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Review

Recent Progress in the Use of Pd-Catalyzed C-C Cross-Coupling Reactions in the Synthesis of Pharmaceutical Compounds

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A grande capacidade do paládio de formar ligações carbono-carbono entre substratos apropriadamente funcionalizados permitiu que os químicos orgânicos efetuassem transformações antes impossíveis ou alcançáveis somente através de rotas muito longas. Neste contexto, uma das mais elegantes e importantes aplicações das reações de acoplamento cruzado catalisadas por paládio é a síntese de compostos de interesse farmacêutico. A presente revisão tem por objetivo apresentar uma visão geral do uso de acoplamentos cruzados na síntese de componentes de medicamentos (ou de candidatos a medicamentos), independentemente da escala, compreendendo o período de 2011 até o final de julho de 2014.

The impressive ability of palladium to assemble C-C bonds between appropriately functionalized substrates has allowed synthetic organic chemists to perform transformations that were previously impossible or only possible using multi-step approaches. In this context, one of the most important and elegant applications of the Pd-catalyzed C-C coupling reactions currently is the synthesis of pharmaceuticals. This review is intended to give a picture of the applications of Pd-catalyzed C-C cross-coupling reactions for the synthesis of drug components or drug candidates regardless of the scale from 2011 through to the end of July, 2014.

Keywords: cross-coupling reactions, Heck reactions, palladium, pharmaceuticals

1. Introduction

Palladium-catalyzed cross-coupling reactions comprise one of the most efficient methods for the construction of carbon-carbon bonds.[1-3] The impressive ability of palladium to assemble C-C bonds between appropriately functionalized substrates has allowed synthetic organic chemists to perform transformations that were previously impossible or only possible using multi-step approaches. Therefore, these cross-coupling methodologies have revolutionized the way of thinking regarding synthetic organic chemistry, having found widespread use in organic synthesis and material science, as well playing an important role in pharmaceutical, agrochemical and fine chemical industries.[4-8] In this scenario, the award of the Nobel Prize in Chemistry in 2010 was a deserved recognition, rewarding jointly Richard F. Heck, Ei-ichi Negishi[9] and Akira Suzuki[10] for their remarkable contributions for the Pd-catalyzed cross-couplings in organic synthesis.[11]

The generally accepted mechanisms for Pd-catalyzed C-C cross-coupling reactions are summarized in Scheme 1. All reactions start with a Pd zerovalent species preformed or formed *in situ* from Pd divalent catalyst precursors. The first step is common for all reactions, consisting of the oxidative addition reaction of organic halide (or pseudohalide) to the Pd zerovalent species affording the R^1-Pd-X intermediate. In the case of coupling reactions involving an organometallic partner (R^2M), the R^1-Pd-R^2 intermediate is formed by a transmetalation step. Finally, reductive elimination provides the R^1-R^2 coupling product, and regenerates the Pd zerovalent species. The Sonogashira reaction involves the coupling between organic halides and alkynes. When copper salts are used as the co-catalyst, copper acetylides are formed *in situ* and are involved in the transmetalation step. A different catalytic cycle is involved in the Heck-Mizoroki reaction. In this case, the alkene is coordinated to the common R^1-Pd-X intermediate. Then,

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This article is dedicated to the memory of Prof Roberto F. de Souza

a *syn* migratory insertion occurs and the organopalladium species formed undergoes β-hydride elimination to form the alkene product. Finally, a base-assisted elimination of HX regenerate the Pd(0) catalyst.[12-17] When an aryldiazonium salt is used in place of an aryl halide, the reaction is known as Heck-Matsuda reaction.[18-21] The difference in terms of mechanism is that the oxidative addition of aryldiazonium salts to the Pd zerovalent species generates a cationic $[R^1\text{-Pd}]^+$ intermediate.

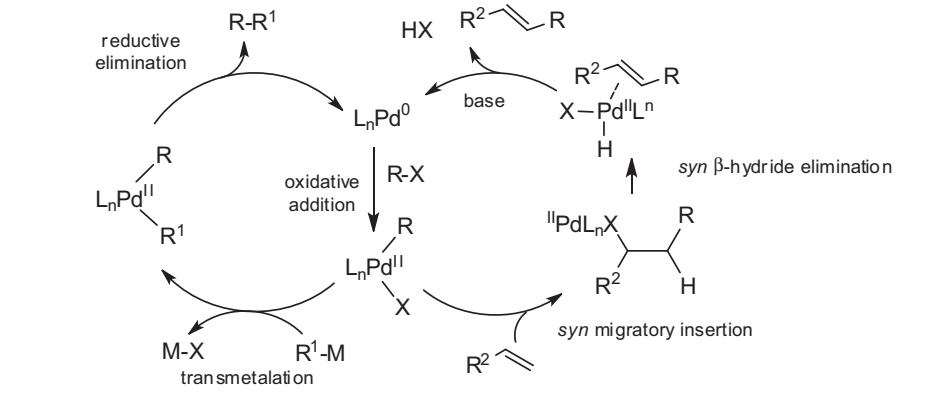
In our opinion, the most important and elegant application of the coupling reactions is the synthesis of pharmaceuticals. In this context, there is an excellent review about the applications of Pd-catalyzed coupling reactions. This review covers the period from 2001 to 2008, and highlights examples that have been performed on at least a kilogram scale in the chemical and pharmaceutical industries.[5] In addition, Pfizer researchers have reviewed the large-scale applications of transition metal-catalyzed coupling reactions for the manufacture of drug components in the pharmaceutical industry through to the end of August, 2010.[4] This review is intended to give a picture of the applications of Pd-catalyzed C-C cross-coupling reactions for the synthesis of drug components or drug candidates, regardless of scale, from 2011 through to the end of July, 2014.

2. Suzuki-Miyaura Reactions

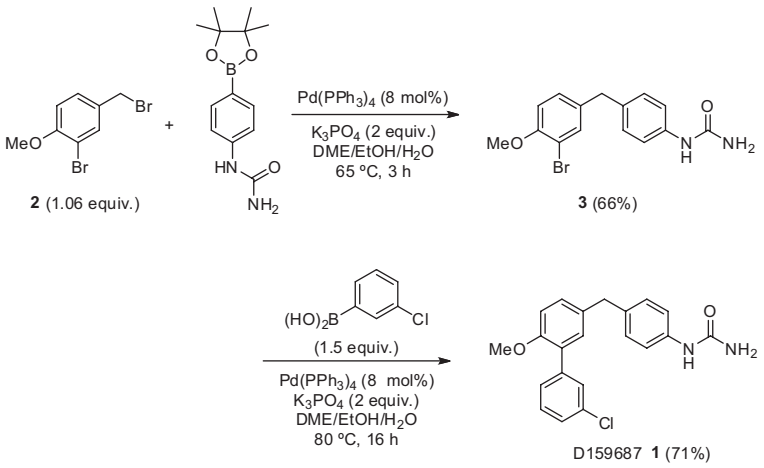
The transition metal-catalyzed reaction between an organoboron compound and a halide or pseudohalide is known as Suzuki-Miyaura cross-coupling.[22] This important reaction is well-known for the assembly of biphenyl motifs.[23] For example, Dalby *et al.*[24] reported a concise synthesis of D159687 (**1**), a partial allosteric modulator of phosphodiesterase 4 (PDE4), an enzyme related to inflammatory and respiratory diseases. The first synthesis of **1** involved six steps, with one Suzuki reaction step, with an overall yield of 8%.[25] By using the benzyl aryl dibromide **2** as starting material, the synthesis of **1** was shortened to two-steps with an overall yield of 47% on the gram scale (Scheme 2).

The more reactive benzyl bromide moiety of dibromide **2** was coupled with a pinacol arylboronic ester, providing diarylmethane **3** in 66% yield. Activation of the remaining bromide in **3** was carried out using the same conditions, only changing the temperature and reaction time, and furnishing **1** at a yield of 71%. The optimal conditions displayed in Scheme 2 were established after a screening of Pd sources [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2/PPh_3$], solvents [dimethoxyethane/EtOH/H_2O, dioxane/H_2O and dimethylformamide (DMF)] and bases (K_3PO_4, K_2CO_3, Na_2CO_3 and Cs_2CO_3). It is worth noting that a reduction of the amount of catalyst increased the conversion in some cases, while higher amounts generally increased the level of impurities and difficult purification. This process was applied to the synthesis of two new PDE4D partial allosteric modulators, D159404 (**4**) and D159153 (**5**) (Figure 1), with overall yields of around 26% for the two Suzuki reactions.

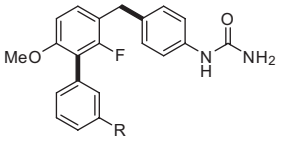
Thiel *et al.* described the preparation of several inhibitors of p38 mitogen-activated protein (MAP) kinases, which are enzymes that positively regulate the production of pro-inflammatory mediators (TNF-α and IL-1).[26] These mediators are involved in rheumatoid arthritis, Crohn's disease and psoriasis. The original synthetic route[27] presented some challenges for scaling-up, most notably the employment of toxic carbon tetrachloride, silver salts and microwave irradiation. Therefore, the authors optimized the route, on a kilogram scale, employing the aryl chloride **6**



Scheme 1. General catalytic cycles for the Pd-catalysed reactions.



Scheme 2. Sequential Suzuki reactions in the synthesis of D159687 (**1**).

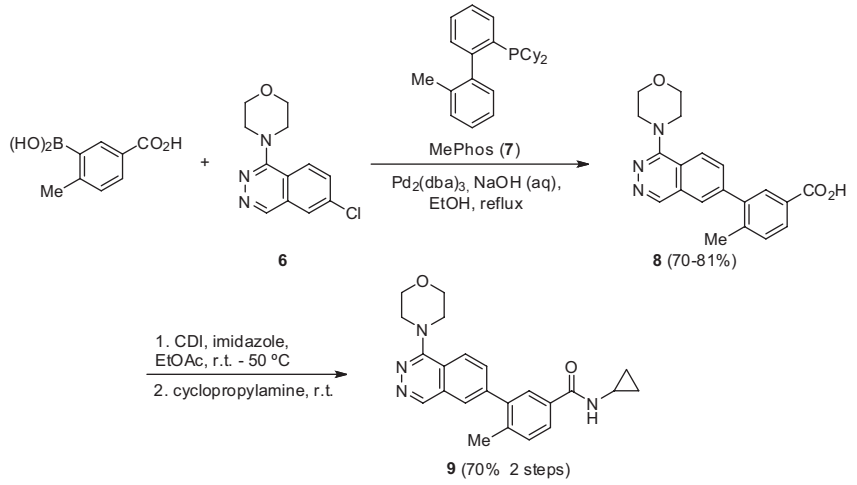


R = Cl (**4**)
R = NO_2 (**5**)

Figure 1. PDE4D allosteric modulators D159404 (**4**) and D159153 (**5**).

as starting material and avoiding the use of toxic solvents (Scheme 3). For activation of the less reactive C-Cl bond, ligand screening was necessary, and MePhos (**7**) was identified as the most effective. Thus, this ligand combined with a mixture of ethanol/aqueous sodium hydroxide was employed with $Pd_2(dba)_3$, where dba = dibenzalacetone, as pre-catalyst to provide **8** in yields between 70 and 81%. In contrast to the medicinal chemistry route, the final step did not employ a palladium-catalyzed reaction, allowing easier removal of this metal: the synthesis of **9** employed 1,1-carbonyldiimidazole (CDI) and cyclopropylamine in ethyl acetate leading to the desired product in 70% yield after two steps. The authors believe that any significant amount of palladium present as an impurity in intermediate **8** was removed quantitatively with the aid of imidazole employed in the carbonyl activation step.

