles (figure 11). The common synthesises of these compound include the condensation of hydrazines with fluorobenzophenones[30], diazomethane cycloaddition with benzynes[31], C-H amidation of aryl hydrazones[32] or catalytic N-N bond formation[33]. In these cases the diversity of

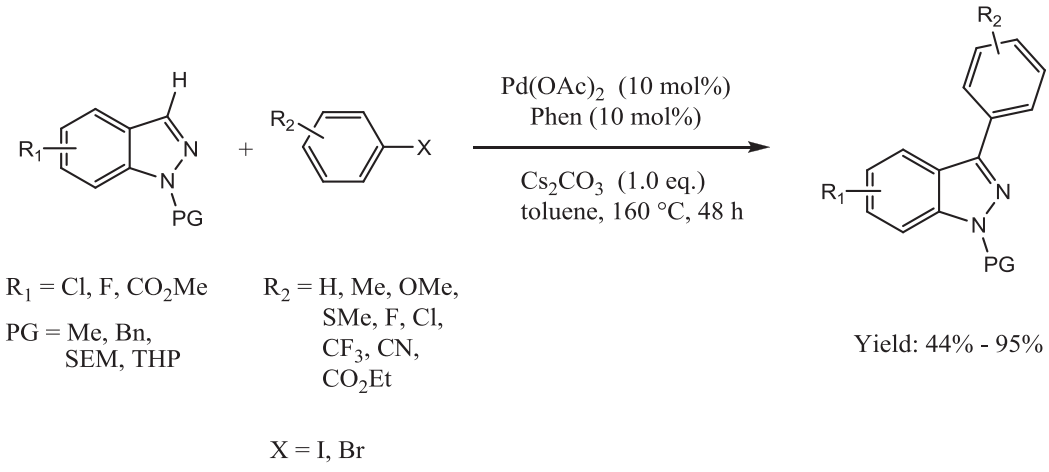
substitution on both the indazole and the aryl group must be introduced early in the synthetic sequence. Moreover, these methods require the use of either explosive or toxic reagents.

Figure 11 – Bioactive 3-aryl-1H-indazoles.



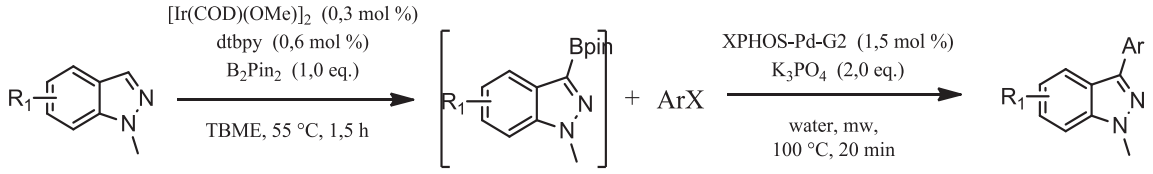
As results, chemists have developed different methods for the direct arylation of 1H-indazoles via C-H activation. However, due to the lack of reactivity at 3-position of indazole, a first example of arylation was reported only in 2013. Yu and co-workers[34] reported the reaction of 1-protected-1H-indazole, catalyzed by Pd^{II} using phenantroline as ligand (scheme 13). Different protecting group were tested: electron-withdrawing protecting group such as Ac, Boc and Ts inhibit the reaction severely, while alkyl protecting group such as Bn, SEM and THP are compatible with this reaction. Aryl iodides and bromides worked well and on the aryl-halides a wide range of functional group was tolerated (both electron-donating and withdrawing).

Scheme 13 – Direct arylation of 1H-indazoles at 3-position.



However the conditions reported require high temperature (up to 160 °C), and long time. In 2014, Burton and Egan[35] described the synthesis of 3-aryl-1H-indazoles via iridium-catalyzed C-H borylation and Suzuki-Miyaura coupling. The catalytic system was formed by $[Ir(COD)(OMe)]_2$ and dtbpy as ligand. The substrate tested was the 1-methyl-1H-indazole and mild conditions for the borylation reaction were used (55 °C for 1,5 hours). A useful one-pot tandem reaction sequence was developed (scheme 14). A wide range of aryl iodides, chlorides and bromides containing both electron-donating and –withdrawing group all reacted in good yield.

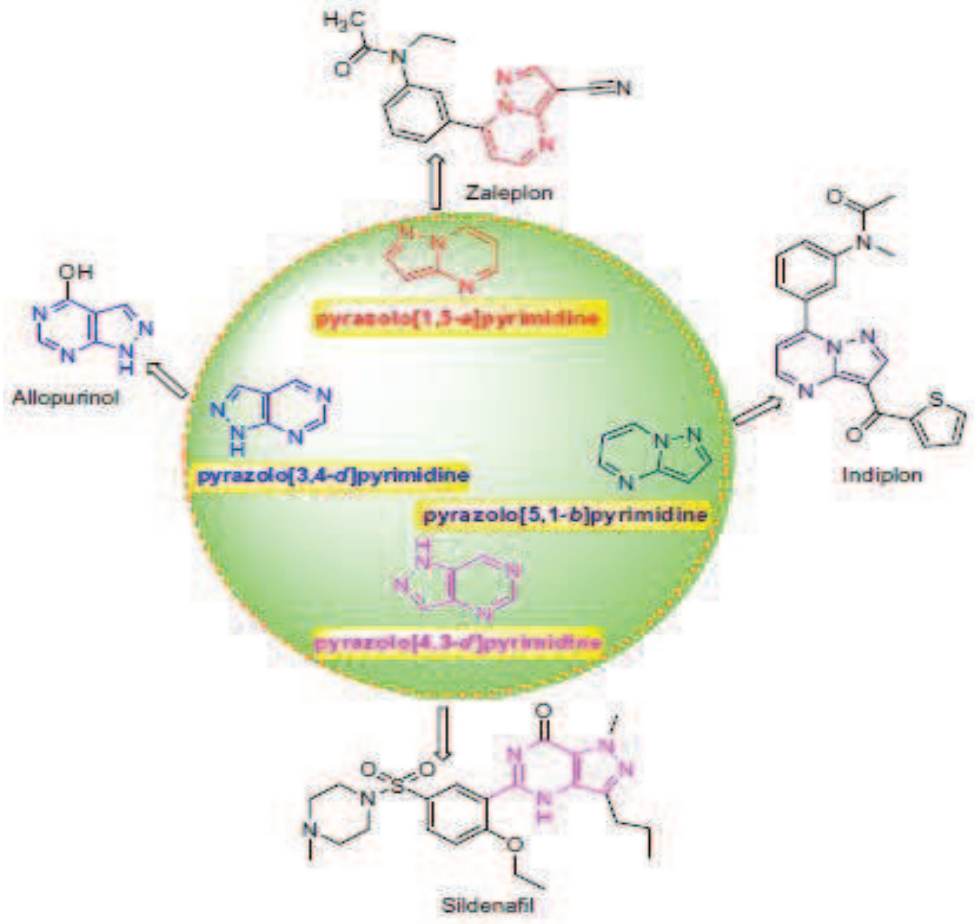
Scheme 14 – One pot indazole borylation and Suzuki-Miyaura coupling.



1.4.2 Pyrazolopyrimidine

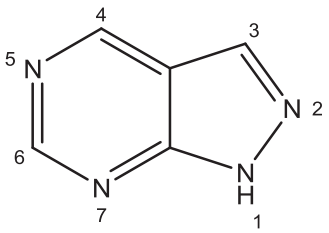
The word "pyrazolopyrimidine" refers to a class of compound in which a pyrazole molecule is fused with a pyrimidine ring. Thus, different combinations are possible, resulting in different molecules such as pyrazolo[3,4-d]pyrimidine, pyrazolo[4,3-d]pyrimidine, pyrazolo[5,1-b]pyrimidine, pyrazolo[1,5-a]pyrimidine, that are contained in many drugs[36] (figure 12).

Figure 12 – Pyrazolopyrimimidine scaffolds in common drugs.



Among these compounds, pyrazolo[3,4-d]pyrimidine has a great importance since its structure (figure 13), is an isostere of adenine, which is fundamental for every aspect of cell life as a constituent of DNA and RNA. Pyrazolo[3,4-d]pyrimidines are active in the inhibition of tyrosine or serine/threonine kinase and they also have antimicrobials, anticancer and anti-inflammatory properties.

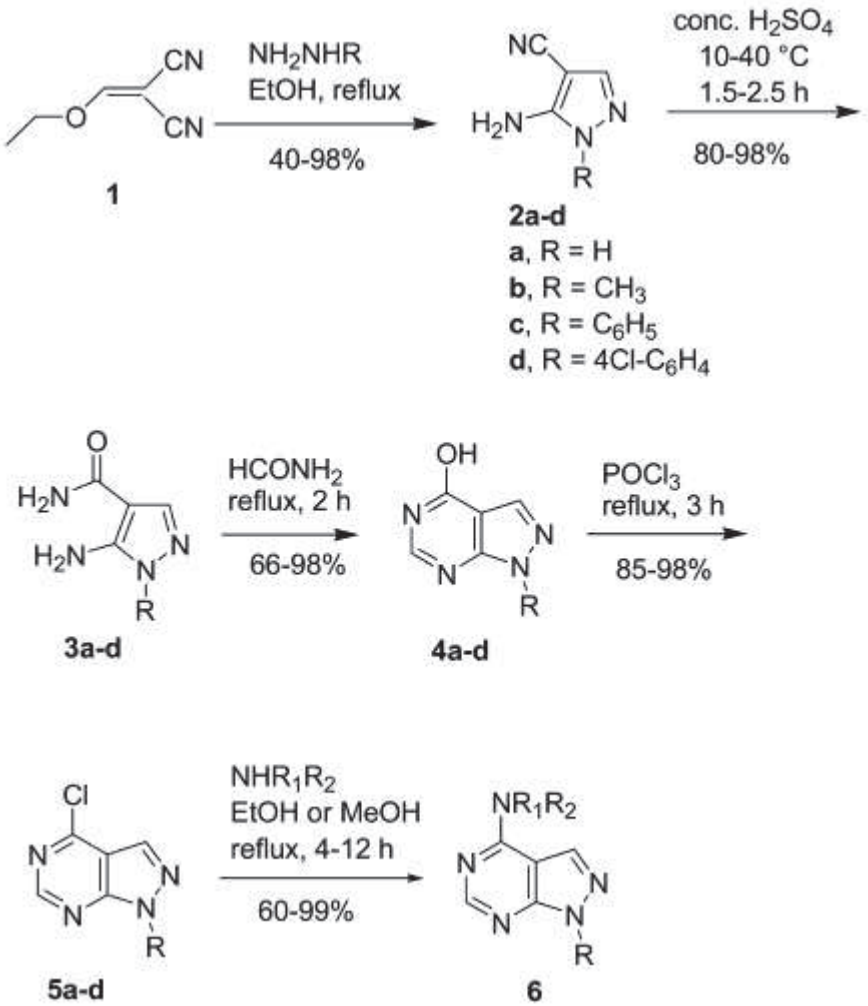
Figure 13 – 1H-Pyrazolo[3,4-d]pyrimidine.



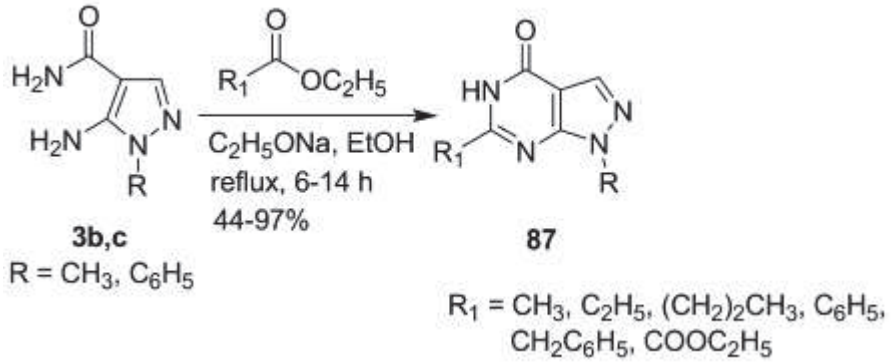
A wide range of synthetics strategies have been developed to arrange substituted pyrazolo[3,4-d]pyrimidine at different position, starting from either the pyrimidine or the pyrazole nucleus. The most common route to this scaffold is the method reported by

Robin[37] in the mid-1950s (scheme 15). Reaction of ethoxymethylenemalononitrile **1** with hydrazine monohydrate without solvent or with different substituted hydrazines in refluxing ethanol, produced 5-amino-1H-pyrazole-4-carbonitriles **2a-d** and similar derivatives, which were then hydrolyzed with concentrated sulphuric acid to the corresponding amides **3a-d**. These amides where subsequently cyclised into the corresponding 1H-pyrazolo[3,4-d]pyrimidin-4-ols **4a-d** by treatment with boiling formamide. C4 chlorination of the latter compounds with $POCl_3$ gave **5a-d**, which underwent nucleophilic displacement of the chlorine atom by primary or secondary amines in refluxing alcoholic solution to afford the 4-amino derivatives **6**. A method[38] for obtaining 1,6-alkyl/aryl disubstituted 1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-ones **87** is represented by the straightforward reaction of carboxamides **3b,c** with different esters in the presence of sodium ethoxide in ethanol (scheme 16).