It is worth noting that the large scale synthesis of **10**, another inhibitor of p38 MAP kinases, demanded a completely different catalytic system for the Suzuki reaction. While the original medicinal chemistry route employed $Pd(PPh_3)_4$ for the coupling of **11** with a boron pinacolate derivative, on a large scale, the authors were capable of reducing the catalyst loading (albeit no amounts were disclosed in the text) by using $PdCl_2$(APhos) (**12**), allowing a very clean reaction to be performed due to the high activity of this catalyst (Scheme 4).[26] Thus, the Suzuki product **13** was obtained in 93% yield by treating **11** with the appropriate arylboronic acid in the presence of **12** and



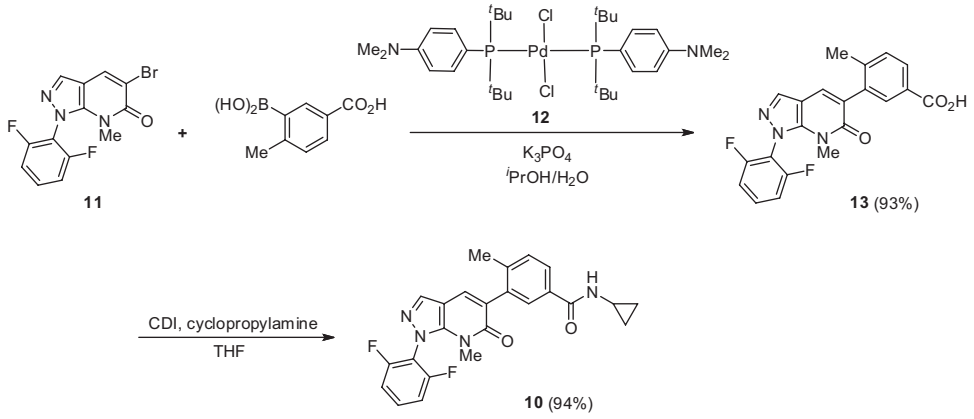
Scheme 3. Suzuki reaction of an aryl chloride en route to **9**.

potassium phosphate, with a mixture of isopropyl alcohol and water as solvent. Finally, treatment of **13** with CDI in tetrahydrofuran (THF) provided **10** in 94% yield.

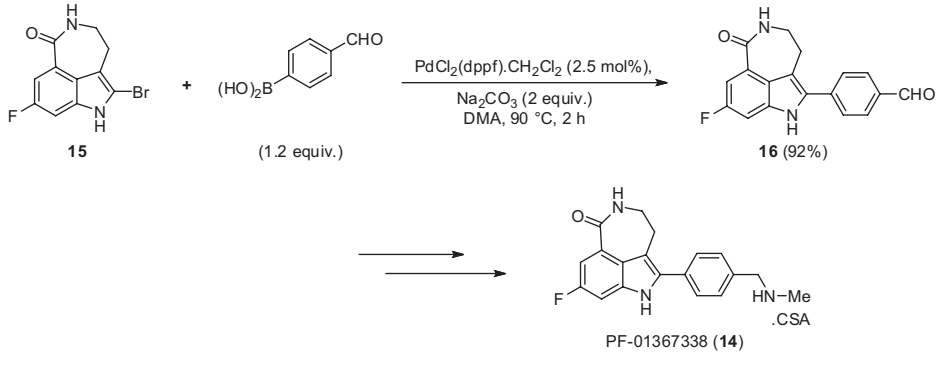
Gillmore *et al.* developed a multi-kilogram preparation of PF-01367338 (**14**), a drug candidate for the treatment of breast and ovarian cancers.[28] It is an inhibitor of poly(ADP ribose) polymerase (PARP), an enzyme that is responsible for repairing damaged DNA in normal and tumour cells.[28] The described synthetic route delivered 2 kg of the salt **14**, and the authors described how they had to overcome some synthetic challenges in order to scale up the synthesis to multi-kilogram scale. The overcome problems include: understanding of the thermal hazards of the Leimgruber-Batcho indole synthesis, installation of the side chain through a reductive alkylation procedure, improvements in the robustness of the Suzuki coupling, removal of hydrogen cyanide generation during a reductive amination reaction, and reliable generation of good-quality free base for the final salt formation step.

The Suzuki reaction between the tricyclic bromide **15** and 4-formylphenylboronic acid was first carried out in multi-kilogram scale using by $Pd(PPh_3)_4$ as catalyst. The reaction did not reach completion requiring an additional catalyst charge. In the sequence, the Suzuki reaction was performed with $[PdCl_2(dppf)\cdot CH_2Cl_2]$ as a pre-catalyst, and full conversion was obtained after 2 h at 90 °C (Scheme 5), providing **16** with yield of 92%.

Grongsaard *et al.* reported a scalable synthetic route of **17**, an inhibitor of Akt kinase, which is an enzyme that is up-regulated in several types of cancer, such as colon, breast, brain, lung and prostate.[29] This interesting polycyclic was prepared on small scale through a Suzuki reaction between a pyridyl chloride and an aryl boronate. However, given the harsh conditions required for this reaction [140 °C, microwave heating, 20 mol% of $Pd(PPh_3)_4$], an improvement of this step was clearly necessary for scale-up. Thus, an optimization study was performed for the Suzuki reaction between triflate **18** and boron pinacolate **19**, with a screening of ligands [XPhos, 1,4-bis(diphenylphosphino)butane (dppb), (*R*)-(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (dppf) and 1,1'-bis(di-i-propylphosphino)ferrocene (dippf)]. Electron-rich, ferrocen-derived phosphines presented superior performances (Scheme 6). Also, a mixture of THF and water was found to be the optimal solvent, but 2-MeTHF was chosen instead of THF because enables a simpler purification by crystallization. Notably, water proved to be essential to this transformation, the yields were lower in anhydrous media. However, the authors did not provide an explanation for this. Optimal conditions were found and are shown in



Scheme 4. Optimized Suzuki reaction for the synthesis of **10**.



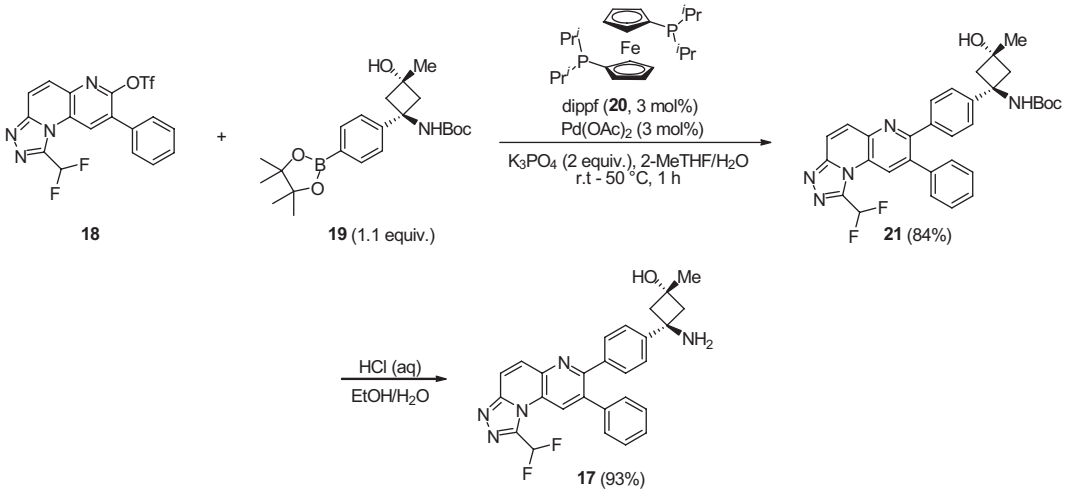
Scheme 5. Suzuki reaction for the synthesis of PF-01367338 (**14**).

Scheme 6: 3 mol% of both $Pd(OAc)_2$ and dippf (**20**) were employed with potassium phosphate as base and a mixture of 2-MeTHF and water as solvent, with the heating temperature steadily raised from room temperature to 50 °C. The desired product **21** was obtained in 84% yield, and removal of the *tert*-butyloxycarbonyl (Boc)-protecting group afforded **17** in 93% yield.

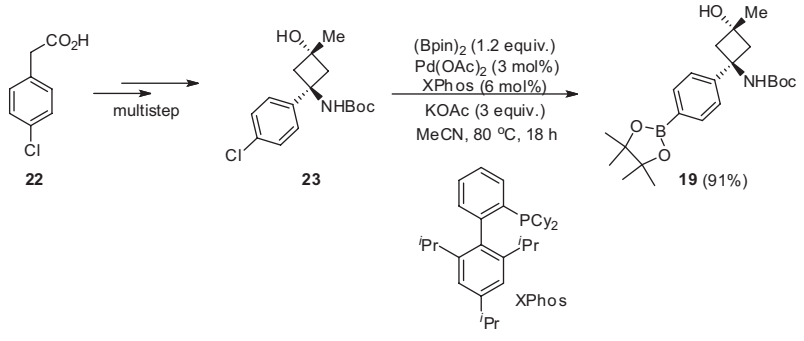
In the Suzuki reaction mentioned above, the valuable boron pinacolate **19** was employed only in slight excess. Even though borylations are out of the scope of this review, the synthesis of **19** deserves particular mention, since this compound demanded more than ten steps to be reached starting from acid **22** and was finally obtained by an elegant Pd-catalyzed borylation of the aryl chloride **23** (Scheme 7).

Tian *et al.* described a convergent synthesis for GDC-0941[30] (**24**), a phosphatidylinositol 3-kinase (PI3K) inhibitor (Scheme 8). The PI3K pathway is frequently activated in tumours and its inhibition has a role in human cancers. The indazole-derived boronic acid **26** was employed as its tetrahydropyran-protected derivative due to solubility issues and to render an easier purification. Previous studies identified Pd- or Ni-catalyzed systems for this Suzuki reaction. The first employed $PdCl_2(PPh_3)_2$ with Na_2CO_3 as base and 1,4-dioxane as solvent; regarding the economically more attractive nickel, $Ni(NO_3)_2.6H_2O/PPh_3$ was identified as an optimal pre-catalyst, with K_3PO_4 as base and acetonitrile as solvent. In the Ni-catalyzed reaction, boronic acid **26** performed better than the corresponding boronate ester. The yield of the Pd-catalyzed reaction was 60%, whereas the Ni-catalyzed reaction provided **27** in 79% yield. Mild removal of the THP-protecting group then provided **24**. Regarding purification after the Suzuki reaction, residual Ni was easily removed through an aqueous ammonia wash followed by crystallization, while the removal of residual Pd demanded expensive scavengers and a large volume of solvents. The easy removal of nickel traces compensated for the high loadings of its pre-catalyst (30 mol%); Pd loadings were lower (4.5 mol%), however the lower yield and difficult purification impaired the use of this noble metal.

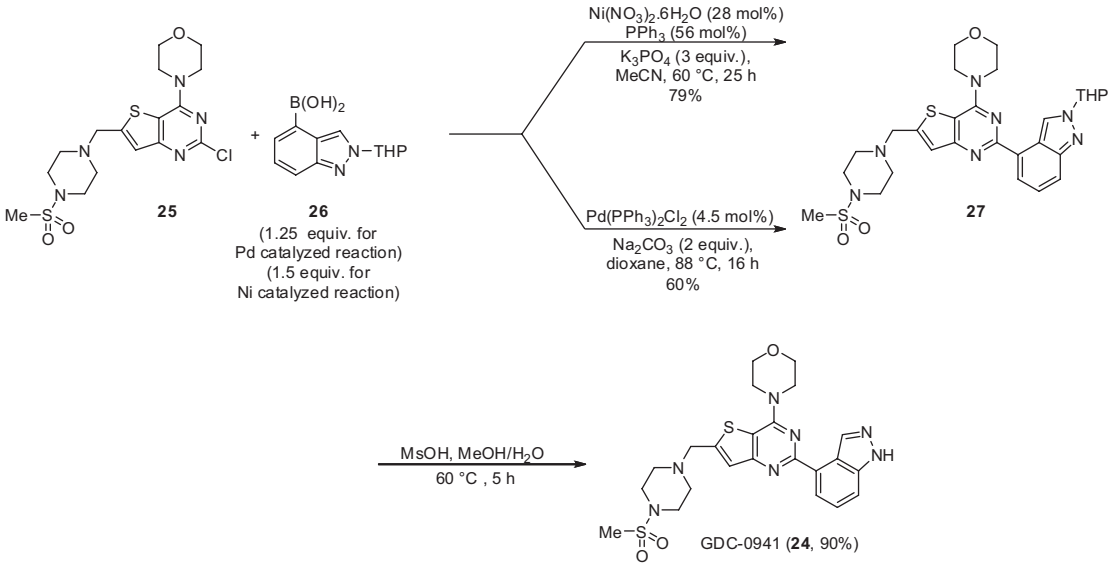
Hicks *et al.* reported the synthesis of **28** (Scheme 9), a molecule connected to PI3K and AKT/PKB signalling pathway that inhibits cell proliferation and tumour growth.[31] Initially, Suzuki coupling of **29** with **30** was performed in the presence of Na_2CO_3, but attempts to decrease the initial loading (3 mol%) of the palladium pre-catalyst



Scheme 6. Synthesis of **17** by means of a Suzuki reaction with the advanced boron pinacolate intermediate **19**.



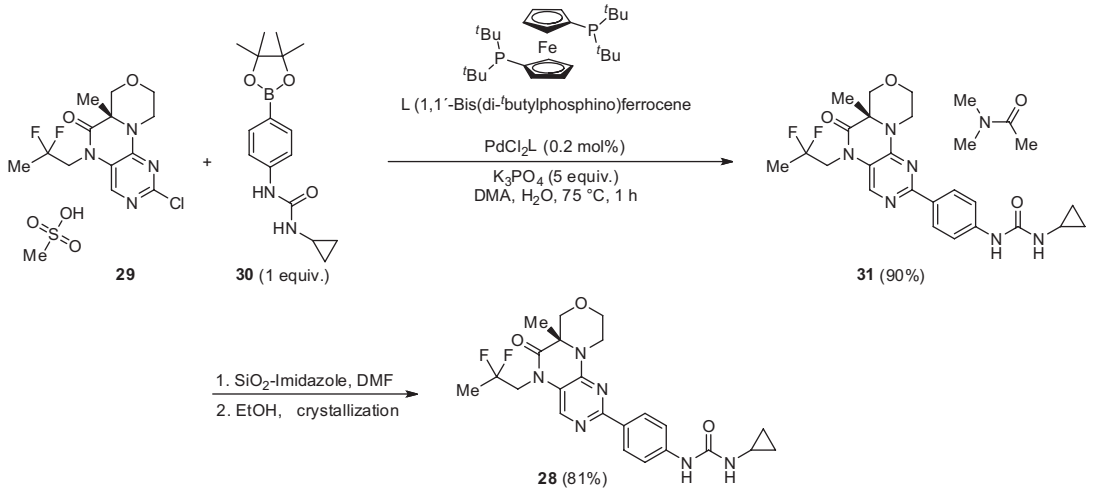
Scheme 7. Synthesis of boron pinacolate derivative **19**.



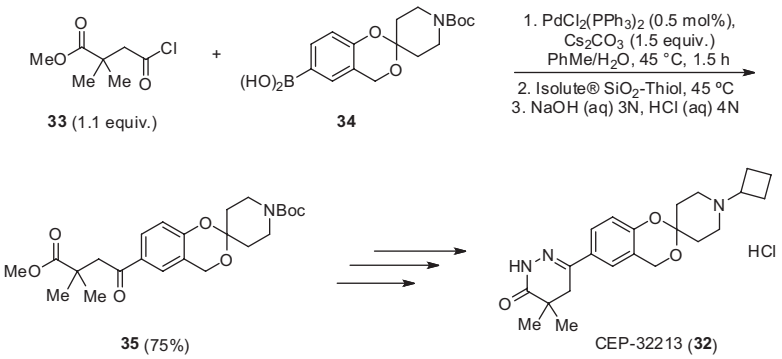
Scheme 8. Synthesis of GDC-0941 (**24**) through a Suzuki reaction of THP-protected boronic acid **26**.

(see Scheme 9) with this base resulted in incomplete conversions. Surprisingly, substitution of sodium carbonate by potassium phosphate allowed an impressive decrease of the Pd loading to 0.2 mol%; nonetheless, careful removal of palladium impurities was necessary, and after some testing with *L*-cysteine, an optimal procedure was disclosed in which the desired Suzuki product was isolated as 1:1 *N,N*-dimethylacetamide solvate **31** and redissolved in DMF, with Pd being removed by means of a scavenger supported on silica. Thereafter, ethanol was added as an anti-solvent for crystallization, providing **28** with palladium amounts lower than 1 ppm.

A process chemistry development was performed for the synthesis of CEP-32215 (**32**) (Scheme 10), an antagonist of the histamine H3 receptor;[32] its antagonists can be used in a variety of central nervous system (CNS) disorders associated with attention and cognitive deficits (wakefulness, attention-deficit hyperactivity disorder, Alzheimer's disease, mild cognitive impairment and schizophrenia). The synthesis of this compound employed a curious Suzuki-type reaction of acid chloride **33** and arylboronic acid **34**: this boronic acid was used in its crude form, since it was more reactive than the chromatography-purified product. The authors attributed this remarkable behaviour to the fact that, in its crude form, the boronic acid was more soluble in toluene than in its purified crystalline version. A screening of different bases, solvents, catalysts and temperatures led to the identification of $PdCl_2(PPh_3)_2$ as an optimal pre-catalyst and cesium carbonate as the most effective base. Toluene proved to be the best solvent, and a small amount of water was necessary in order to solubilize the cesium carbonate. Additional ligands generally impaired the reaction. Therefore, ketone **35** was obtained in 75% yield.



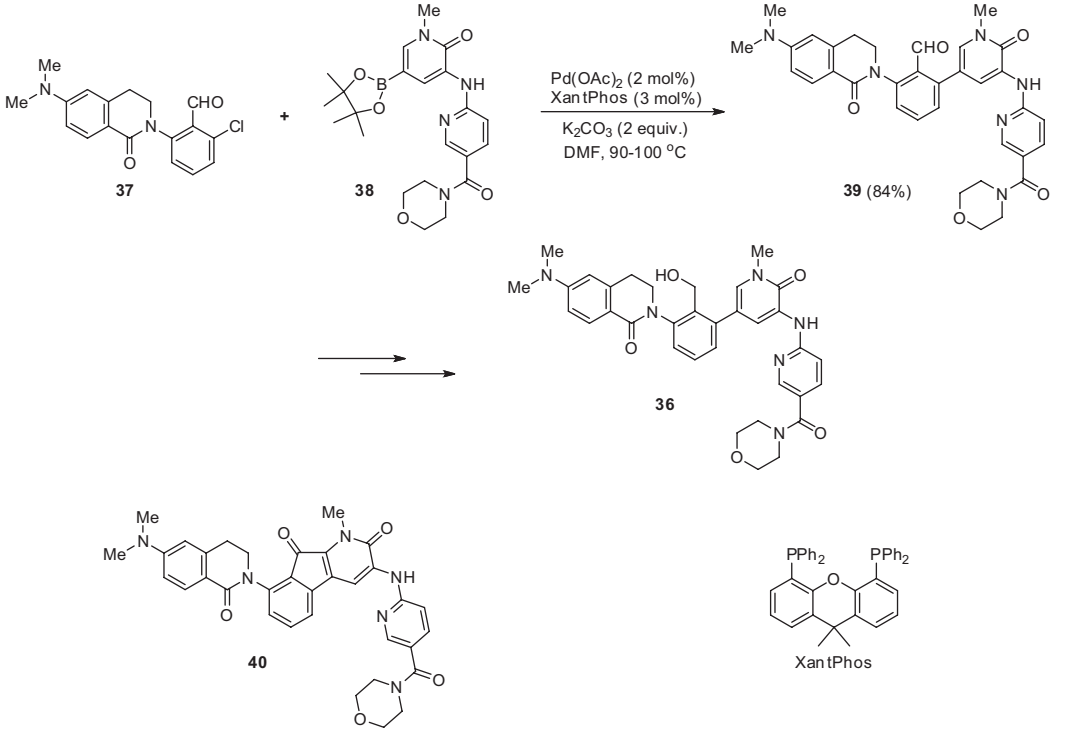
Scheme 9. Optimized Suzuki reaction en route to **28**.



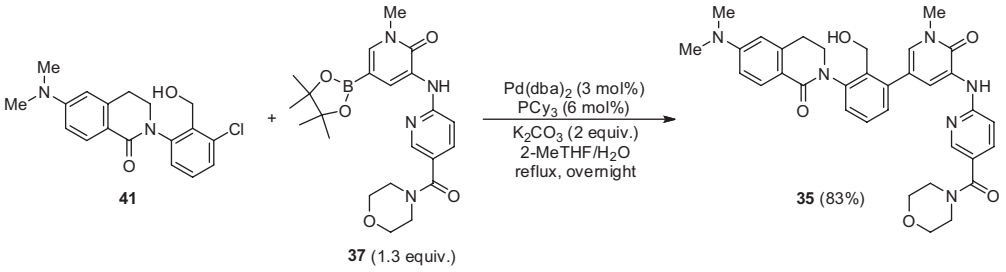
Scheme 10. Suzuki-like reaction of acid chloride **33** for the synthesis of **32**.

Hong *et al*. developed a scalable synthesis of a Bruton's tyrosine kinase (BTK) inhibitor (**36**), an important cell signalling enzyme involved in early B cell development and mature B cell activation and survival.[33] These cells play a key role in autoimmune and inflammatory diseases. In the first approach for this compound, a Suzuki reaction between aryl chloride **37** and boronate ester **38** was applied in a late synthetic stage (Scheme 11).

Even though this reaction was successful in providing the desired product **39**, up to 20% of impurities (**40**) arising from condensation of the aldehyde moiety of **39** were detected by high performance liquid chromatography (HPLC) when the reaction was carried out for longer times (as it is commonly the case in large scale synthesis). Therefore, a new strategy for this final coupling was necessary. An initial attempt was performed by protection of the free nitrogen of **38** with the Boc group, thus rendering the pyridinone ring of **39** less nucleophilic: indeed, a cyclization like that observed in **40** was avoided after the Suzuki reaction; nonetheless, conditions for removal of the Boc group cleaved the morpholine moiety as well. Thus, instead of aldehyde **39**, the authors envisioned a Suzuki coupling between alcohol **41** and boron pinacolate **38**. However, this change in the electronic nature of the aryl halide coupling partner demanded re-optimisation of the Suzuki reaction, and then tricyclohexylphosphine and $Pd(dba)_2$ were identified as the optimal ligand and pre-catalyst, respectively. The solvent could be switched from DMF to 2-MeTHF with no yield losses. Once the Suzuki reaction had been performed, palladium was removed by treatment with activated charcoal, and **36** was obtained in 83% yield and 99% purity as judged by HPLC (Scheme 12).



Scheme 11. First generation conditions or the Suzuki reaction aiming at **36**.



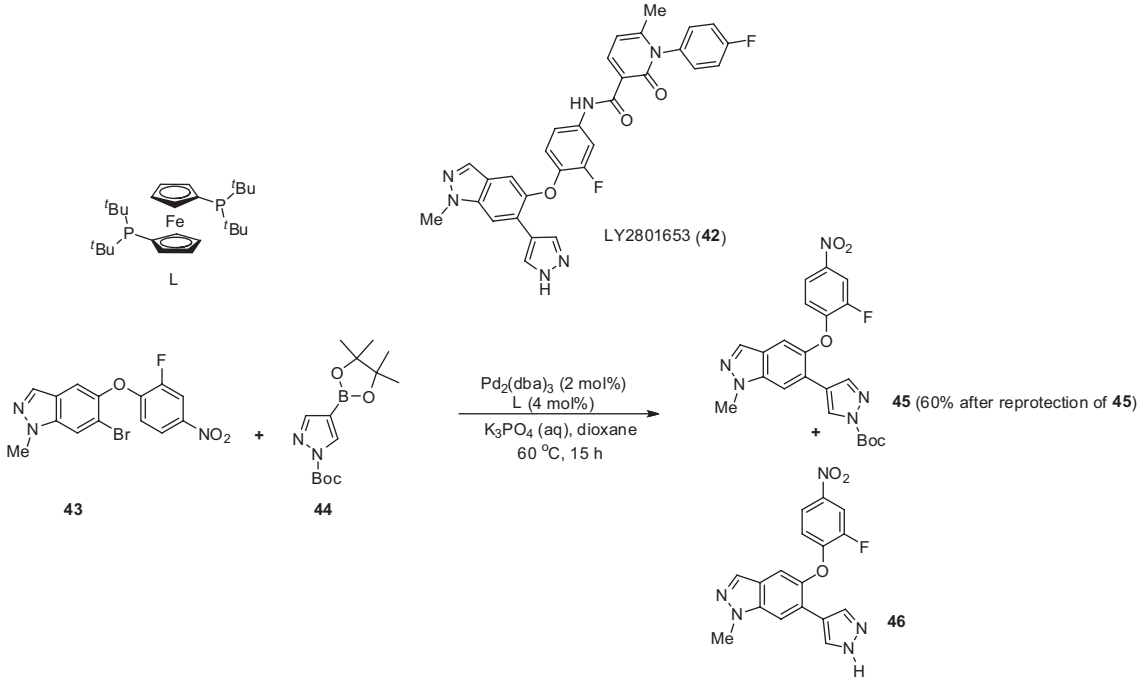
Scheme 12. Optimized Suzuki reaction in the synthesis of **36**.