Scheme 15 – Synthesis of 4-amino-substituted 1H-pyrazolo[3,4-d]pyrimidine.

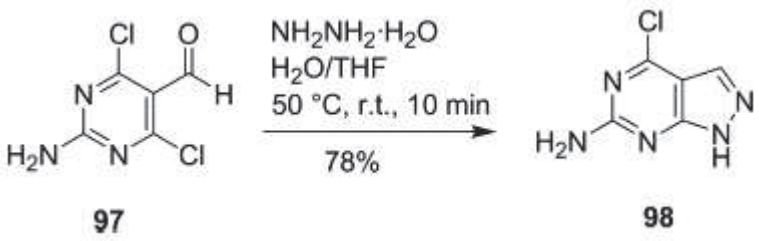


Scheme 16 – Synthesis of 1,6-disubstituted 1H-pyrazolo[3,4-d]pyrimidin-4-ones.



The synthesis of pyrazolo[3,4-d]pyrimidine scaffold can also start from pyrimidine ring, although this procedure has been using less than cyclization starting from pyrazole intermediate. The synthesis[39] generally involves reaction of pyrimidines possessing a carbonyl function at 5-position with hydrazine derivatives. 2-amino-4,6-dichloro-pyrimidine-5-carbaldehyde **97** was cyclised with hydrazine hydrate to give 4-chloro-1H-pyrazolo[3,4-d]pyrimidin-6-amine **98** (scheme 17).

Scheme 17 – Synthesis of 4-chloro-1H-pyrazolo[3,4-d]pyrimidin-6-amine starting from 2-amino-4,6-dichloro-pyrimidine-5-carbaldehyde.



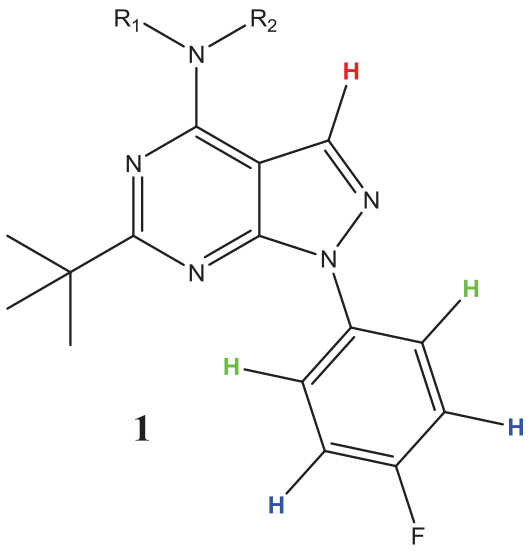
2 Project

In drug discovery, a "lead compound" is a chemical compound that shows desired pharmacologically or biologically activity on a validated molecular target, but it could still have suboptimal features. The properties of the lead compound can be influenced by chemical modification, using the lead chemical structure as starting point. The aim is to generate analogues of the initial lead with improved potency, reduced off-target activities and desirable physiochemical/metabolic properties. Usually, hundreds of different variations are made and tested in biological systems providing additional information for

the chemists. Therefore, the design of methods permitting the direct transformation of a lead compound, in analogue scaffolds with slightly modified structure, is highly desirable. In this context, predictable, efficient and both chemo- and regioselective transformations of specific C-H bonds applied to a late stage functionalization strategy, is particularly appealing.

The project described in this report, was developed in AstraZeneca´s laboratories, at Mölndal (Sweden) research and development site. In this case, the lead compound at the heart of the project is shown in figure 14. Due to patent issues, the amine moiety at 4-position is masked. The molecule consists of a pyrazolo[3,4-d]pyrimidine scaffold, substituted at 1-position with a *p*-fluorophenyl moiety.

Figure 14 – 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine.



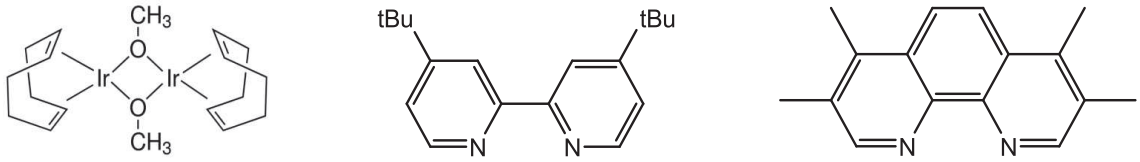
1

The lead optimization process requires the screening of a wide range of functionalized compound, that are synthesized from 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine. In order to save time and money, a general but chemo- and regioselective procedure leading to a large panel of analogues, needs to be developed. The project aims to develop a protocol for the metal-catalyzed C-H borylation of 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine and to demonstrate its applications to the late stage functionalization.

In the last years, efficient methods for metal-catalyzed borylation reactions, have been developed and many metal-ligand combinations have been screened. The first combination chosen in the project was composed by $[Ir(COD)OMe]_2$ (bis(1,5-cyclooctadiene)di-iridium(I)-dimethoxide) and dtbpy (4,4′-di-tert-butyl bipyridine) as ligand (figure 15). This system has been reported to be very active in the borylation of

arenes and heteroarenes. Moreover, Burton[35] described the borylation of 1-methyl-1H-indazole at 3-position with this system under mild condition (55 °C, overnight, MTBE as solvent). Indazoles have a structure similar to that of pyrazolo[3,4-d]pyrimidine since they share a pyrazole ring, fused with an aromatic system and their C-H borylation has been reported. For these reasons, the scope of the borylation reaction will be broadened to 1-susbstituted-1H-indazoles, in order gather more data. The second ligand chosen was the Me_4phen (3,4,7,8-tetramethyl-1,10-phenantroline) (figure 15). Me_4phen has grater electron-donating ability and backbone rigidity compared to those of dtbpy. Its activity in borylation of heteroarenes was reported by Hartwig[40] in 2014.
The reaction condition (time, temperature, solvent), were taken from the already cited papers by Burton and Hartwig.

Figure 15 – The iridium complex and the ligands chosen for borylation experiments.



[Ir(COD)OMe]$_2$ dtbpy Me_4phen

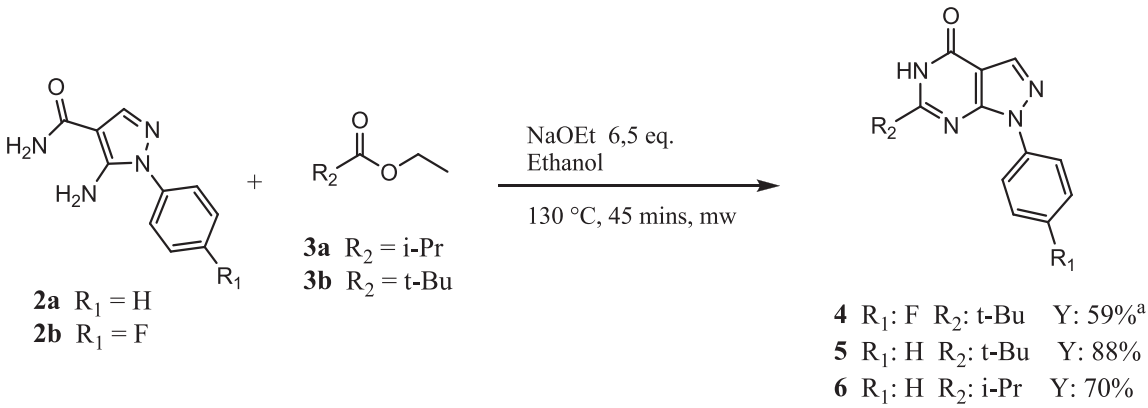
During the development of the borylation method for this kind of substrates, two main problems usually arise. First, since 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine contains three different C-H bond, the selective activation of one of those bond must be achieved. Second, the basicity of the nitrogen at 2-position of the pyrazole ring could lead to a non-productive coordination between the heteroatom and the metal catalyst. However, the reaction protocol will be aimed to obtained specific regioselectivity.
Application of C-H borylation to late stage functionalization will be demonstrated by converting the borylated intermediate: the boronic ester will be transformed into an alcoholic moiety through an oxidation reaction, using sodium perborate.

3 Results and discussion

3.1 Synthesis of substrates

In the beginning, most of the time was dedicated to the synthesis of the substrates that were used in the borylation experiments. The synthesis of the pyrazolopyrimidine scaffold was accomplished by the reaction of a carboxamides **2a, 2b** with esters **3a, 3b**, in presence of sodium ethoxide and ethanol as solvent (scheme 18). The reactions were conducted in a microwave reactor using a 5 ml vial. Product **5** and **6** were obtained in good yield, but due to low solubility in MTBE and THF, these two compounds were discharged.

Scheme 18 – Synthesis of pirazolopyrimidine on a 5 ml scale. [a] Reaction run on a 13 ml scale.