Kallman *et al.* reported a synthesis of LY2801653 (**42**), a type-II ATP competitive inhibitor of mesenchymal epithelial transition factor (MET), which is a member of the receptor tyrosine kinase family.[34] The MET pathway has been associated with the progression of some tumours and MET overexpression has been observed in many, including colon, renal, lung, head and neck squamous cell carcinoma and gastric cancer. In a first study, Suzuki coupling between bromide **43** and protected pinacolboron **44** furnished a mixture of **45** and **46**, showing that the Boc protecting group was not stable under the employed Suzuki conditions. Moreover, **46** significantly poisoned the Pd catalyst (Scheme 13).

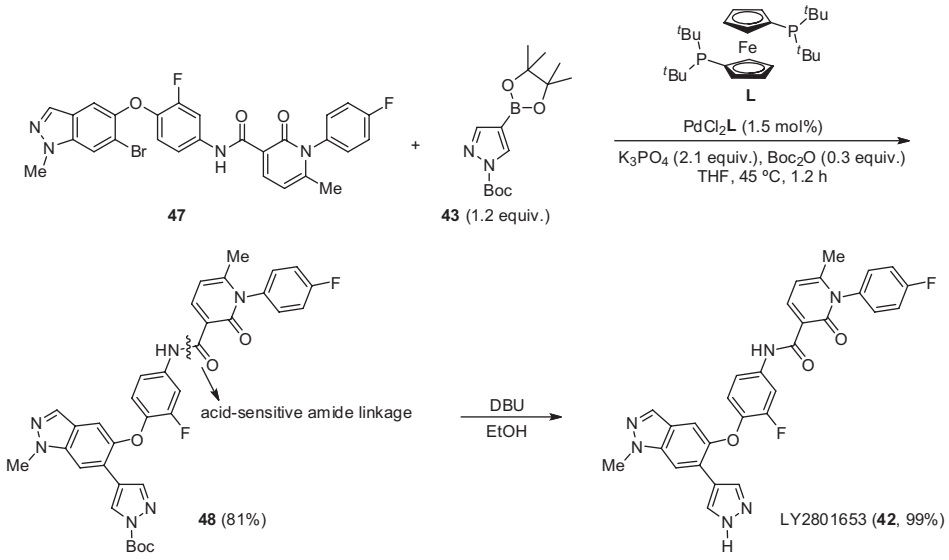
The conditions for the Suzuki reaction were screened again, and with THF as solvent and Boc_2O as additive, the yield of **45** could be improved to 75%. Nonetheless, further manipulation of **45** led to cleavage of the Boc group and gave rise to dangerous, mutagenic impurities. As a result, the authors decided to investigate a different approach to the synthesis, performing a Suzuki reaction with aryl bromide **47**, which is very close to the final product, thus minimizing the manipulation of the Boc-containing product. Removal of this protecting group could then be performed in basic media, which prevented the amide linkage of **48** from being cleaved (Scheme 14).

Tetrasubstituted tiophenes **49**-**51** were identified by Huang *et al*. as highly promising candidates for the selective inhibition of the PI3K receptor, a property that is associated with the treatment of some types of cancer (Figure 2).[35]

The initial routes to these compounds displayed no cross-coupling reactions, with the benzene rings of **49**-**51** being introduced in the first step of the synthesis, therefore making a common intermediate impossible. For the scale-up, a synthesis featuring a Suzuki reaction between substituted iodothiophenes **51** and the corresponding arylboronic acids was envisioned (Scheme 15); however, some challenges were anticipated, such as the poor reactivity of iodothiophenes in the coupling step and the sterically



Scheme 13. Aiming at **42** by means of a Suzuki reaction.



Scheme 14. Optimized synthesis of **42**.

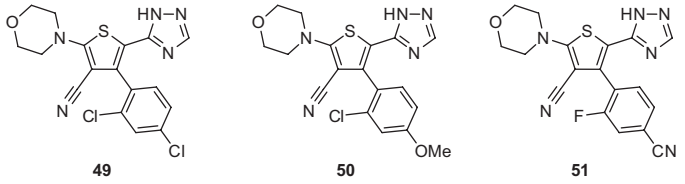
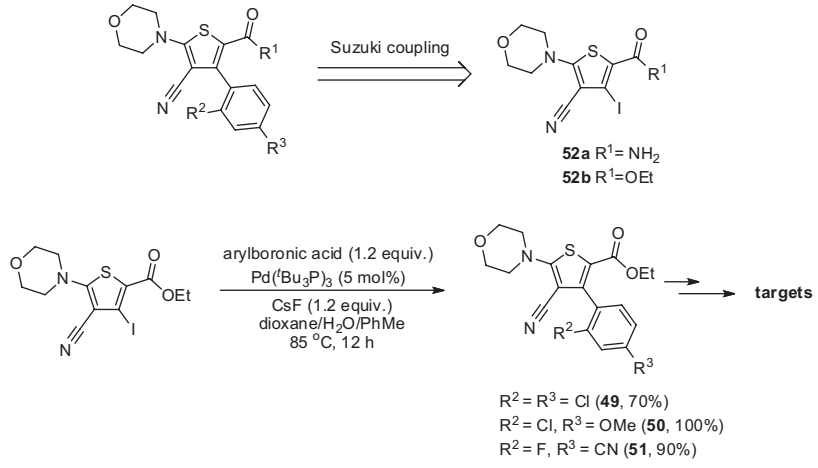


Figure 2. Examples of PI3K selective inhibitors.

demanding nature of **51**. The Suzuki cross-coupling reaction indeed proved itself to be difficult; for example, reaction with **51a** furnished only low to moderate yields of the desired product after approximately 100 conditions being tested, with large amounts of deiodinated by-products being observed. The authors believe that the poor solubility of **52a** impaired the Suzuki reaction, and an additional drawback was the fact that the corresponding cross-coupling product was also poorly soluble, therefore making purification difficult. On the other hand, when the corresponding ethyl ester **52b** was investigated, very satisfactory conditions could be identified after the employment of a high-throughput experimentation methodology, with catalysts [Pd(^{t}Bu$_3$P)$_4$, Pd(PPh$_3$)$_4$, PdCl$_2$(dppf)], bases (CsF, diisopropylethylamine, K_2CO_3, K_3PO_4) and solvents (toluene, dioxane, ethanol, water) being combined under 200 different conditions. After data analysis, the conditions displayed in Scheme 15 were identified, with the three desired coupling products being obtained in good to excellent yields after purification by crystallization.

Walker *et al*. developed a large-scale synthesis of a GPR40 receptor agonist, a class of compounds that



Scheme 15. Suzuki reaction of iodothiophenes.

is being currently investigated as possible therapeutic agents for the treatment of type 2 diabetes.[36] The target compound, AMG 837 (**53**), was obtained in a convergent way by joining Suzuki cross-coupling derived biphenyl **54** with enantiomerically pure β-alkynylcarboxylic acid **55** (Scheme 16).

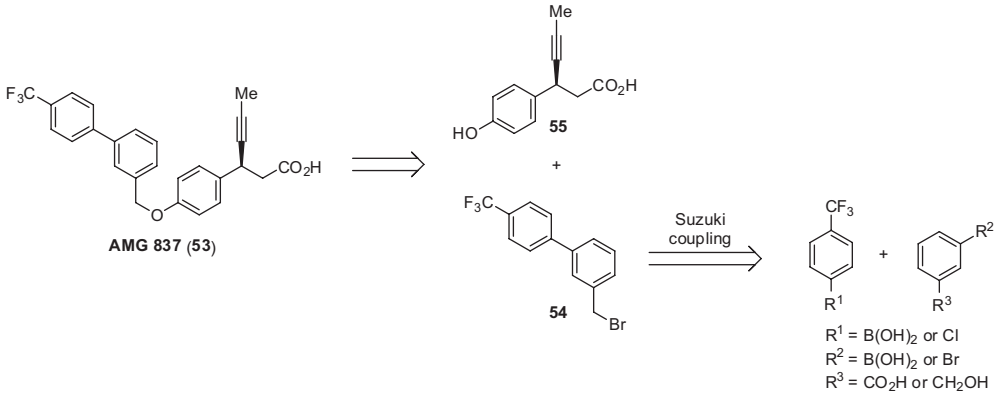
The first synthetic approach to **53** was based on a Suzuki reaction between aryl bromide **55** and arylboronic acid **56**. A catalytic system containing palladium supported on charcoal, sodium carbonate and diisopropylamine/water as solvents was employed (Scheme 17), providing biphenyl **57** in 91% yield. In turn, compound **53** was obtained by borane-mediated reduction of **57** and bromination of the resulting benzylic alcohol.

Further investigation, however, was carried out in order to shorten the preparation of **54** and to avoid the reduction step. Thus, the authors were able to couple economically more attractive aryl chloride **59** with arylboronic acid **60** employing 1 mol% of $Pd_2(dba)_3$ as a pre-catalyst and 2.2 mol% of tricyclohexylphosphine as a ligand in a mixture of water and THF, **61** was obtained in an excellent yield of 95% (Scheme 18). Hydroxyl displacement with $SOBr_2$ then furnished biphenyl **54** in an overall yield of 86% starting from the aryl chloride **59**.

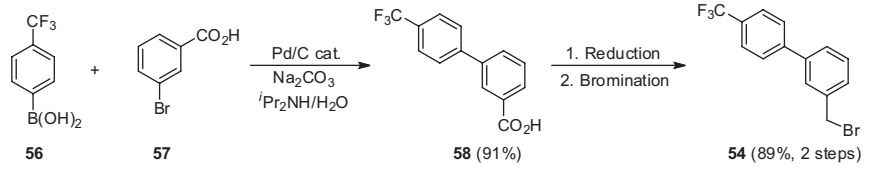
En route to producing large quantities of Crizotinib (**62**), a c-Met/anaplastic lymphoma kinase (ALK) inhibitor in advanced clinical tests, De Koning *et al.* employed a Suzuki reaction in order to generate an advanced intermediate.[37] However, before describing the large-scale synthesis itself, it is worth noting some aspects of the initial medicinal chemistry screening: compounds with the basic structure **63** were obtained through a sequence of protection, palladium-catalyzed borylation, deprotection and Suzuki reactions (Scheme 19) in order to allow for late-stage functionalization with substituted bromopyrazoles.

Then, once crizotinib (and its *R* isomer) had been identified as the most promising candidate, the Suzuki cross-coupling was performed in an inverse way: the pyrazol moiety was employed as its boron pinacolate derivative (**64**, Scheme 20). Even though **64** was obtained in a moderate 40% yield, its Suzuki reaction furnished the desired product in excellent quantities, thus allowing a better use of the valuable chiral intermediate **65**.

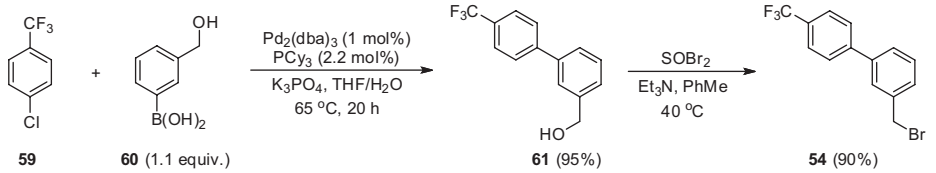
The large-scale synthesis demanded further modifications: the preparation of multi-kilogram amounts of imidazole **64** presented high levels of dimerization; therefore, the palladium-catalyzed borylation was abandoned in favour of a Knochel-type procedure.[38]



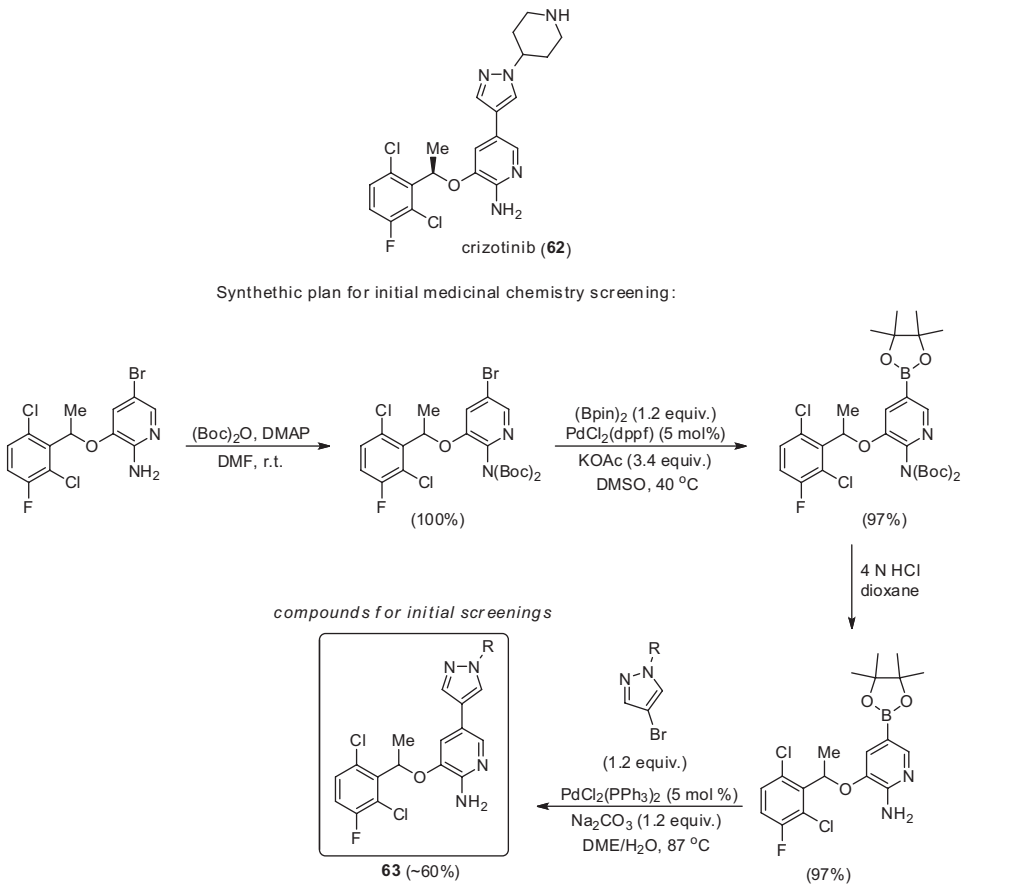
Scheme 16. Retrosynthetic plan for the final steps of the Walker *et al.*[36] large-scale synthesis of AMG 837 (**53**).