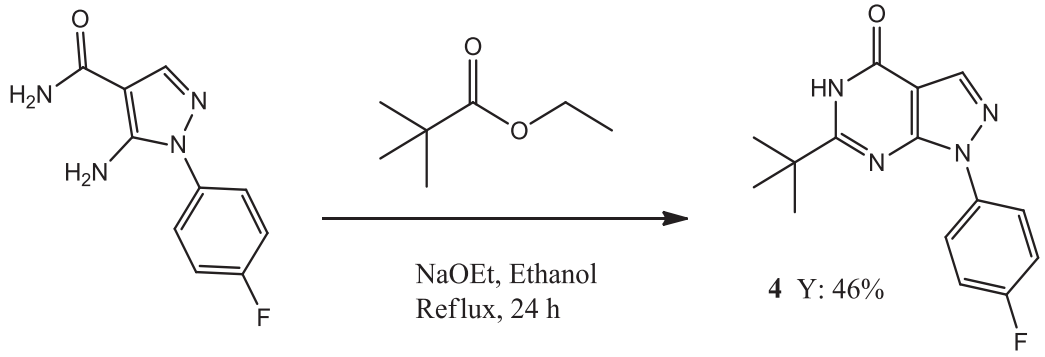
2a R_1 = H
2b R_1 = F

3a R_2 = i-Pr
3b R_2 = t-Bu

4 R_1: F R_2: t-Bu Y: 59%[a]
5 R_1: H R_2: t-Bu Y: 88%
6 R_1: H R_2: i-Pr Y: 70%

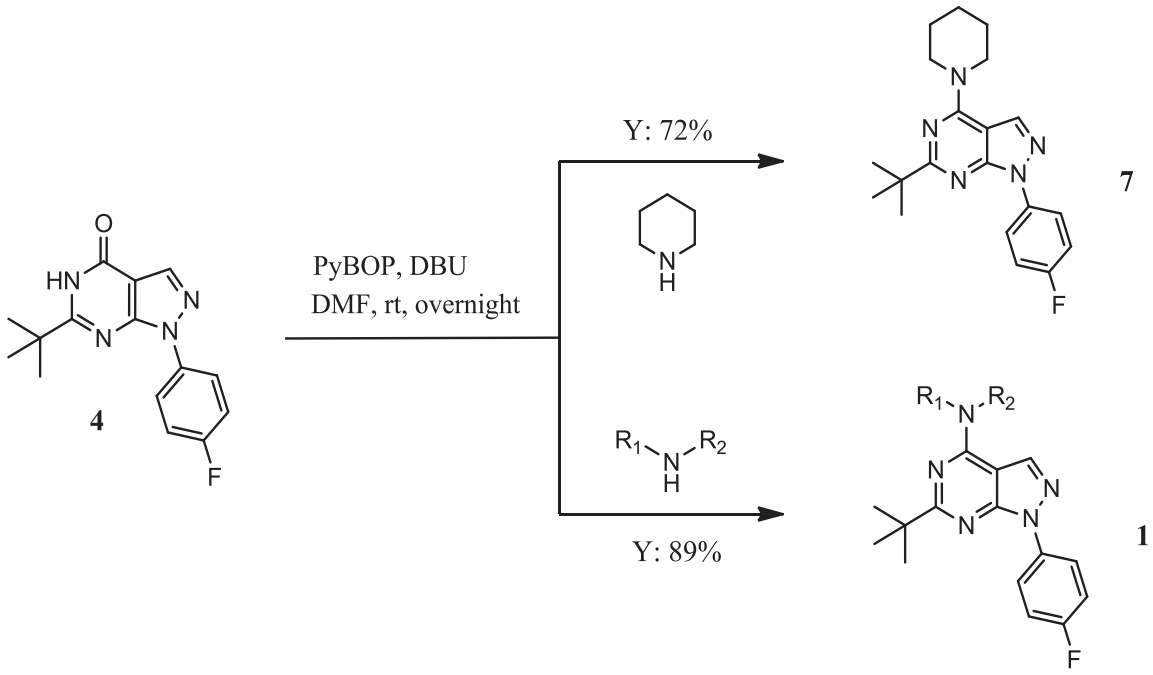
Compound **4** showed good features and the synthesis was scaled up to a 20 ml microwave vial, using 750 mg of starting material. The yield varied from 52% to 59%. Nevertheless, the need for a bigger amount of product, required an increase in the reaction scale. Therefore, the reaction between 5-amino-1-(4-fluorophenyl)-1H-pyrazole-4-carboxamide (1500 mg) and ethyl pivalate, was carried out in a two neck 100 ml round bottom flask and kept under reflux for 24 h (scheme 19). 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**4**) was isolated to give a 46% yield.

Scheme 19 – Synthesis of 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one.



The following step, was the synthesis of the lead compound 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine, through a C-N cross coupling reaction between compound **4** and an amine (scheme 20). The reaction worked well both with piperidine (to give product **7** in 72% yield), and with the masked amine to give the product of interest (**1**) in Astrazenca´s project (89% yield).

Scheme 20 – C-N cross coupling reaction. PyBOP: benzotriazol-1-yl-oxytrpyrrolidinophosphonium hexafluorophosphate; DBU: 1,8-diazobicyclo[5.4.0]undec-7-ene; DMF: dimetilformammide.



On the other hand, the indazoles used in the experiments were purchased or taken from an in-house source.

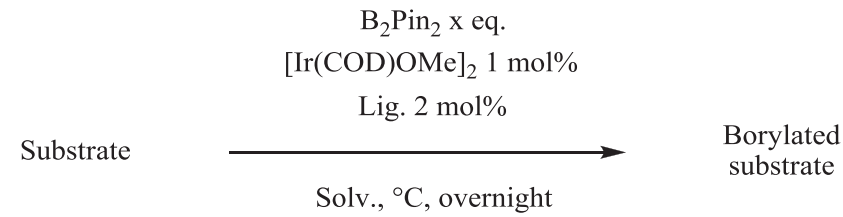
3.2 Borylation experiments

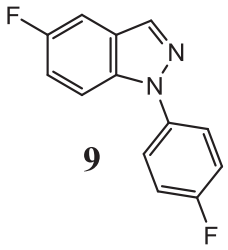
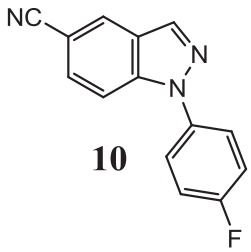
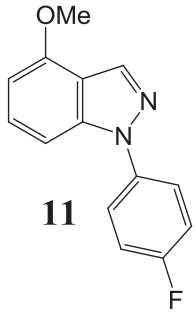
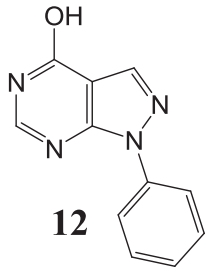
In the first part of this work, two different reaction conditions were used to perform borylation:

- B_2Pin_2 as boron source; a combination of $[Ir(COD)OMe]_2$ (bis(1,5-cyclooctadiene)di-iridium(I)-dimethoxide) and dtbpy (4,4′-di-tert-butyl bipyridine) as catalyst; MTBE as solvent;
- B_2Pin_2 as boron source; a combination of $[Ir(COD)OMe]_2$ (bis(1,5-cyclooctadiene)di-iridium(I)-dimethoxide) and Me_4phen (3,4,7,8-tetramethyl-1,10-phenantroline) as catalyst; THF as solvent.

We began our studies by employing these conditions to substituted indazoles and a pyrazolopyrimidine system (table 2). Comparing the crude product NMR with the starting material NMR, no conversion for all the experiments was observed. Except for entries 2a and 4a, where the low solubility of the substrates in MTBE was an issue, the poor results can be explained with the instability of the catalyst in oxygen. During the preparation of the reaction mixture, the metal-ligand complex was exposed to air oxygen, causing its deactivation.

Table 2 – Borylation of indazoles and pyrazolopyrimidine system.

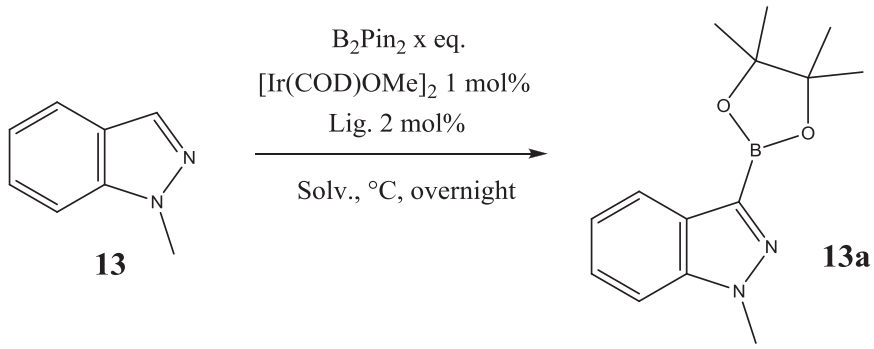


Entry	Substrate	x	Ligand	Temperature	Solvent	Conversion
1a[a]	 **9**	0.5	dtbpy	55 °C	MTBE	0%
1b[b]		1	Me_4phen	80 °C	THF	0%
2a[a]	 **10**	0.5	dtbpy	55 °C	MTBE	0%
2b[b]		1	Me_4phen	80 °C	THF	0%
3a[a]	 **11**	0.5	dtbpy	55 °C	MTBE	0%
3b[b]		1	Me_4phen	80 °C	THF	0%
4a[a]	 **12**	0.5	dtbpy	55 °C	MTBE	0%
4b[b]		1	Me_4phen	80 °C	THF	0%

[a] Reaction conducted on a 0.6 mmol scale, 0.2 M. [b] Reaction conducted on a 0.5 mmol scale, 0.5 M.

In order to confirm this hypothesis, further experiments were performed with 1-methyl indazole (**13**) as substrate (table 3). Substrate **13** was chosen, since borylation experiments on this compound are reported in literature.

Table 3 – Borylation of 1-methyl indazole.



13 **13a**

Entry	x	Ligand	Temperature	Solvent	Glovebox	Conversion
1[a]	0.5	dtbpy	55 °C	MTBE	Out	48%
2[b]	0.5	dtbpy	55 °C	MTBE	In	58%
3[c]	1	Me_4phen	80 °C	THF	Out	0%
4[c]	1	Me_4phen	80 °C	THF	In	80%

[a] Reaction conducted on a 0.3 mmol scale, 0.1 M. [b] Reaction conducted on a 0.6 mmol scale, 0.2 M. [c] Reaction conducted on a 0.5 mmol scale, 0.5 M.

When the experiments were set up outside the glovebox, we got different results. With dtbpy as ligand and MTBE as solvents (entry 1), the conversion was 48% (reactivity of 1-methyl indazole under these conditions was reported in literature). If Me_4phen and THF were used, no conversion was observed. On the other hand, an improvement of conversion was obtained by working inside the glovebox: for the dtbpy system (entry 2) the conversion increased from 48% to 58%, while for the Me_4phen ligand (entry 4) the increase was from 0% to 80%.

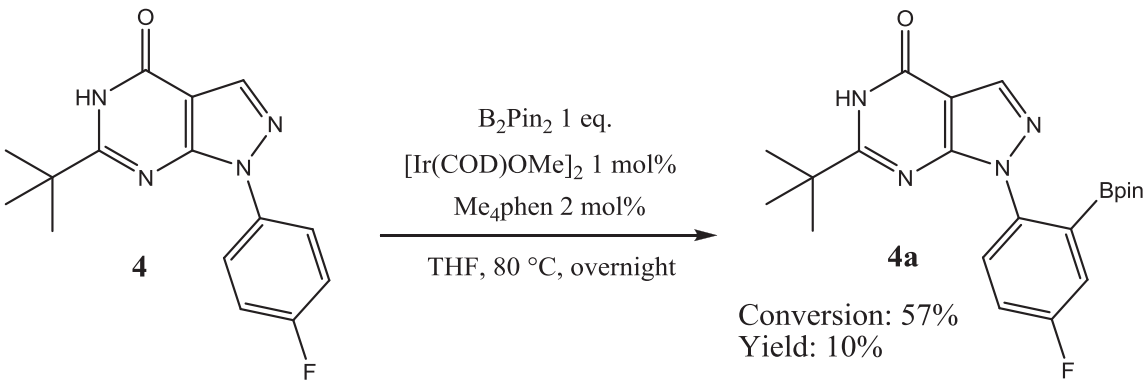
These results confirmed the need to avoid the contact with oxygen, while preparing the reaction mixture. Furthermore, considering the value of conversion and the solubility issue with MTBE, the combination of $[Ir(COD)OMe]_2$, Me_4phen and THF was found to be a better system for borylation.

For these reasons, the following reactions were set up inside the glovebox and dtbpy and MTBE weren´t used anymore.

By NMR analysis of **13a**, it was possible to state that the borylation occurred at 3-position of the 1-methyl indazole (consistent with literature findings[35]).

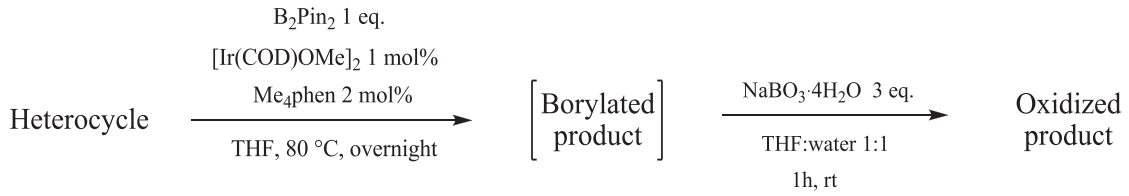
Later, borylation was tested on pyrazolopyrimindine **4** (scheme 21): the conversion was 57% and product **4a** was obtained in a 10% yield. The low value of yield was due to an inefficient purification process and to the presence of many side products. Since in substrate **4** three different C-H bond can be activated, a structure elucidation was done to figure out what regioisomer was obtained. From ^{1}H NMR, the presence of the signal of the hydrogen at the 3-position and the integration of the aromatic signal, suggested that the borylation occurred in the phenyl substituent. The high resolution ^{13}C NMR revealed the coupling between the fluorine atom and the carbon atoms in the aromatic substituent. Therefore, exploiting the values of coupling constants and COSY, HSQC and HMBC analysis, was possible to identify the molecule **4a** as the *ortho* regioisomer.

Scheme 21 – Borylation of 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one.



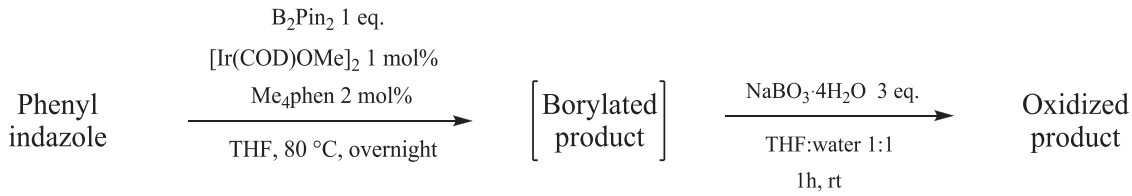
Thereafter we turned our attention to a tandem reaction sequence (scheme 22). We decided to use the crude product of the borylation reaction to run an oxidation[40] with sodium perborate, in order to convert the boronic ester into an alcoholic moiety. The choice to conduct these tandem reactions was made to showcase the potential of late stage activation. Moreover, the borylated products are not very stable because of hydrolysis reaction, thus arising problems in the analysis step (especially in NMR and LC-MS).

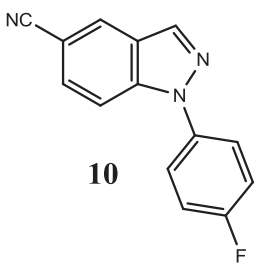
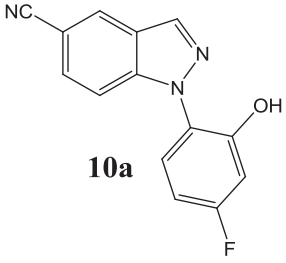
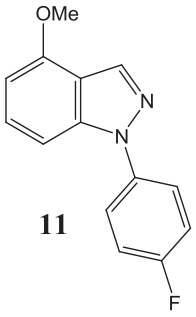
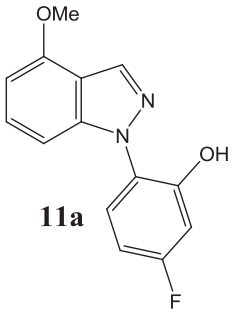
Scheme 22 – Tandem reaction on heterocycle: borylation followed by oxidation.



First, we went back to 1-(4-fluorophenyl)-1H-indazole-5-carbonitrile (**10**) and 1-(4-fluorophenyl)-4-methoxy-1H-indazole (**11**): the results are shown in table 4. For both indazoles, the conversion was very good (80% and 88%), while the yield was low (19% and 5%), due to the formation of side products.

Table 4 – Tandem borylation/oxidation of phenyl indazole.



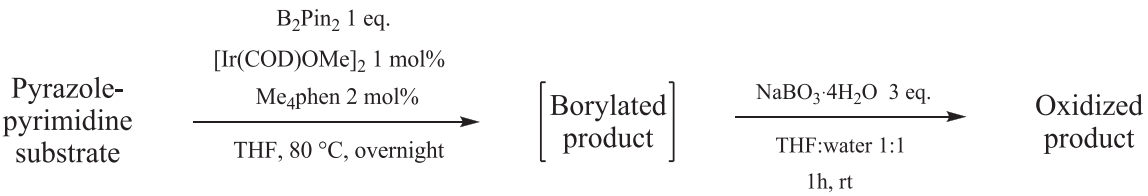
Entry	Phenyl indazole	Product	Conversion	Yield[c]
1[a]	 **10**	 **10a**	88%	19%
2[b]	 **11**	 **11a**	80%	5%

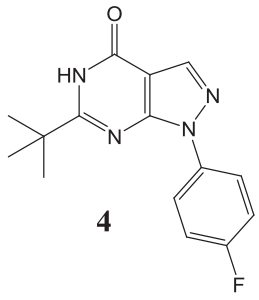
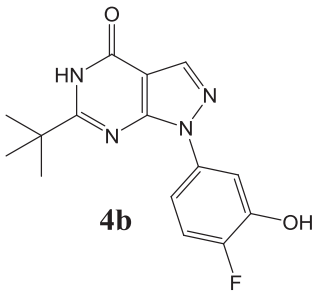
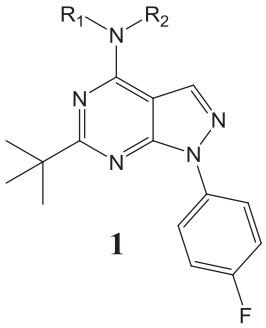
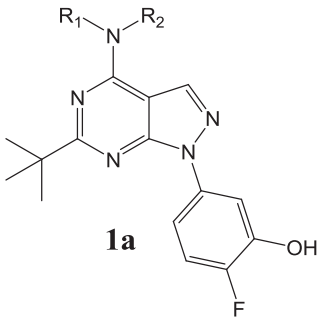
[a] Reaction conducted on a 0.5 mmol scale, 0.6 M. [b] Reaction conducted on a 0.4 mmol scale, 0.6 M. [c] Yield over two steps.

From NMR analysis it was clear that no reaction occurred in 3 position. After purification and structure elucidation, the OH group was found to be in the phenyl moiety, to give the *ortho*-phenol product **10a** and **11a**.

We next investigated pyrazolopyrimidine systems. The results are shown in table 5.

Table 5 - Tandem borylation/oxidation of pyrazolopyrimidine system.



Entry	Substrate	Product	Conversion	Yield
1[a]	 **4**	 **4b**	53%	13%
2[b]	 **1**	 **1a**	97%	35%

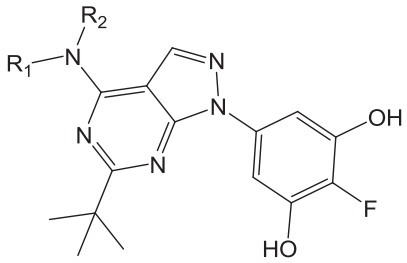
[a] Reaction conducted on a 0.12 mmol scale, 0.3 M. [b] Reaction conducted on a 0.17 mmol scale, 0.4 M

Substrate **4** (entry 1), reacted with a conversion of 53%. After purification and structure elucidation of the oxidized product **4b** (13% yield), it was possible to state that the tandem reaction led to *meta*-phenol regioisomer.

For 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**1,** entry 2), the conversion was 97%. From ^{19}F NMR of crude product, the presence of two products in a ratio of 1,5:1 was observed. After purification and structure elucidation, the main product

was identified as the *meta*-phenol regioisomer **1a** (35% yield). The minor product was isolated and was identified as the *meta*-diol **1b** (34% yield, figure 16).

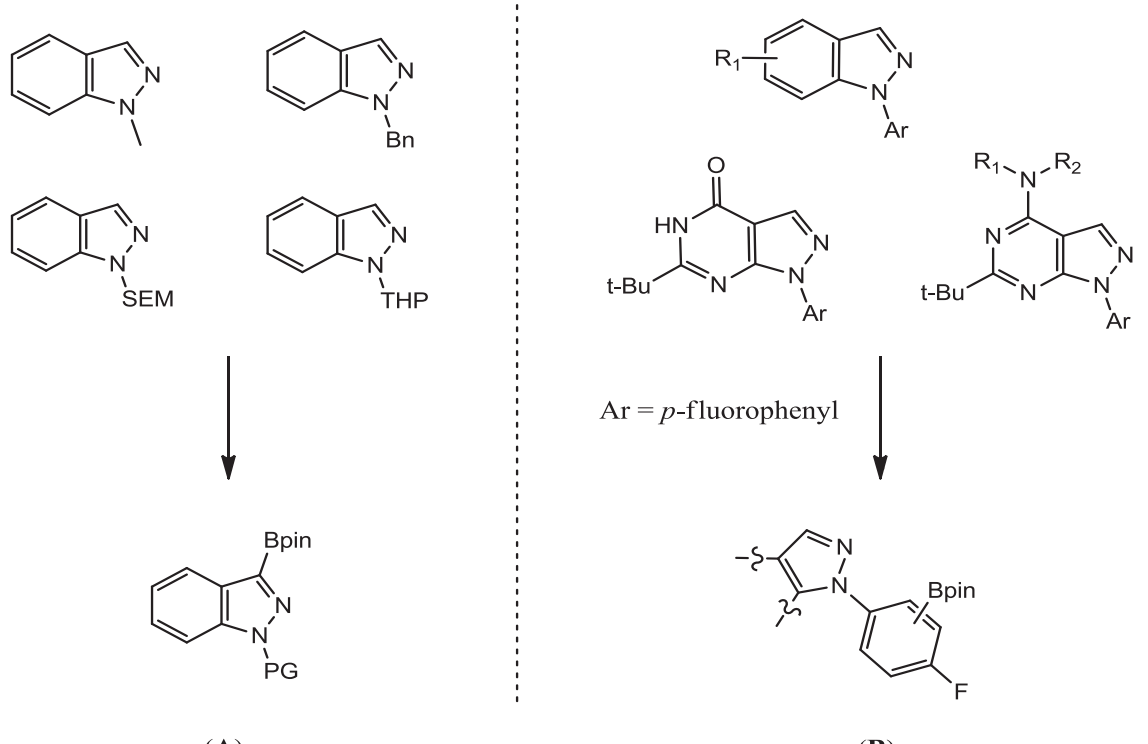
Figure 16 – Secondary product obtained from tandem reactions of substrate 1.



1b

Comparing the results in table 3,4 and 5 (reaction carried out under the same condition), a different regioselectivity can be noticed. As reported in literature, borylation of 1-protected-1H-idazoles (with alkyl protecting group such as methyl, Bn, SEM, THP), usually occurs at the 3-position[35] (figure 17A). This kind of regioselectivity was followed when borylation was carried out with 1-methyl-1H-indazoles (table 3). As a consequence, we expected that also 1-phenyl indazoles and 1-phenyl pyrazolopyrimidine could react with B_2Pin_2 at the 3-position of the pyrazole ring. However a different regioselectivity was followed, since for substrates **1**, **4**, **10** and **11** (table 4 and 5), the borylation occurred in the arylic substituent (figure 17B).

Figure 17 – Different regioselectivity for indazoles and pyrazolopyrimidine. PG = protecting group.



(A) **(B)**

Moreover, the reaction in the *p*-fluorophenyl substituent occurred at different position, since we got *ortho* regioisomers for products **4a**, **10a**, **11a** and *meta*-phenols for products **1a** and **4b**. In order to figure out the reasons of this strange regioselectivity, we focused on the procedures that were used to run the borylation.

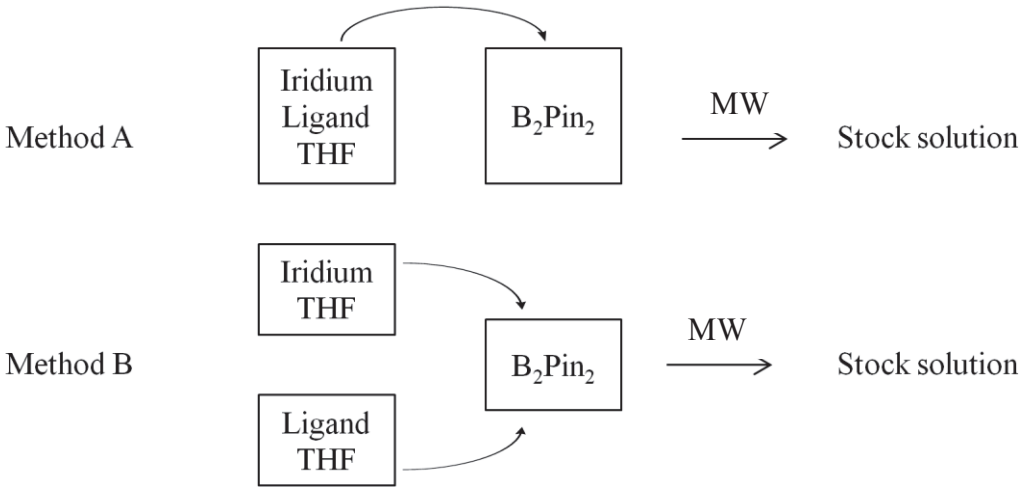
Since we had many compounds to screen, we prepared a stock solution containing the active catalyst and THF. Then, an aliquot of the stock solution was added to the substrates. The preparation of the stock solution consisted of two steps:

1- making of a mixture of B_2Pin_2, $[Ir(COD)OMe]_2$, Me_4phen and THF;
2- heating of the mixture at 80 °C for 1h in a microwave reactor.

Two different protocols were followed in the formation of the mixture of Iridium, ligand, B_2Pin_2 and solvent:

- method A: $[Ir(COD)OMe]_2$, Me_4phen and THF were added in a vial and later poured into a different vial, where B_2Pin_2 was previously weighed (figure 18);
- method B: $[Ir(COD)OMe]_2$ and THF were added to a vial; Me_4phen and THF were added to a different vial; both mixtures were poured in a vial where B_2Pin_2 was previously weighed (figure 18).

Figure 18 – Method of preparation of stock mixture. MW = microwave.