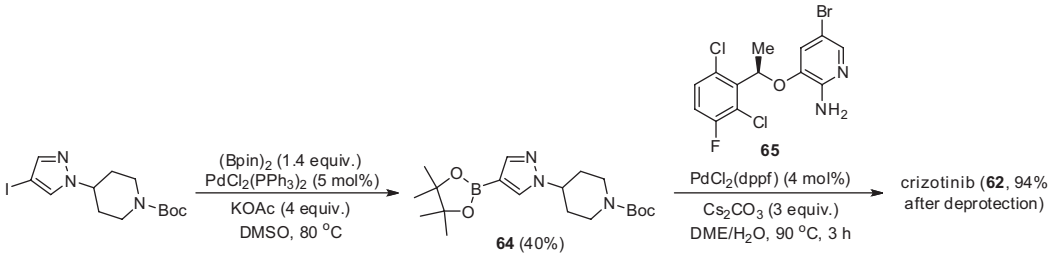
Scheme 17. Original Suzuki reaction employed for the synthesis of biphenyl **54**.



Scheme 18. Optimized preparation of biphenyl **54**.



Scheme 19. Simplified initial route for preparation of compounds **63**.

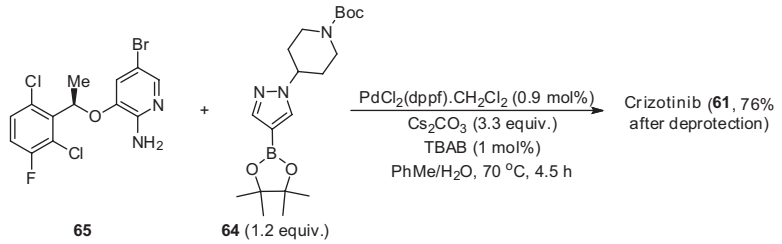


Scheme 20. Modified Suzuki reaction in the synthesis of **62**.

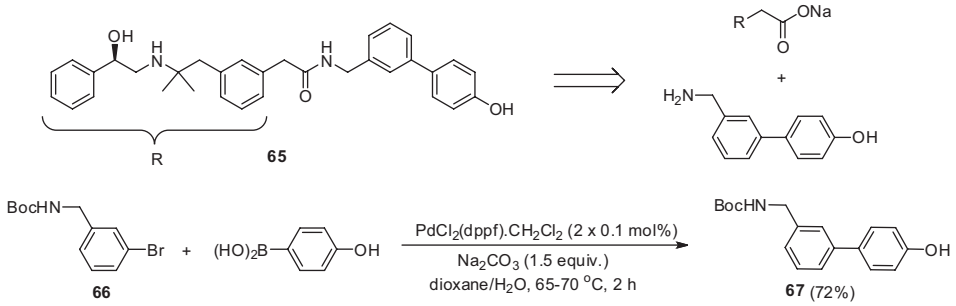
The Suzuki cross-coupling was performed in a different solvent system: in order to avoid the undesirable DME, toluene and water were employed together with the phase-transfer catalyst tetrabutylammonium bromide (TBAB). This new procedure allowed the catalyst loading to be reduced to 0.9 mol% with a significant simplification of the purification procedure, once the cross-coupling product was soluble in toluene and hence easily separated from the water layer (Scheme 21).

The β_2-adrenoreceptor PF-00610355 (**66**, Scheme 22), recently found to be effective in the treatment of respiratory diseases, was synthesized on a large scale by Thomson *et al*..[39] The biaryl moiety of the target compound was assembled by means of Suzuki cross-coupling, which delivered **67** in good yield with a very low charge of palladium pre-catalyst (Scheme 22). Interestingly, in this reaction, 3% of the aryl bromide **68** remained unconverted after 2 h of reaction, demanding a second loading of the same initial amount of the pre-catalyst in order to achieve full conversion.

Bowles *et al.* developed a large-scale preparation of PF-03052334-02 (**69**), a pyrazole displaying reduced risk of musculoskeletal side effects in the treatment of coronary diseases (Scheme 23).[40] For coupling of the diol-containing side chain, the authors envisioned a Suzuki cross-coupling between triflate **70** and vinylboronic acid **71**; however, due to stability issues surrounding **71**, this reaction failed to deliver the desired product.



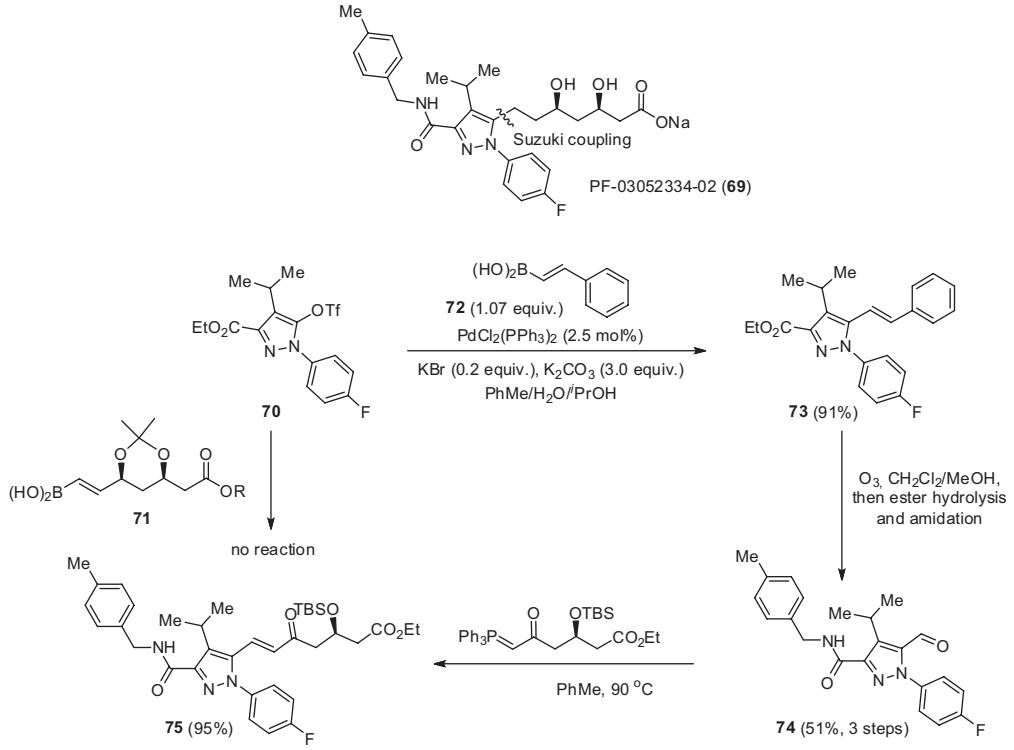
Scheme 21. Employment of a different solvent system for the Suzuki reaction en route to **62**.



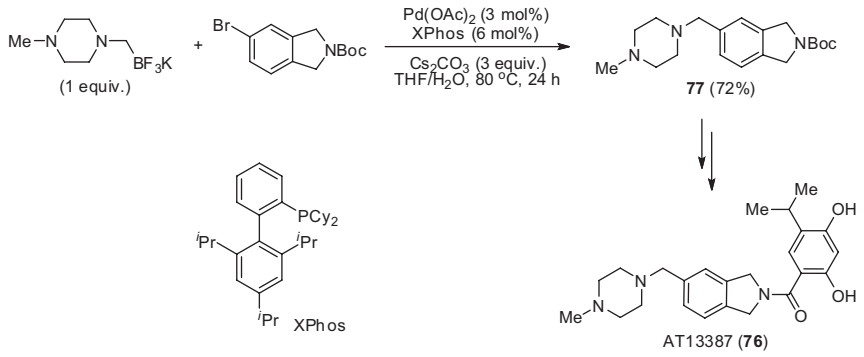
Scheme 22. Low loading of Pd in a Suzuki reaction for the synthesis of **66**.

Therefore, an alternative was found in which **70** was coupled with styrenyl boronic acid **72**, delivering the Suzuki product **73** in excellent yield. After that, **73** was submitted to ozonolysis, providing aldehyde **74** in 76% yield. The side chain was then installed by a Wittig reaction, whose product **75**, after chemo- and regioselective reductions and deprotections, afforded **69**.

Regarding bench-scale processes, Patel and Barret achieved a total synthesis of AT13387 (**76**), a molecule that is capable of interacting with chaperones that are essential for the survival of cancer cells.[41] In their synthesis, the piperazino-*iso*-indoline **77** was assembled by a sp^3-sp^2 Suzuki cross-coupling reaction employing the Molander protocol (Scheme 24).[42]



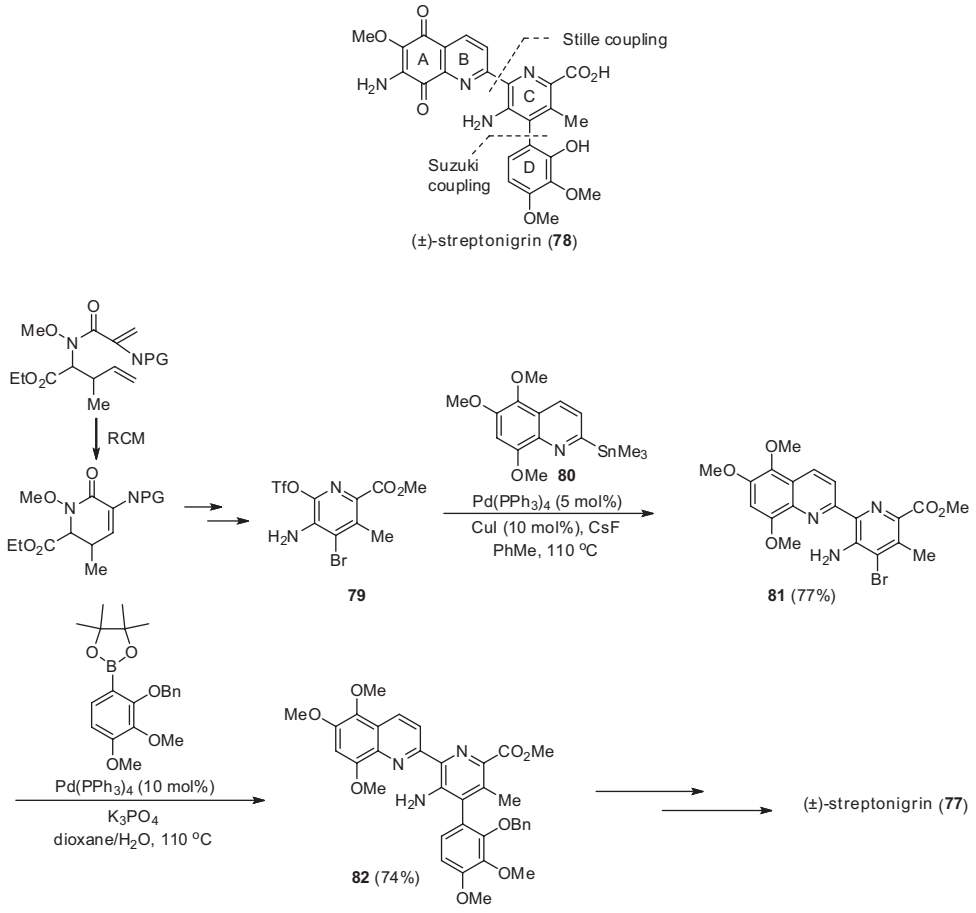
Scheme 23. A Suzuki reaction followed by ozonolysis for the preparation of **69**.