While a sample was prepared with method B, we noticed that the Me_4phen had low solubility in THF ($[Ir(COD)OMe]_2$ and B_2Pin_2 were totally soluble). To arrange the active catalyst in the right way, it was necessary a ratio of 2:1 between Me_4phen and $[Ir(COD)OMe]_2$. But, because the Me_4phen solubility was an issue, when the ligand/THF mixture was poured into the B_2Pin_2 vial (method A and B), it was impossible to know

how much ligand the mixture would contain. So we could have stock solutions with the right ratio between ligand and metal, stock solutions with the wrong ratio or stock solutions with no ligand, each reacting in a different way and leading to different product.

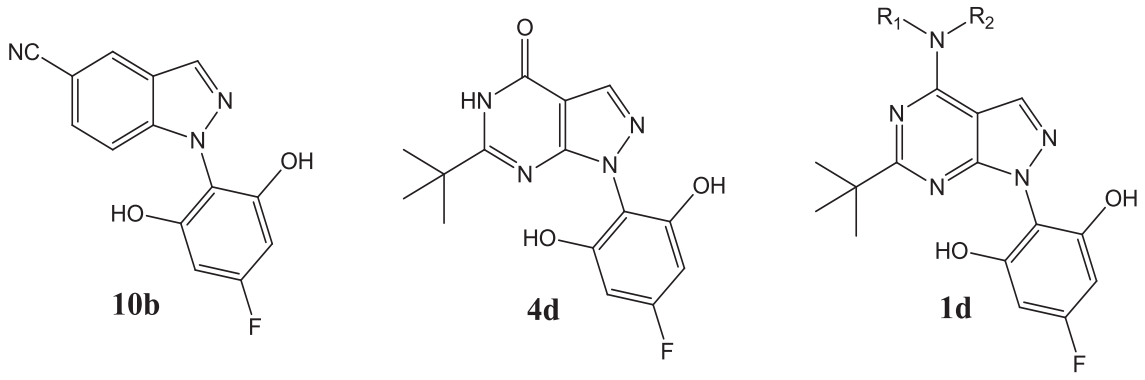
Therefore we decided to run some reactions without ligand and some reactions with a procedure that would guarantee the right ratio between Me_4phen and $[Ir(COD)OMe]_2$:

- protocol C: the substrate, B_2Pin_2, $[Ir(COD)OMe]_2$ and THF were added in a vial. The mixture was heated at 80 °C overnight;
- protocol D: $[Ir(COD)OMe]_2$ and THF were added to a vial and later poured into a different vial, where B_2Pin_2 and Me_4phen were previously weighed. The mixture was heated at 80 °C for 1h in a microwave reactor to form a stock solution. The stock solution and the substrate were later added to the same vial that was heated at 80 °C overnight.

The protocols C and D were ran on substrates **1**, **4** and **10**. The results obtained with protocol C are shown in table 6. For all the substrates, the regioselectivity led to the *ortho*-phenol in all the experiments.

For substrate **10** (entry 1), the conversion was very good (87%) and the *ortho*-phenol **10a** (35% yield) was the main product. Also the *ortho*-diol **10b** (figure 19) was isolated (4% yield).

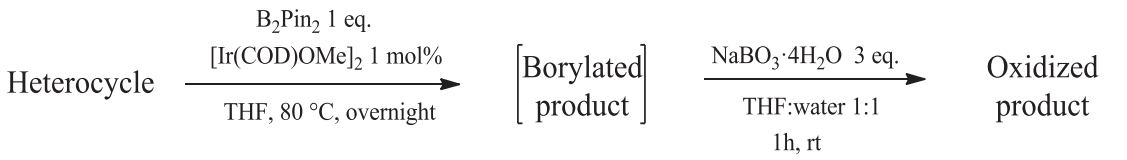
Figure 19 - Secondary products from the reactions in table 5.

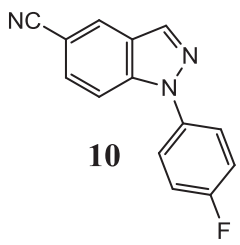
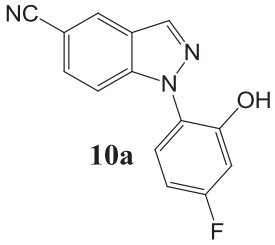
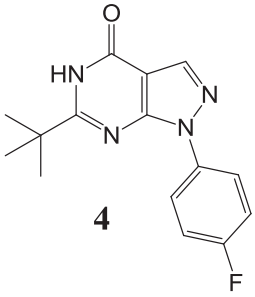
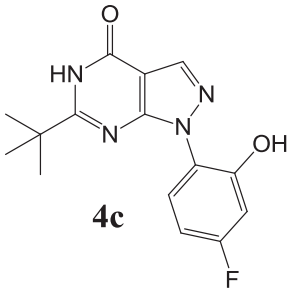
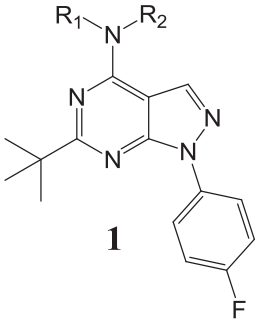
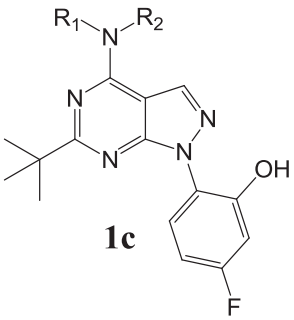


Five reactions were run on substrate **1** and for all of them the *ortho*-phenol **1c** was obtained. Also the *ortho*-diol **1d** (figure 19) was isolated. In the entries 4 and 5 the yield for the mono phenol was 24% and 25%. When the reaction was run with 0,5 eq. of B_2Pin_2 (entry 6), an increase of selectivity to product **1c** was observed (M:D = 7.5:1),

together with a decrease in conversion (60% against 94% and 75% of entries 4 and 5), but with a similar value of yield (22%).

Table 6 - Tandem borylation/oxidation with protocol C.



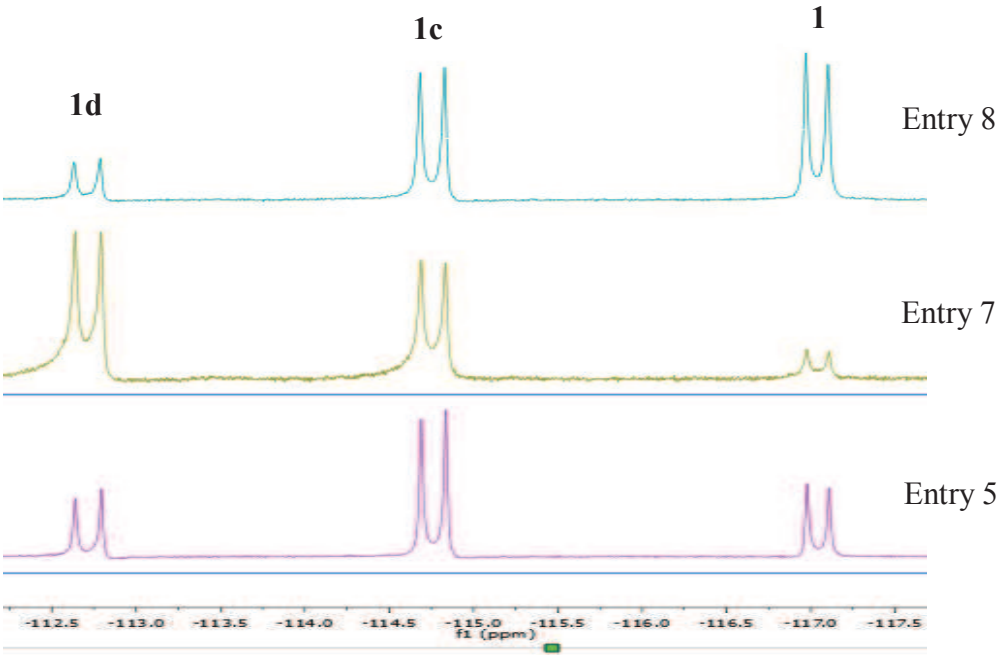
Substrate	Entry	Product	Conv[f]	Yield[g]	M:D[h]
 **10**	1[a]	 **10a**	87%	35%	2.13:1
 **4**	2[b]	 **4c**	82%	-	1.54:1
	3[a]		75%	-	5.24:1
 **1**	4[a]	 **1c**	94%	24% (30%)	1:1.47
	5[a]		75%	25% (7%)	2.33:1
	6[c]		60%	22% (3%)	7.5:1
	7[d]		92%	-	1:1.36
	8[e]		56%	-	3.15:1

[a] Reaction conducted on a 0.17 mmol scale, 0.4 M. [b] Reaction conducted on a 0.12 mmol scale, 0.6 M. [c] Reaction conducted on a 0.17 mmol scale, 0.4 M, B_2Pin_2 0.5 eq.. [d] Reaction conducted on a 0.17 mmol scale, 0.4 M, over weekend. [e] Reaction conducted on a 0.17 mmol scale, 0.4 M, over weekend, B_2Pin_2 0.5 eq.. [f] Conversion. [g] In parentheses the yield of ortho diol product. [h] Ratio between ortho mono and ortho diol calculated from crude mixture ^{19}F NMR.

In entries 7 and 8 the reaction were ran over weekend. When 1 eq. of B_2Pin_2 was used, high conversion was obtained and **1d** was the main product. On the other hand, with 0,5 eq. of B_2Pin_2, a lower conversion was obtained and **1c** was the main product. Considering the results for substrate **1**, an optimization of the borylation reaction condition, would lead to better values of selectivity and conversion.

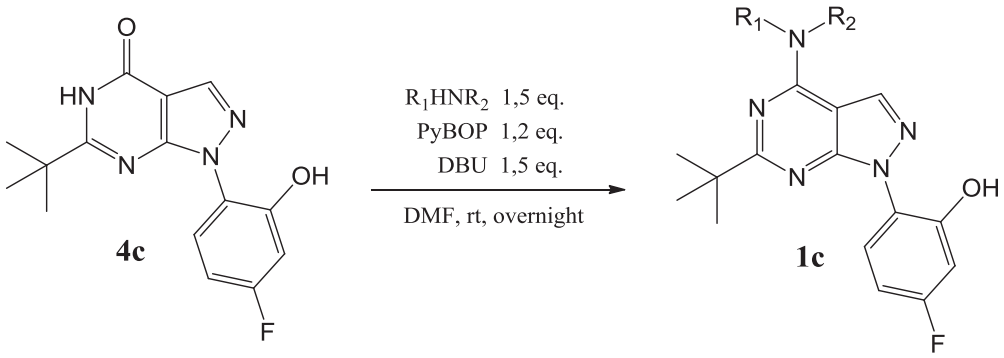
For the entries 4, 5 and 6 the product **1c** was purified and the structure was solved by NMR analysis. In the last two experiments (entries 7 and 8), no purification was done: the structure of the product was confirmed by comparing the ^{19}F NMRs of the crude mixtures with the spectrum of the crude of entry 5 (figure 20). The peak around 117 ppm is the unconverted substrate **1**; the peak around 114.75 ppm is the product **1c**; the peak around 112.7 ppm is the product **1d**.

Figure 20 - Comparison between spectra of entries 5, 7 and 8.



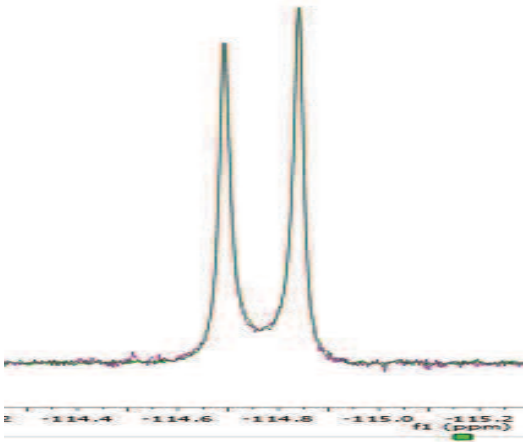
For substrate **4** (entries 2 and 3), the conversion was good (82% and 75%), and both products **4c** and **4d** were observed. Nevertheless, the crude mixtures were not purified: they were combined and another synthetic step was done on them. The purpose was to convert the products **4c** and **4d** in the molecules **1c** and **1d**, through a coupling reaction (scheme 23).

Scheme 23 - Coupling reaction for molecule 4c to 1c.