Scheme 24. Preparation of **76** by means of a Suzuki reaction with activation of a sp^3 carbon.

Donohoe *et al.* achieved a total synthesis of the antitumor antibiotic (±)-streptonigrin (**78**), employing a variety of transition metal-catalysed reactions.[43] While out of the scope of this text, it is worth noting that pentafunctionalized pyridine **79** was obtained by means of a challenging ring-closing metathesis reaction. Then, for constructing the AB-C ring system, the authors expected the triflate moiety of **79** to be more reactive towards Pd(0) oxidative addition in comparison to the bromide, mostly due to the increased reactivity of cross-coupling active substituents at the 2-position of pyridine (Scheme 25).

Thus, Stille reaction of pyridine **79** with stannylquinoline **80** provided the AB-C core of the desired product in 77% yield. Thereafter, Suzuki reaction with activation of the bromine substituent in **81** provided the tetracyclic compound **82** in 74% yield. Once the C-D ring system is configurationally stable, giving rise to atropoisomers, the authors also tried to perform the above Suzuki cross-coupling in an enantioselective fashion, with the best ratio between yield and enantioselectivity being achieved by means of the phosphino hydrazone **83** as a ligand (Figure 3) (65% yield and 42% ee).



Scheme 25. Key steps in the synthesis of **77**.

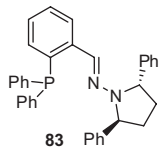


Figure 3. Chiral ligand employed for the asymmetric Suzuki reaction of **81**.

3. Negishi Reaction

The Negishi reaction is the coupling between an aryl (or vinyl) halide and an organozinc compound.[44,45] This coupling presents a greater tolerance towards sensitive groups like esters or amides when compared to organomagnesium or organolithium-based reactions; moreover, the enhanced reactivity of organozinc compounds allows this reaction to be performed at or even below room temperature, while boron or tin coupling partners demand harsher conditions.

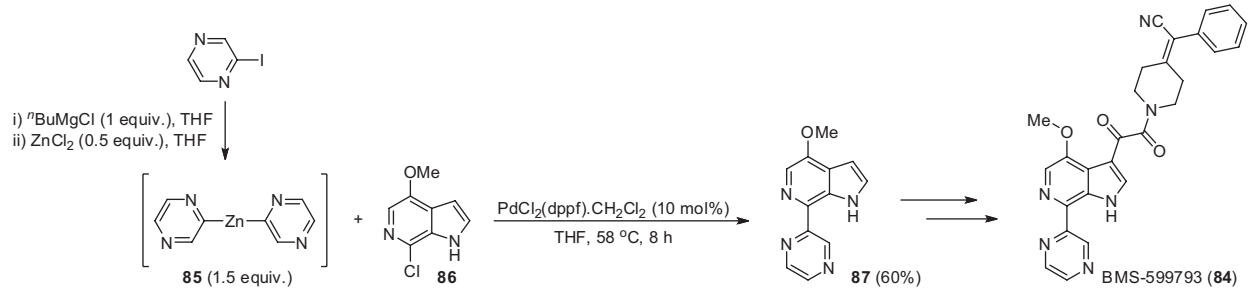
In 2013, a Negishi coupling was employed as one of the key steps in a new synthetic approach to BMS-599793 (**84**), an HIV entry inhibitor licensed from Bristol-Myers Squibb (BMS) by the International Partnership for Microbicides aiming towards its further development as a topical microbicide candidate for use in underdeveloped countries.[46] While the original medicinal chemistry route employed a Stille coupling as the last step of the sequence, this new synthetic approach anticipates the metal-catalyzed C-C bond forming reaction using a Negishi coupling as the first step, which eliminated the inconvenience of high levels of toxic tin residues previously observed in the final product. The coupling between diarylzinc reagent **85** and azaindol **86** led to adduct **87**, obtained in 41 to 59% yield for several batches of 400 g each. A single experiment carried out at a 1.5 kg scale afforded **87** in 54% yield and 99.6% HPLC purity (Scheme 26).

Acylation of the adduct's azaindole moiety with methyl chlorooxalate followed by ester hydrolysis and amidation afforded the final product which, however, still exhibited a high residual content of palladium (16 ppm) and zinc (100 ppm), requiring additional purification steps. At the end of the synthetic sequence, product treatment with activated charcoal followed by several washes, a precipitation step and polymorphic conversions led to the final active pharmaceutical ingredient (API) with Pd and Zn contents of only 1 ppm each.

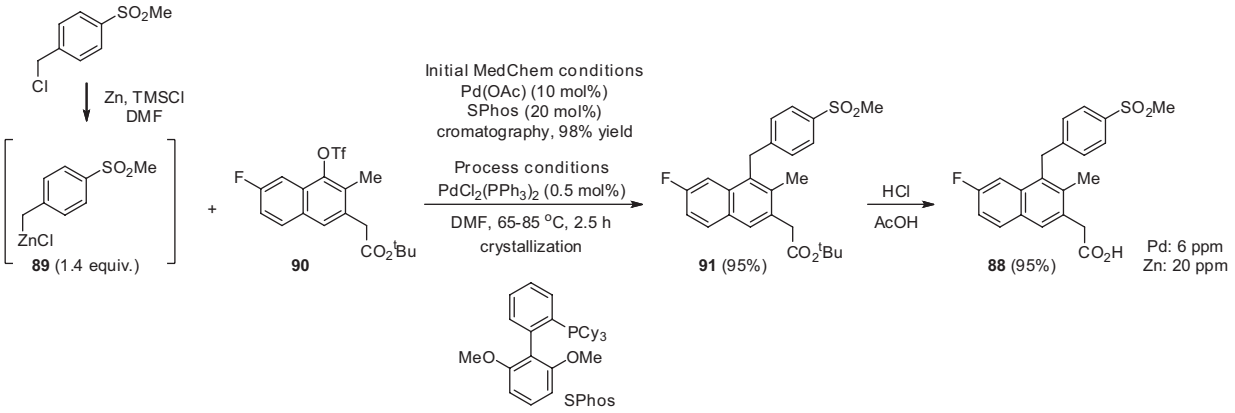
A Negishi reaction was also used in a multi-gram synthesis of compound **88**, a CHRT2 receptor antagonist with good pharmacological profile that was previously identified by Roche.[47] Since it is believed that CHTR2 plays a pro-inflammatory role in allergic processes, its antagonists are viewed as potential new drugs for the treatment of asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD) and atopic dermatitis, among other diseases. En route to **88**, the Negishi coupling between benzylzinc reagent **89** and aryl triflate **90** represented a major challenge. According to the previously developed medicinal chemistry synthetic route, the arylzinc preparation required a highly exothermic zinc activation process and the subsequent coupling step employed very high catalyst loadings, both of which are serious drawbacks for the scaling-up of the synthesis (Scheme 27).

During the process development, a traditional zinc activation approach was found to be effective, and by using trimethylchlorosilane in DMF, 237 g of zinc dust could be activated with only a 5 °C temperature increase over a 30 min period.

Regarding the proper Negishi coupling step, in a first moment, the authors were able to perform a 20-fold reduction in both palladium and phosphine quantities; however, the high cost of SPhos ligand was still prohibitive for large-scale production, even at 1 mol% loading. Fortunately, the inexpensive $PdCl_2(PPh_3)_2$ complex was equally effective when employed as the sole catalyst at 0.5 mol% loading. Due to safety reasons associated with transferring a high reactive zinc reagent, the coupling reaction was performed at the same pot of zincate formation by the sequential addition of the Pd source and aryl triflate followed by heating to 60-65 °C, which initiated the reaction. Without further heating, a temperature increase of up to 30 °C in a 10 min period was observed for batches involving 500 g of trifate **90**, which should be bypassed



Scheme 26. Synthesis of **84** with a Negishi coupling as key step.



Scheme 27. Synthesis of **88** with low loadings of Pd in a Negishi coupling.

for further scale-up. Filtration of the reaction crude trough Celite and treatment with *N*-acetyl-*L*-cysteine followed by crystallization afforded the coupling product **91** in 95% yield and > 99% HPLC purity. The final hydrolysis step afforded the desired API, which displayed well-controlled levels of residual palladium and zinc (6 and 20 ppm, respectively).

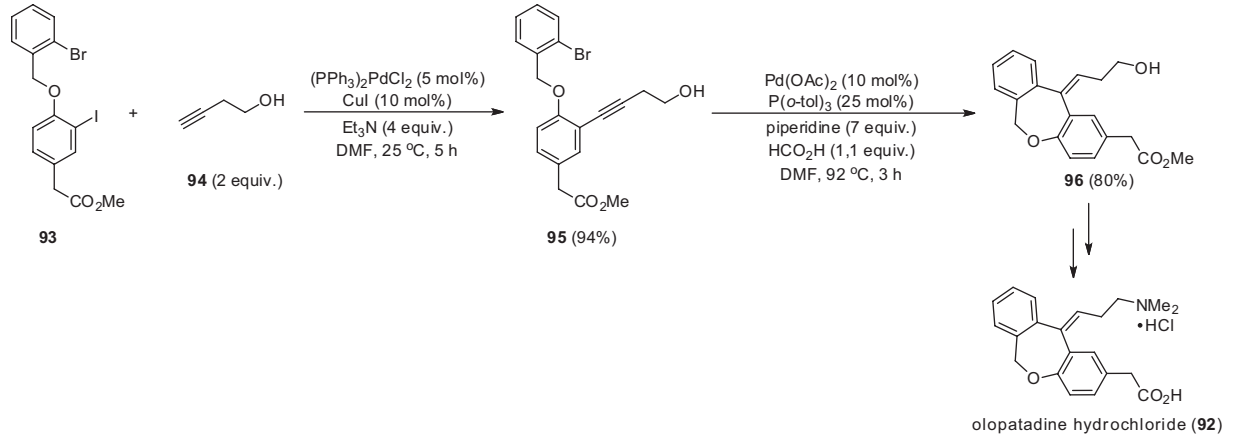
4. Sonogashira Reactions

The construction of a new bond between sp^2- and sp-hybridized carbons is known as the Sonogashira reaction,[48] and it is nowadays a widely employed methodology for the construction of arylacetylenes.[3,49,50] For example, a Sonogashira coupling was employed by the research and development group of Kyowa Hakko Kirin in a new and concise synthetic route for olopatadine hydrochloride (**92**), a commercial anti-allergic drug that was previously developed by the same company.[51]

The reported synthesis goes through the Sonogashira reaction between the easy accessible aryl halide **93** and alkyne **94** leading to adduct **95** in 94% yield. This adduct is then subjected to a second metal-catalyzed transformation, a stereospecific palladium-catalyzed intramolecular cyclization, whose optimum conditions were identified based on an elegant and comprehensive Design of Experiments (DoE) investigation to provide **96** (Scheme 28).

Elaboration of the cyclization product **96** through aminomethylation and ester hydrolysis followed by acid work-up completes the synthesis of the final target. Although the presented synthetic route is very promising and concise, providing olopatadine hydrochloride in 54% overall yield for 6 steps from commercially available materials, it has so far been reported only on a laboratory scale (5 g for the Sonogashira coupling and 200 mg for the cyclization step).

In 2012, in order to obtain necessary quantities for preclinical and phase 1 clinical studies, investigators at Wyeth Research reported the process implementation for the multi-kilogram preparation of GRN-529 (**97**), a highly selective mGluR5 negative allosteric modulator that was previously identified by the same company.[52] The authors opted for the development of the synthetic route initially presented by the medicinal chemistry group, which featured a Sonogashira coupling as one of the key steps. Despite the



Scheme 28. Optimal Sonogashira conditions for the synthesis of **92**.

good yield observed for this transformation, the conditions originally employed were not amenable for the scale-up of the reaction, requiring high loadings of metallic catalysts and drastic reaction conditions, as well as chromatographic purification of the product. During the developmental work, process friendly conditions were identified for the effective coupling between aryl halide **98** and alkyne **99**, resulting in at least 10-fold reduction of metal catalyst loadings and considerably lower reaction temperatures (Scheme 29).

A purification process involving the treatment of the crude reaction with an aqueous cysteine and ammonia solution followed by crystallization of the product afforded the coupling adduct **100** with high purity, acceptable levels of residual palladium and copper, and an even higher yield (86%). Elaboration of the coupling product **100** through ester hydrolysis followed by amidation furnished the final API, which was further purified via crystallization, leading to even lower residual levels of palladium and copper (< 1 and 15 ppm, respectively). This process was successfully employed in the preparation of 5.5 kg of **97**.

Process chemistry researchers from Merck recently employed Heck and Sonogashira reactions in the multi-gram preparation of the macrocyclic compound MK-1220 (**101**),[53] a potent hepatitis C virus (HCV) protease inhibitor with good therapeutic profile which has been evaluated as a potential new drug for the treatment of hepatitis C.[54]

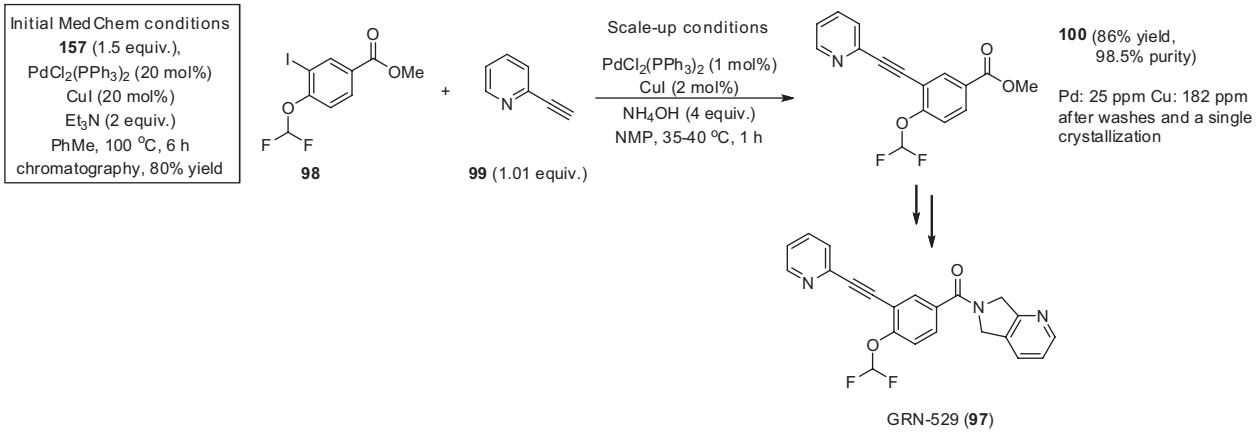
As an early synthetic step, a Heck reaction was used to introduce the nitrogen and two carbon atoms of the isoquinoline moiety present in the final target. The presence of a bulky substituent in the olefin **102** allowed the achievement of a 90:10 regioselectivity favouring the arylation of the terminal carbon, leading to adduct **103** in 76% isolated yield (Scheme 30).

A Sonogashira reaction was employed at a later stage of the synthesis, allowing the coupling of the advanced fragments **104** and **105** in 90% yield. The reaction conditions for this coupling were chosen based on a high throughput screening (HTS) study, which evaluated, among other factors, the use of 12 distinct ligands. Among them, only $P^tBu_3.HBF_4$ led to a clean reaction and satisfactory conversion. The triple bond reduction of the coupling adduct **106** with concomitant removal of carboxybenzyl (CBz) protecting group led directly to the substrate for the key macrocyclization step (**107**). The side chain installation in **107** completed the total synthesis of MK-1220. According to the authors, this synthetic sequence could be successfully scaled-up to produce kilograms of the final API.

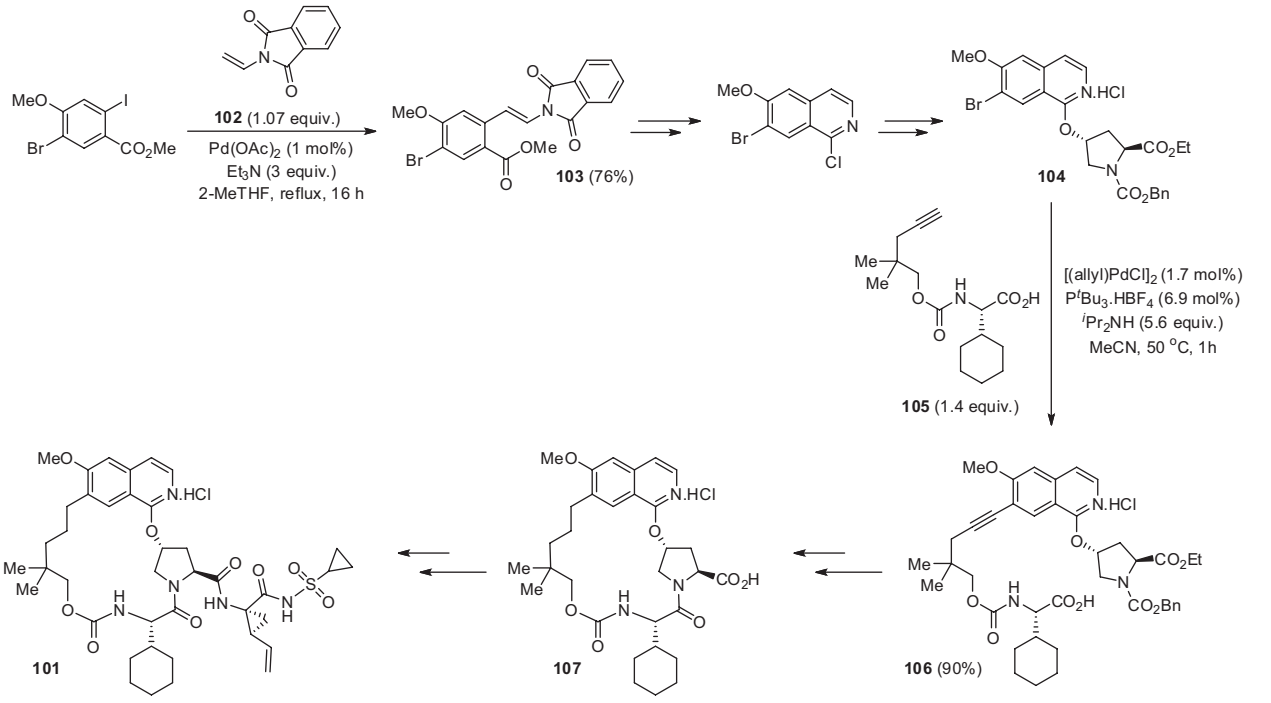
The Sonogashira reaction has also recently been used in the synthesis of Filibuvir (**108**), a potential drug for hepatitis C treatment, which acts as an inhibitor of RNA polymerase and has been evaluated by clinical and toxicological studies.[55]

The coupling between the alkyne **109** and aryl bromide **110** (Scheme 31), employed to introduce the pyridine moiety present in the final target, required the careful exclusion of oxygen from the reaction medium and addition of the palladium source prior to the copper catalyst, taking special care to avoid the formation of by-products through the oxidative coupling of the alkyne coupling partner (Scheme 31).

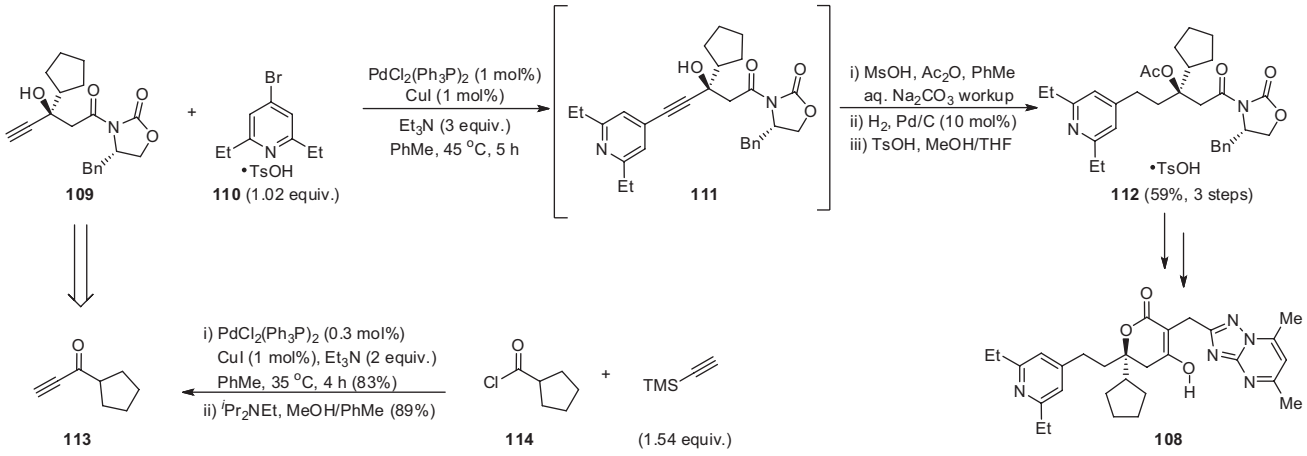
The coupling adduct **111** was then subjected to an acylation reaction followed by reduction of the triple bond to afford **112**. One of the drawbacks initially observed in this sequence was the high catalyst loading required for the hydrogenation step, which was attributed to poisoning of the metallic catalyst by residues of copper and phosphine derived from the initial Sonogashira coupling. Thus, previous purification of the acylated coupling product by washes with aqueous ethylenediaminetetraacetic acid (EDTA) followed by filtration through activated charcoal was necessary. This sequence of reactions was carried out on a pilot scale, producing 11.95 kg of the advanced intermediate **112**.



Scheme 29. Sonogashira cross-coupling with alkynyl pyridine **99**.



Scheme 30. Heck reaction as a tool for assembling the isoquinoline ring of **101**.



Scheme 31. Sonogashira reaction between bromide **110** and advanced alkyne **109**.

It should be mentioned that alkyne **109** is prepared by an aldol addition to the ketone **113** which, in turn, may also be prepared through a Sonogashira-type reaction involving the acid chloride **114** followed by desilylation. Although the authors present alternative and possibly more suitable synthetic routes for the preparation of this alkynyl ketone, the procedure based on the coupling between **109** and **110** could be successfully employed in the preparation of 100 kg of this material.

5. Stille Cross-Coupling

The coupling between an organic electrophile and an organotin compound is known as the Stille reaction.[56] It may be employed for the construction of vinyl-vinyl, aryl-vinyl or aryl-aryl bonds. Although the toxicity and difficult removal of tin compounds, which can present problems on an industrial scale, the Stille coupling reaction presents similar advantages to the Suzuki reaction (accessibility of organostannanes, air and moisture stability, tolerance towards most functional groups) and is usually superior for the synthesis of complex molecules, affording an alternative for the synthesis in medicinal chemistry scale. For instance, a Pd-catalyzed intramolecular Stille cross-coupling was applied as a key macrolide formation in a total synthesis of the iejimalide B (**115**) (Scheme 32), an anticancer compound isolated from the tunicate species *Eudistoma cf. rigida,* which is native to the coral reefs in Japan.[57] A