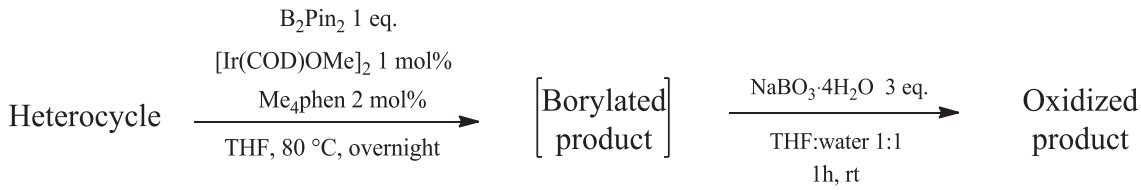
The product **1c** was isolated to give a 6% yield over three steps (borylation, oxidation and coupling). To prove the structure, its ^{19}F NMR was compared with the spectrum of the pure compound in the entry 5 (figure 21). The match was perfect, thus confirming the presence of the *ortho*-phenol. The *ortho*-diol product wasn´t observed and it was likely lost during the reaction work up.

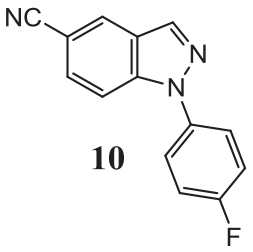
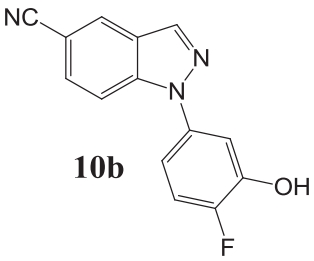
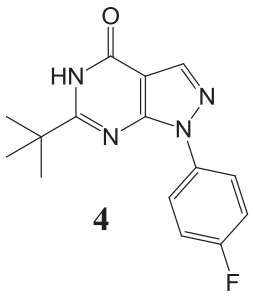
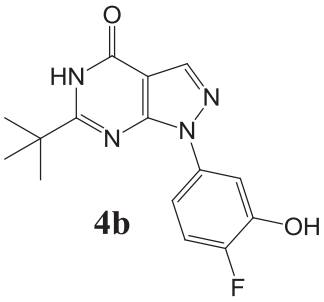
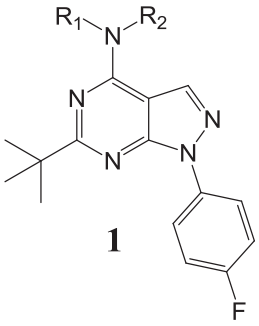
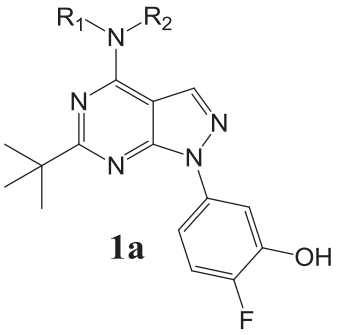
Figure 21 - ^{19}F NMR comparison between the coupled product and the product from entry 5.



The results obtained with protocol D are shown in table 7. For all the substrates, the regioselectivity led to the *meta*-phenol in all the experiments.

Table 7 - Tandem borylation/oxidation with protocol D.



Substrate	Entry	Product	Conv[b]	Yield[c]	M:D[d]
 **10**	1[a]	 **10b**	~ 90%	-	-
 **4**	2[a]	 **4b**	45%	-	-
 **1**	3[a]	 **1a**	100%	37% (32%)	1.35:1

[a] Reaction conducted on a 0.17 mmol scale, 0.4 M. [b] Conversion. [c] In parentheses the yield of ortho diol product. [d] Ratio between ortho mono and ortho diol calculated from crude mixture ^{19}F NMR.

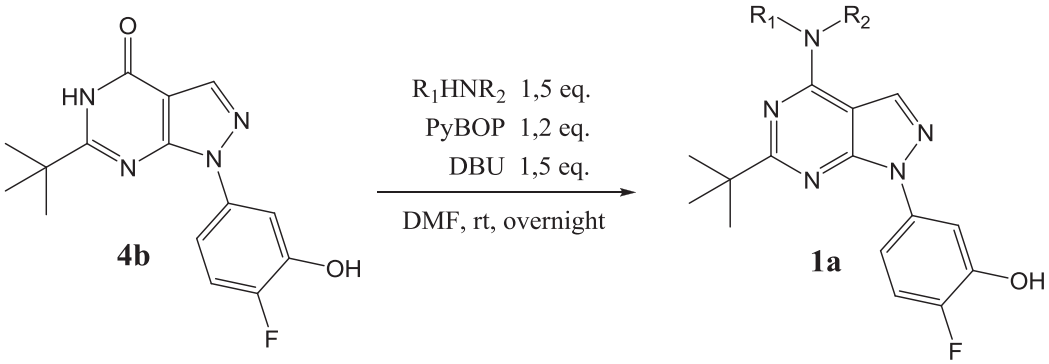
For substrate **10** (entry 1), high conversion was obtained (~ 90%). From NMR of crude product, a complex mixture with five main products was observed, therefore we decided to skip the purification step. Likely, borylation occurred both in the aryl substituent and in the aromatic ring fused with the pyrazol. However, we compared the ^{19}F NMR of the crude mixture with the spectrum of the pure *ortho*-phenol **10a** (table 6, entry 1). The

peak of the *ortho* regioisomer didn´t fit with any peaks of the crude mixture. So it could be possible that the borylation occurred in the *meta* position of the aryl substituent.

The tandem reactions for substrate **1** (entry 3), with a 100% conversion, led to both product **1a** (37% yield) and **1b** (32% yield).

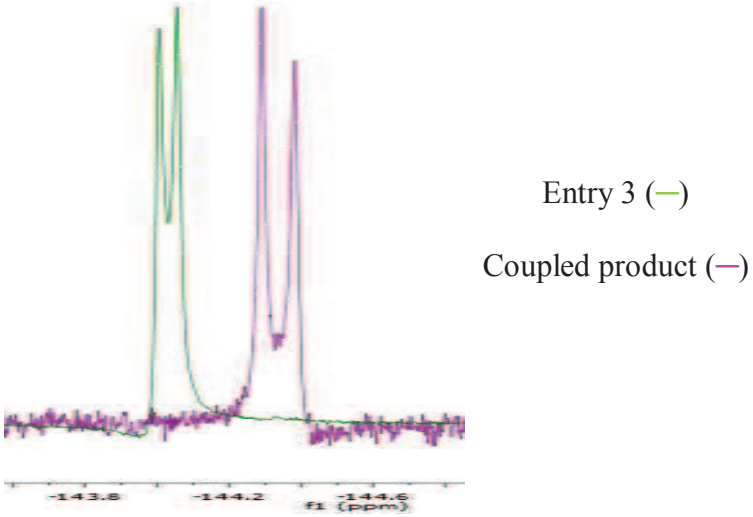
For substrate **4** (entry 2), the conversion was 45%, and only the mono phenol **4b** was observed. Nevertheless the crude mixture wasn´t purified and another synthetic step was done on it. The purpose was to convert the products **4b** in the molecule **1a**, through a coupling reaction (scheme 24).

Scheme 24 - Coupling reaction for molecule 4b and 1a.



The product **1a** was isolated to give a 5% yield over three steps (borylation, oxidation and coupling). To prove the structure, its ^{19}F NMR was compared with the spectrum of the pure compound in the entry 3 (figure 22). The match between the peaks confirmed the presence of the *meta*-phenol regioisomer.

Figure 22 - ^{19}F NMR comparison between the coupled product and the product from entry 3.



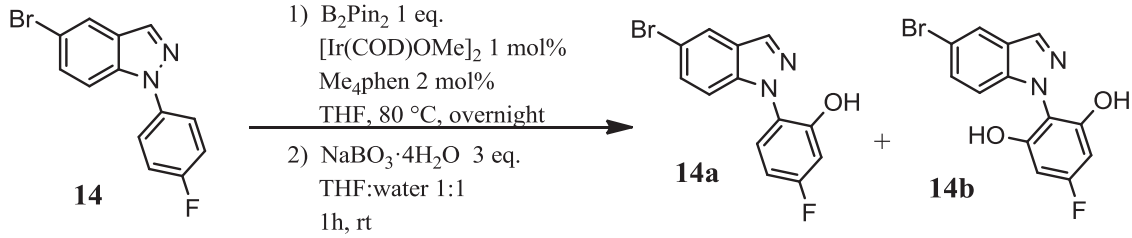
The results in tables 6 and 7 show different regioselectivity, depending on the procedure that was used to run the experiments. The Ir-catalyzed borylation shows regioselectivity controlled by steric effects. When $[Ir(COD)OMe]_2$ and Me_4phen made up the catalytic system (protocol C), the Bpin ended up in the *meta* position, that is less hindered position in the phenyl substituent. Therefore, when protocol C is applied, a sterically controlled mechanism is followed.

If the reaction is carried out with no ligand (protocol D), the borylation occurs in the *ortho* position. So, in this case, no steric effect is shown. It´s possible that the nitrogen at 2-position could act as directing group. As a consequence it would drive the borylation to the closer C-H bond, which is placed in the ortho position of the arylic substituent.

Since one of the procedure that we tested worked without ligand, no problems should arise by setting up the reactions outside the glovebox. The lack of Me_4phen prevented the formation of the air sensitive catalyst, enabling the contact with air.

So we decided to test 5-bromo-1-(4-fluorophenyl)-1H-indazole (**14**): protocol D was used and the samples were prepared both inside and outside the glovebox. The results are shown in table 8.

Table 8 - Tandem Borylation/oxidation of 5-bromo-1-(4-fluorophenyl)-1H-indazole.



Entry	Glovebox	Conversion	Yield[a]	M:D[b]
1	In	95%	14% (22%)	1:1.83
2	Out	87%	27% (13%)	1.2:1

[a] In parentheses the yield of ortho diol product **14b**. [b] Ratio between ortho mono and ortho diol calculated from crude mixture ^{19}F NMR.

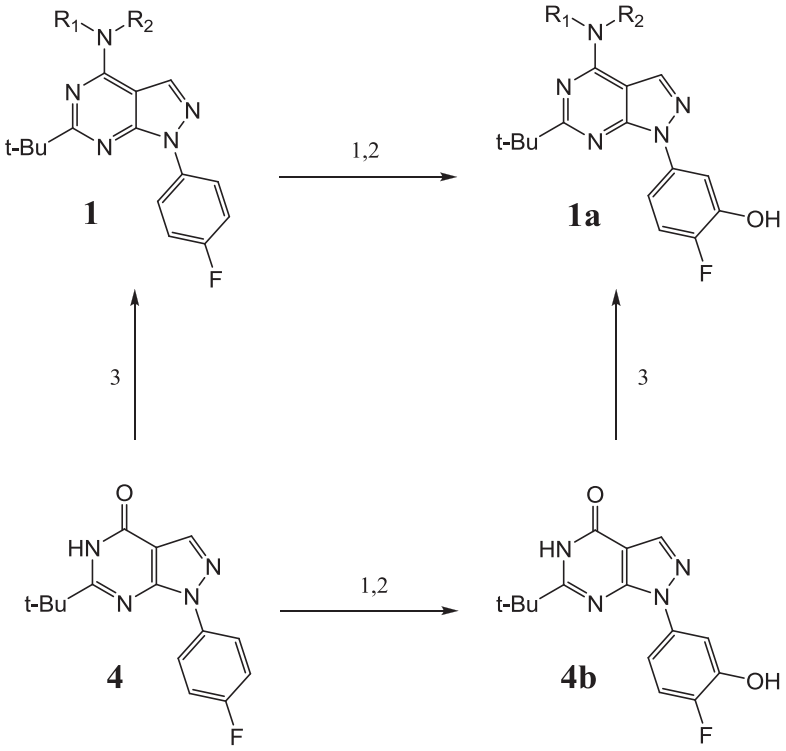
In both experiments high conversion was observed (95% and 87%). When the reaction was set up in the glovebox (entry 1), the *ortho*-phenol **14a** was isolate in a 14% yield, while the main product was the *ortho*-diol **14b** (22% yield). On the other hand, without

the glovebox (entry 2), the ratio between mono and diphenol was 1.2:1. The product **14a** was isolated in 27% yield and the product **14b** in 13% yield.
Since the tandem borylation/oxidation worked also when the reactions were set up outside the glovebox, we demonstrated that would be possible to perform protocol C in an easier way.

4 Conclusions

The aim of the project was the development of a protocol, for the metal catalyzed C-H borylation of 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (figure 14), a compound with biological activity within an AstraZeneca's project.
A key feature in borylation, was the setting up of the reactions inside the glovebox, in order to avoid the deactivation of the active catalyst. In all the experiments the boron source was B_2Pin_2 and the metal was supplied by the complex $[Ir(COD)OMe]_2$, since iridium has been widely reported in literature as one of the best metals in borylation reaction. Investigation of the borylation of 1-methyl-1H-indazoles (table 3), revealed that reactions conducted overnight with Me_4phen as ligand, THF as solvent and 80 °C were more efficient than the reaction conducted overnight with dtbpy as ligand, MTBE as solvent and 55 °C.
Borylation of indazoles has been reported to occur at the 2-position in the five-membered ring. Nevertheless, we found that aryl pyrazolopyrimidine and aryl indazoles react exclusively in the phenyl substituent.
To showcase the potential of late stage functionalization, the substrates underwent a tandem borylation/functionalization (scheme 22). The crude product from the borylation reaction underwent oxidation with sodium perborate, in order to transform the boronic ester in an OH group.
By following this one-pot procedure, substrate **1** could be easily transformed into the corresponding phenol. When the catalytic system Ir- Me_4phen was used, the reactions led to the *meta*-phenol regioisomer **1a**, since the borylation reaction followed a steric controlled mechanism. Also substrate **4** could be borylated yielding the same regioisomer: this was confirmed by transforming **4b** in **1a** (scheme 25).

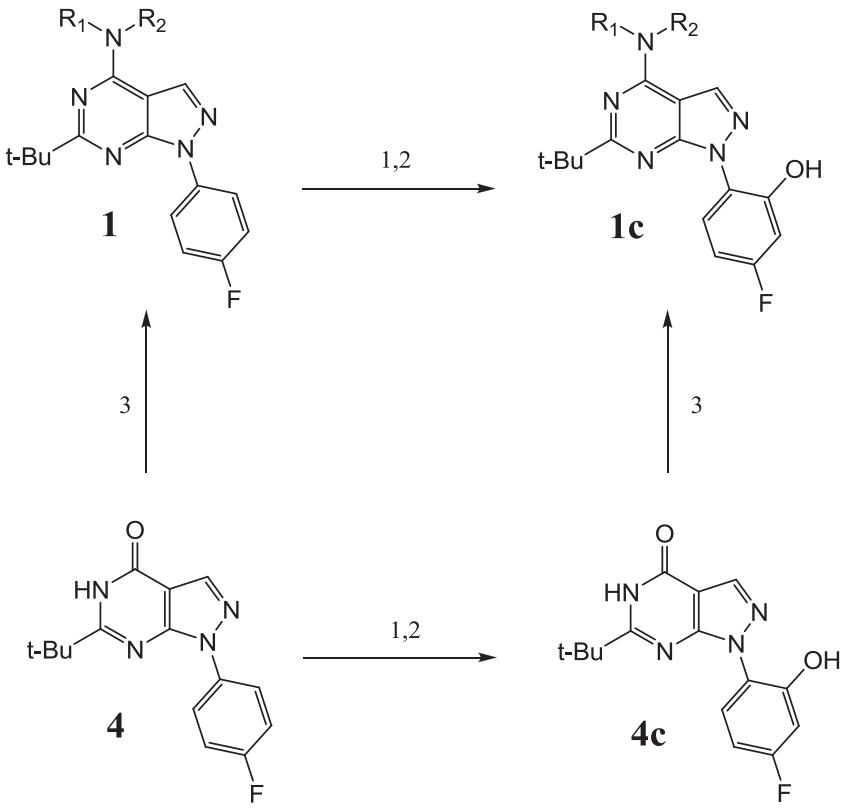
Scheme 25 – Tandem borylation/oxidation leading to *meta* regioisomer.



1) B_2Pin_2, $[Ir(COD)OMe]_2$, Me_4phen, THF, 80 °C, ovnight
2) $NaBO_3 \cdot 4\ H_2O$ (3 equiv), THF, H_2O, RT, 1 h
3) Amine, DBU, PyBop, DMF, ovnight

When the borylation reactions were carried out without Me_4phen, the reactions led to the *ortho*-phenol regioisomer **1c**, since in this case the nitrogen at the 2-positon in the pyrazole ring could act as directing group. Also substrate **4** could be borylated yielding the same regioisomer: this was confirmed by transforming **4c** in **1c** (scheme 26).

Scheme 26 – Tandem borylation/oxidation leading to ortho regioisomer.



1) B_2Pin_2, $[Ir(COD)OMe]_2$, THF, 80 °C, ovnight
2) $NaBO_3 \cdot 4\ H_2O$ (3 equiv), THF, H_2O, RT, 1 h
3) Amine, DBU, PyBop, DMF, ovnight

5 Experimental section

General information

Reagents and solvents were purchased from Sigma-Aldrich, Fluka, Enamine, Combi-blocks, Strem and Alfa Aesar. All indazoles were purchased or taken from inhouse source. A part from 1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol, the other prazolopyrimidine substrate were synthesized using in-house protocol. All reagents, solvents and starting materials were used with no further purification.

Borylation reactions requiring an inert atmosphere were conducted in a Braun gloveboxe. Experimental procedures that do not mention the use of an inert atmosphere were

conducted in air. THF used as a solvent for the borylation reactions was degassed with Argon for 45 minutes. Glassware was oven dried before all borylation reactions.

TLCs were performed on Merck glass-backed plates with a silica gel layer. Microwave reactions were carried out in sealed vials using a Biotage microwave reactor.

Flash chromatographies were performed with an automated Biotage instrument on pre-packed silica SNAP cartridge.

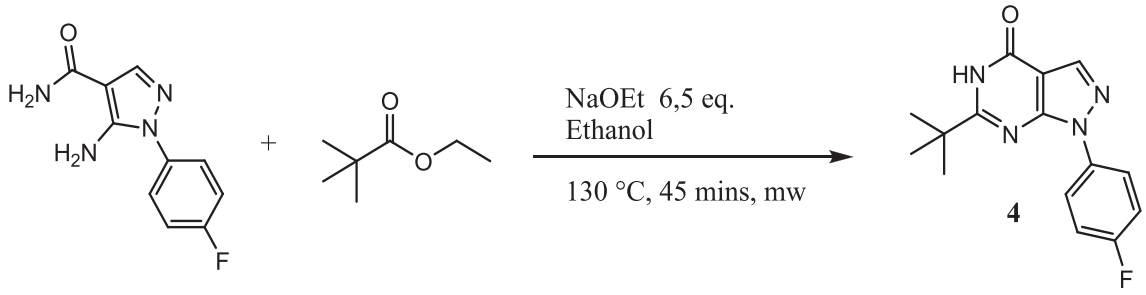
LC/MS analyses were recorded on a Waters ZMD, LC column x Terra MS C_8 (Waters), detection with a HP 1100 MS-detector diode array.

NMR spectra were recorded using a Neptune 500 MHz instrument, in $CDCl_3$ solutions ($CDCl_3$ ^1H = 7.26 ppm, ^{13}C = 77.15 ppm). All chemical shifts are reported in ppm relative to TMS, and the coupling constants are reported in Hz. Multiplicities are reported using the following abbreviations; s (singlet), d (doublet), dd (doublet of doublet), ddd (double of double of doublet), dt (doublet of triplet), t (triplet), q (quartet), m (multiplet) and br (broad).

Conversion was calculated from ^{19}F NMR of the crude mixture through the ratio between the integrals of the peaks of products and reagent. The yield was calculated by weighing the product after purification.

Due to patent reason, for 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**7**) and its derivatives, only NMR shifts for the fluorophenyl moiety are reported.

Synthesis of 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (3.4 mmol scale)

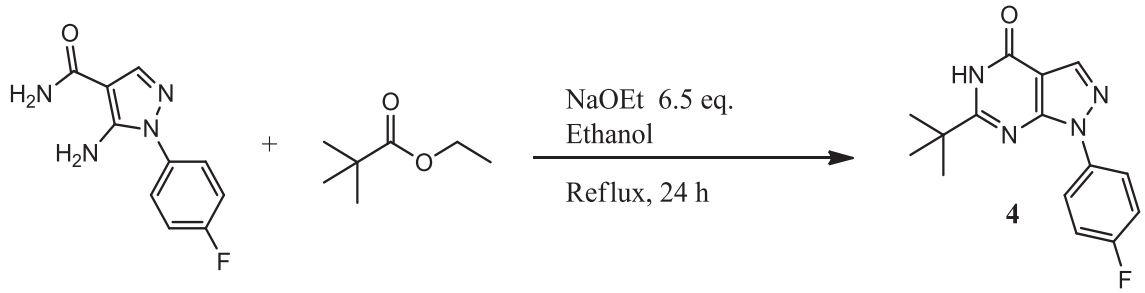


5-amino-1-(4-fluorophenyl)-1H-pyrazole-4-carboxamide (755 mg, 3.43 mmol, 1 eq.) and ethyl pivalate (5.2 ml, 34.3 mmol, 10 eq.), were suspended in absolute ethanol (6 ml) in a

20 ml microwave vial equipped with a magnetic stirrer. Sodium ethoxide (8.3 ml, 22.2 mmol, 6.5 eq.), was carefully added. Then the vial was sealed and heated for 45 minutes at 130 °C in a microwave reactor. The reaction was cooled down at room temperature, diluted with EtOAc and brine, and poured in a separatory funnel. The pH was adjusted to 7 by addition of HCl (3.8 M), and the water layer was extracted three times with EtOAc (20 ml). The combined organic extracts were filtered through a phase separator and concentrated with a rotary evaporator. LC-MS and NMR were run on the crude product. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 20% to 60% of EtOAc in heptane over 10CV was used as mobile phase. The product was collected using the wavelength 280 nm. The collected fractions were concentrated at the rotary evaporator and 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one was obtained as a white solid.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 1.48 (s, 9H), 7.17 – 7.23 (m, 2H), 8.13 – 8.18 (m, 2H), 8.21 (s, 1H), 10.23 (s, 1H).
^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -115.15.

Synthesis of 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (6.8 mmol scale)

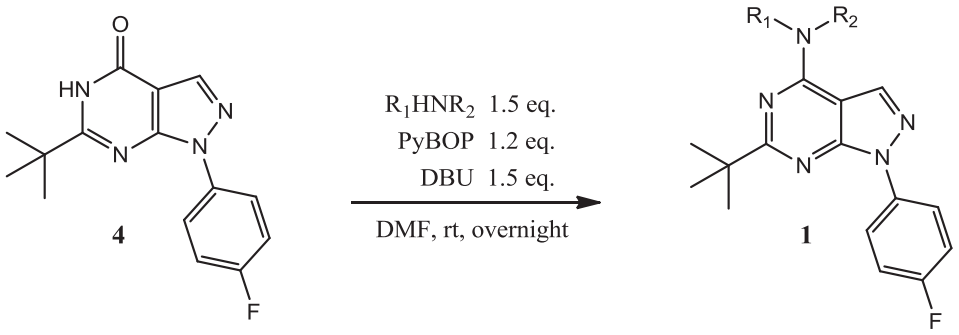


5-amino-1-(4-fluorophenyl)-1H-pyrazole-4-carboxamide (1500 mg, 6.8 mmol, 1 eq.) and ethyl pivalate (10.3 ml, 68 mmol, 10 eq.), were suspended in absolute ethanol (12 ml) in a two neck 100 ml round bottom flask, equipped with a condenser, a septa and as magnetic stirrer. Sodium ethoxide (19 ml, 51 mmol, 7.5 eq.), was carefully added. The flask was kept under a nitrogen atmosphere and went under reflux for 24 hours. The reaction was cooled down at room temperature, diluted with EtOAc and brine, and

poured in a separatory funnel. The pH was adjusted to 7 by addition of HCl (3.8 M), and the water layer was extracted three times with EtOAc (20 ml). The combined organic extracts were filtered through a phase separator and concentrated with a rotary evaporator. LC-MS and NMR were run on the crude product. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 100g column. A gradient from 20% to 60% of EtOAc in heptane over 10CV was used as mobile phase. The product was collected using the wavelength 280 nm. The collected fractions were concentrated at the rotary evaporator and 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one was obtained as a white solid.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 1.48 (s, 9H), 7.17 – 7.23 (m, 2H), 8.13 – 8.18 (m, 2H), 8.21 (s, 1H), 10.23 (s, 1H).
^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -115.15.

Procedure for the amination of 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (440 mg, 1.54 mmol, 1 eq.) and PyBOP (962 mg, 1.85 mmol, 1.2 eq.) were dissolved in DMF (11 ml), in a 50 ml round bottom flask equipped with a magnetic stirrer. DBU (1M in ethyl acetate) (2.3 mL, 2.31 mmol, 1.5 eq.) and R_1HNR_2 (1,5 eq.) were added to the flask. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (20 ml). The organic phase was washed twice with sodium bicarbonate (8%) and twice with brine. Later the organic phase was filtered through a phase separator and concentrated with a rotary evaporator. The residue was purified by automated flash

chromatography on a Biotage® KP-SIL 100g column. A gradient from 20% to 60% of EtOAc in heptane over 10CV was used as mobile phase. The product was collected using the wavelength 280 nm. The collected fractions were concentrated at the rotary evaporator and 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (**7**) was obtained as a transparent oil.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 7.18 (t, 2H), 8.29 – 8.42 (m, 2H).
^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -117.06.

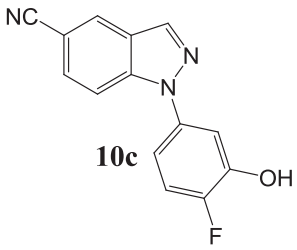
General procedures for tandem borylation/oxidation of 1-phenyl indazoles and pyrazolopyrimidine

A – Synthesis of *meta*-phenol regioisomer

Inside a glovebox, di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (4.51 mg), B_2Pin_2 (172 mg), Me_4phen (3.2 mg) and THF (0.8 ml) were added to a 2 ml microwave vial. The vial was equipped with a magnetic stirrer and sealed. It was taken out the glovebox and heated at 80 °C for 1h in a microwave reactor. After that, inside a glovebox, 0.2 ml of the mixture of B_2Pin_2 (43 mg, 0.17 mmol, 1 eq.), $[Ir(COD)OMe]_2$ (1.13 mg, 0.0017 mmol, 1%) and Me_4phen (0.8 mg, 0.0034 mmol, 2%), was added to a 2 ml vial (equipped with a magnetic stirrer), where the substrate (0.17 mmol) was previously added. To the vial was added 0.2 ml of THF. The vial was sealed and taken out from the glovebox. The vial was heated at 80 °C overnight. The reaction was cooled down at room temperature and the mixture was transferred to a 10 ml vial, equipped with a magnetic stirrer. The reaction mixture was diluted with 4 ml of THF and 4 ml of water. Then sodium perborate (78 mg, 0.51 mmol, 3 eq.) was added and the vial was stirred at room temperature for 1h. The reaction mixture was diluted with EtOAc (20 ml) and later poured into a separatory funnel, where it was washed with ammonium chloride (10%, 20 ml). The organic phase was filtered through a phase separator and concentrated with a rotary evaporator. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 25g column. A gradient from 30% to 80% of EtOAc in heptane over 10CV was used as mobile phase. The product was collected using the wavelength 250 nm. The collected

fractions were concentrated at the rotary evaporator and the meta phenol product was obtained.

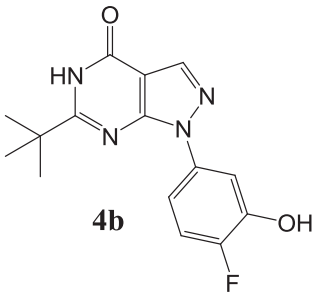
1-(4-fluoro-3-hydroxyphenyl)-1H-indazole-5-carbonitrile



10c

The synthesis was conducted according to the general procedure with 1-(4-fluorophenyl)-1H-indazole-5-carbonitrile (40 mg), as starting material. In the ^{19}F NMR of the crude mixture, five products were observed. Therefore no further purification was done.

6-*tert*-butyl-1-(4-fluoro-3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



4b

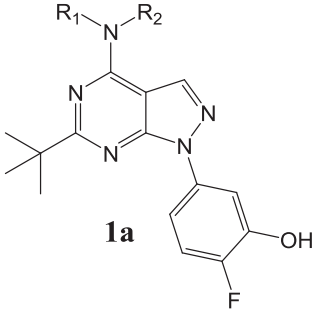
The synthesis was conducted according to the general procedure with 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (48 mg), as starting material.

^{1}H NMR 500 MHz, DMSO, δ (ppm): 1.37 (s, 9H), 7.31 (dd, 1H), 7.60 (dt, 1H), 7.76 (dd, 1H), 8.24 (s, 1H), 10.32 (s, 1H), 11.98 (s, 1H).

^{13}C NMR 500 MHz, DMSO, δ (ppm) 27.86 (CH_3), 37.61 (C), 105.45 (C), 110.77 (CH), 111.82 (CH, *J* = 19.6), 116.32 (CH, *J* = 19.6), 134.95 (C), 135.59 (CH), 145.12 (C), 149,52 (C), 167.30 (C).

^{19}F NMR 500 MHz, DMSO, δ (ppm): -138.31.

1-(4-fluoro-3-hydroxyphenyl)-pyrazolopyrimidine



1a

The synthesis was conducted according to the general procedure with 1-(4-fluorophenyl)-1H-pyrazolopyrimidine as starting material.

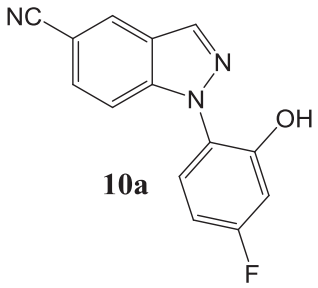
^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 7.17 (t, 1H), 7.92 (dt, 1H), 8.13 (dd, 1H).

^{13}C NMR 500 MHz, $CDCl_3$, δ (ppm): 110.60 (CH), 113.26 (CH, *J* = 6.4), 115.57 (CH, *J* = 19.1), 136.56 (C, *J* = 3), 143.72 (C, *J* = 14.9), 149.00 C, (*J* = 237).
^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -144.03

B – Synthesis of *ortho*-phenol regioisomer

Inside a glovebox di-μ-methoxobis(1,5-cyclooctadiene)diiridium (I) (16.9 mg) and THF (3 ml), were added to a 5 ml vial. In a different 5 ml vial B_2Pin_2 (129 mg) and THF (0.6 ml) were added. In a 2 ml vial was weighed the substrate (0.17 mmol) and later 0.2 ml of $[Ir(COD)OMe]_2$ solution (1.13 mg, 0.0017 mmol, 1%) and 0.2 ml of B_2Pin_2 solution (43 mg, 0,17 mmol, 1 eq.), were added. The vial was taken out from the glovebox and heated at 80 °C overnight. The reaction was cooled down at room temperature and the mixture was transferred to a 10 ml vial, equipped with a magnetic stirrer. The reaction mixture was diluted with 4 ml of THF and 4 ml of water. Then sodium perborate (78 mg, 0.51 mmol, 3 eq.) was added and the vial was stirred at room temperature for 1h. The reaction mixture was diluted with EtOAc (20 ml) and later poured into a separatory funnel, where it was washed with ammonium chloride (10%, 20 ml). The organic phase was filtered through a phase separator and concentrated with a rotary evaporator. The residue was purified by automated flash chromatography on a Biotage® KP-SIL 25g column. A gradient from 30% to 80% of EtOAc in heptane over 10CV was used as mobile phase. The product was collected using the wavelength 250 nm. The collected fractions were concentrated at the rotary evaporator and the *ortho* phenol product was obtained.

1-(4-fluoro-2-hydroxyphenyl)-1H-indazole-5-carbonitrile



10a

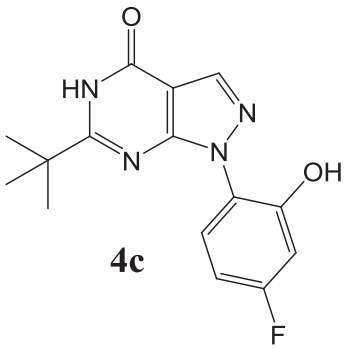
The synthesis was conducted according to the general procedure with 1-(4-fluorophenyl)-1H-indazole-5-carbonitrile (40 mg), as starting material. To perform the flash chromatography, a gradient from 25% to 65% of EtOAc in heptane over 10CV was used as mobile phase.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 6.80 (ddd, 1H), 6.94 (dd, 1H), 7.51 (dd, 1H), 7.70 (dd, 1H), 7.83 (d, 1H), 8.25 – 8.27 (m, 1H), 8.37 – 8.4 (m, 1H), 8.88 (s, 1H).

^{13}C NMR 500 MHz, $CDCl_3$, δ (ppm): 106.30 (C), 106.56 (CH, *J* = 25.7), 107.51 (CH, *J* = 23.4), 118.99 (C), 121.77 (C, *J* = 3.0), 122.93 (CH, *J* = 10.4), 123.92 (C), 128.23 (CH), 130.31 (CH), 135.96 (CH), 139.84 (C), 151.73 (C, *J* = 12.7), 162.44 (C, *J* = 247.8).

^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -110.92

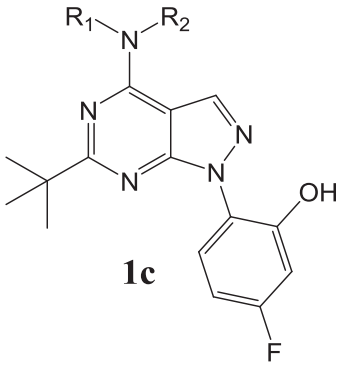
6-*tert*-butyl-1-(4-fluoro-2-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



4c

The synthesis was conducted according to the general procedure with 6-*tert*-butyl-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (48 mg) as starting material.

1-(4-fluoro-2-hydroxyphenyl)-pyrazolopyrimidine



1c

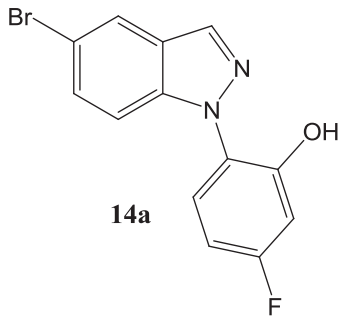
The synthesis was conducted according to the general procedure with 1-(4-fluorophenyl)-1H-pyrazolopyrimidine as starting material.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 6.67 – 6.77 (m, 1H), 6.85 (dd, 1H), 7.89 (dd, 1H), 12.24 (s, 1H).

^{13}C NMR 500 MHz, $CDCl_3$, δ (ppm): 107.43 (CH, *J* = 8.0, 23.6), 124.93 (CH, *J* = 10.3), 125.02 (C), 150.17 (C, *J* = 12.5), 162.47 (C, *J* = 245.6).

^{19}F NMR 500 MHz, $CDCl_3$, δ (ppm): -144.77.

2-(5-bromo-1H-indazol-1-yl)-5-fluorophenol



14a

The synthesis was conducted according to the general procedure with 5-bromo-1-(4-fluorophenyl)-1H-indazole (49 mg), as starting material. To perform the flash chromatography, a gradient from 10% to 80% of EtOAc in heptane over 14CV was used as mobile phase.

^{1}H NMR 500 MHz, $CDCl_3$, δ (ppm): 6.76 (td, 1H), 6.91 (dd, 1H), 7.51 (dd, 1H), 7.56 – 7.6 (m, 1H), 7.65 (d, 1H), 8.00 (s, 1H), 8.20 (s, 1H), 9.32 (s, 1H).

^{13}C NMR 500 MHz, $CDCl_3$, δ (ppm): 106.33 (CH, *J* = 25.6), 107.12 (CH, *J* = 23.3), 112.28 (CH), 115.54 (C), 122.22 (C), 122.30 (CH), 124.28 (CH), 125.86 (C), 131.56 (CH), 134.20 (CH), 137.75 (C), 151.58 (C, *J* = 12.7), 161.98 (C, *J* = 246.4).

6 Acknowledgments

I wish to thank professor Paolo Righi (University of Bologna), and Daniel Pettersen (AstraZeneca, Mölndal), for giving me the opportunity to work in AstraZeneca's laboratories. I wish to thank Häns Emtenas (AstraZeneca, Mölndal), for teaching me a lot of things about C-H activation chemistry.

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