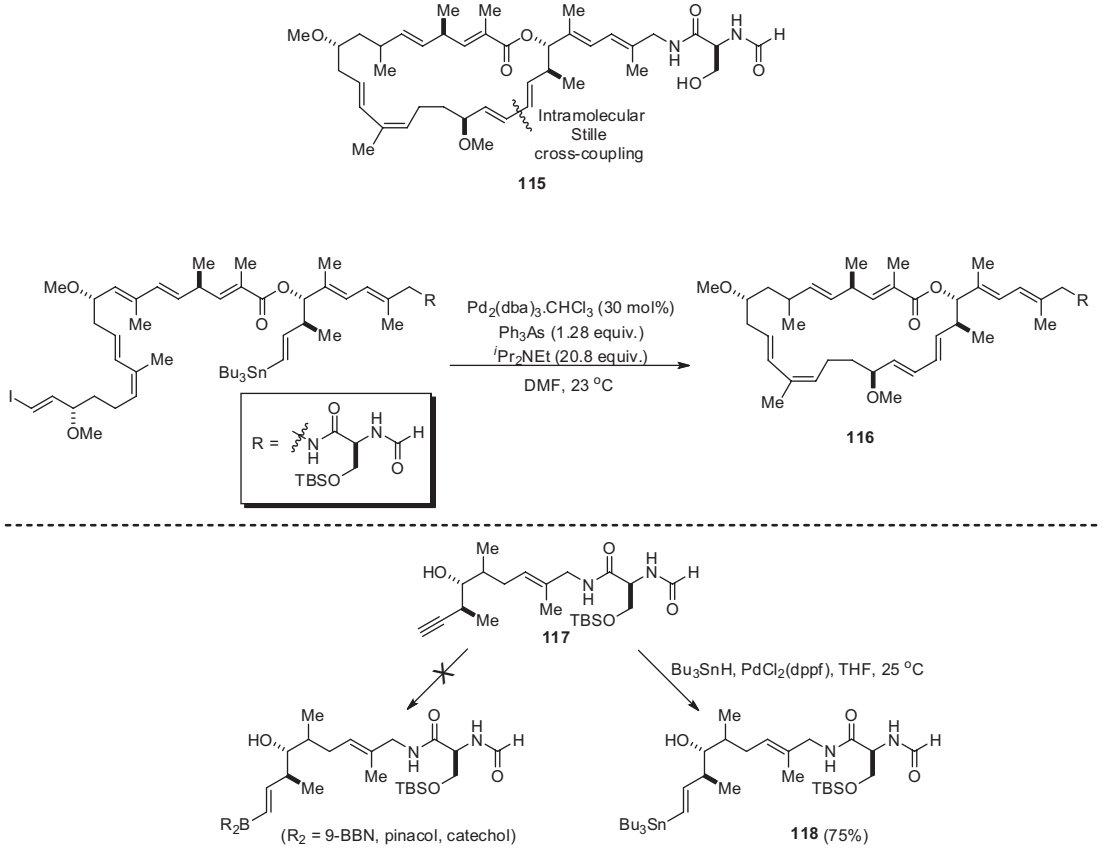
system based on $Pd_2(dba)_3.CH_3Cl$ and Ph_3As provided cyclic advanced intermediate **116** with 72% yield. However, it must be mentioned that 60 mol% of palladium was employed in the reaction. The Stille coupling was chosen instead of a Suzuki reaction for this macrocyclization due to the fact that hydroboration of the alkyne intermediate **117** proved difficult to generate the Suzuki partner while the hydrostannylation afforded the intermediate stannane **118** with 75% yield. This result was attributed to the high functional group tolerance of the hydrostannylation in comparison with hydroboration.

In 2013, the total synthesis of the HIV-1 integrase inhibitor **119** was described in a nine step route (Scheme 33).[58] The authors employed the bromopyridine **120** as starting material and the target compound was obtained with 18% overall yield. In the insertion of a side chain in the pyridinone central ring, the Stille cross-coupling of a vinyl stannane was applied and led to the product **121** with 83% yield after 1 h of reaction in DMF. A large amount (10 mol%) of the pre-catalyst $PdCl_2(PPh_3)_2$ in combination with a 20% excess of the tin reagent was necessary to provide high yields. It must be mentioned that the iodinated substrate was also applied in the cross-coupling; however, according to the authors, the bromo derivative was preferred due to a simpler chromatographic purification.

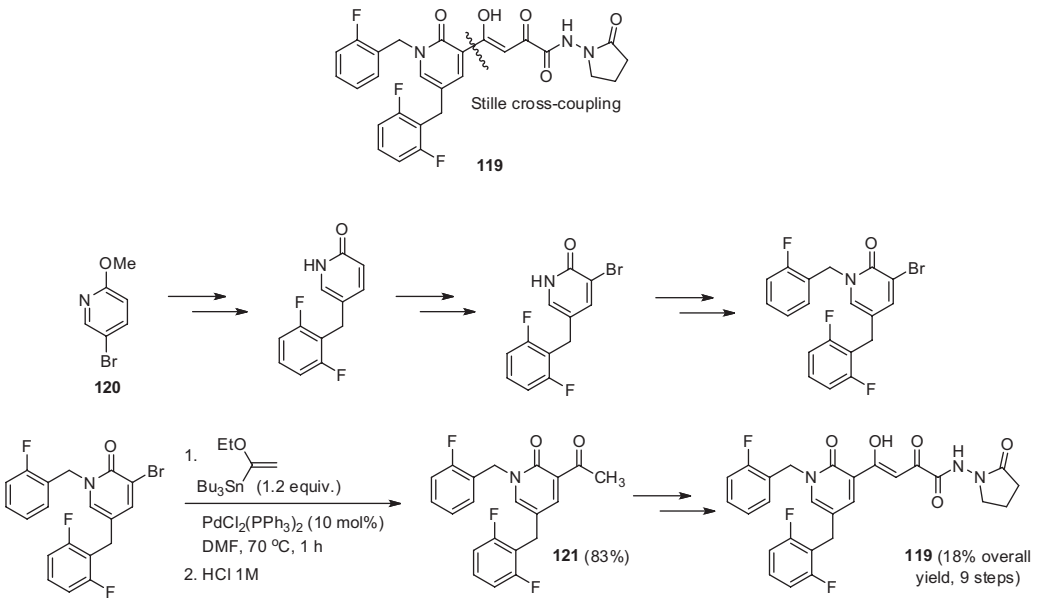
6. Kumada Cross-Coupling

The coupling of organomagnesium compounds and organic electrophiles is known as the Kumada reaction and is normally catalyzed by palladium or nickel complexes.[59] ST1535 (**122**) is a highly selective adenosine A_{2A} receptor ligand antagonist with good pharmacological properties, which might be considered a potential new drug for the treatment of Parkinson's disease.[60] Previous approaches for its synthesis explored Stille or Suzuki couplings for the installation of the alkyl side chain present in the final target.[61,62] Despite the good yields observed, both approaches suffered from major drawbacks such as drastic reaction conditions, low turnover number and frequency for the palladium catalysts employed, the need to prepare organoboron or tin reagents and the toxicity of starting materials and by-products in the special case of Stille reaction.

In this context, in 2014, the authors described a new approach exploring the Kumada coupling of a Grignard reagent, one of the cheapest organometallic



Scheme 32. Intramolecular Stille reaction to provide macrocycle **116**.



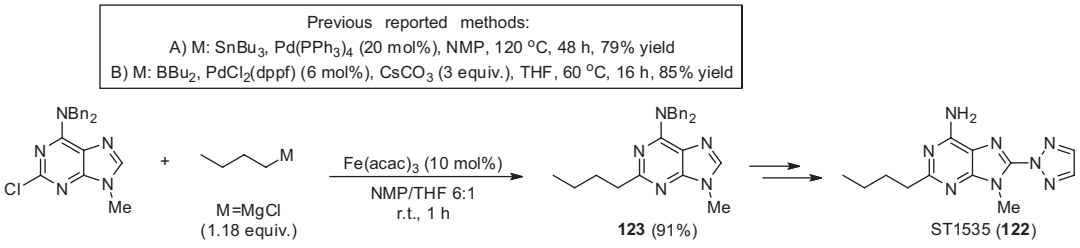
Scheme 33. Total synthesis of the HIV-1 integrase inhibitor **119** using a Stille reaction to append the carbonylated side-chain to the central pyridine ring.

reagents available, catalyzed by $Fe(acac)_3$, where acac = acetylacetonate, which is also a low-cost and easily removable catalyst. Besides the advantages regarding the cost of reagents and catalysts, the new procedure also generates less waste, due to the intrinsic higher atom-economy and also by not requiring an excess base, as seen for the Suzuki coupling approach. This procedure was successfully employed in the preparation of 38.5 g of **123**, which could be converted to **122** through bromination and bromine displacement with triazole followed by benzyl protecting group removal, as previously described in the literature (Scheme 34).

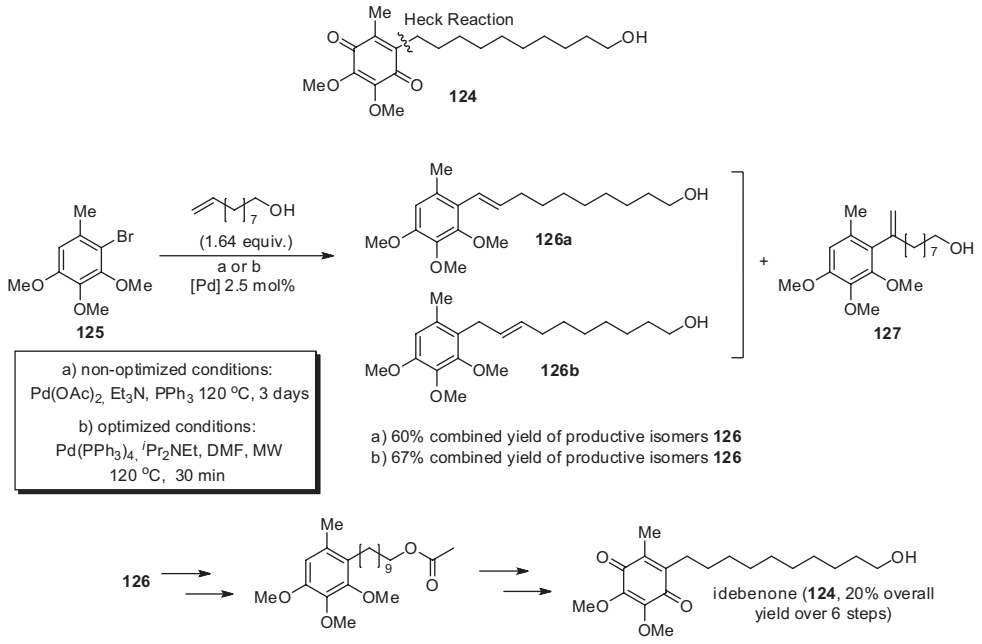
7. Heck Reactions

The palladium-catalyzed olefination of a sp^2 or benzylic carbon attached to a (pseudo)halogen is known as the Heck reaction.[2,63] It is a powerful tool, mainly used for the synthesis of vinylarenes, and it has also been employed for the construction of conjugated double bonds. The widespread application of this reaction can be illustrated by numerous examples in both academia small-scale[64] and industrial syntheses.[5] As an example, in 2011, a idebenone (**124**) total synthesis based on a Heck reaction was described (Scheme 35).[65] This compound, initially designed for the treatment of Alzheimer's and Parkinson's diseases, presented a plethora of other interesting activities, such as free radical scavenging and action against some muscular illnesses. The key step in the synthesis was the coupling of 2-bromo-3,4,5-trimethoxy-1-methylbenzene (**125**) with dec-9-en-1-ol affording products **126**. Under non-optimized conditions ($Pd(OAc)_2$, PPh_3, Et_3N, 120 °C), a mixture composed of 60% linear olefins **126** and 15% of the undesired branched product **127** was obtained after three days of reaction. Therefore, the conditions were optimized, allowing the preparation of **126** in 67% yield with no detection of **127** after only 30 min of reaction employing DMF, $Pd(PPh_3)_4$, $^iPr_2NEt$ under microwave heating. To conclude the synthesis, the Heck adducts were submitted to hydroxyl protection/deprotection, hydrogenation, and ring oxidation. After these reactions, idebenone was obtained with 20% overall yield over 6 steps.

A similar strategy to link an aryl and an alkyl group by means of a Heck reaction was applied in 2013 in the synthesis of ginkgolic acid (13:0) (**128**), a tyrosinase



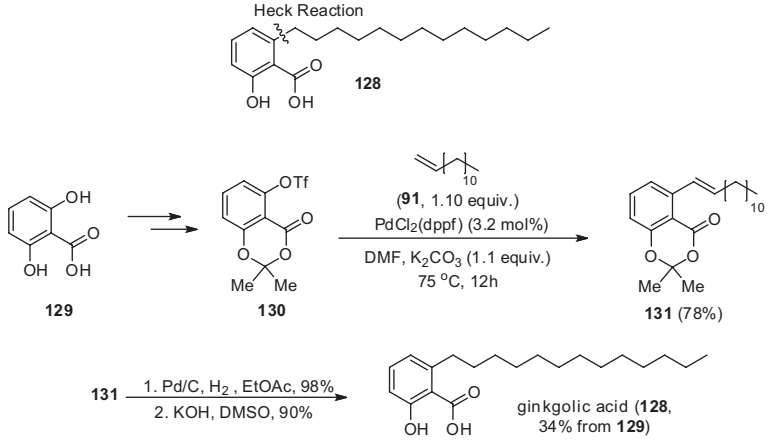
Scheme 34. Example of an iron-catalyzed Kumada reaction in the synthesis of **122**.



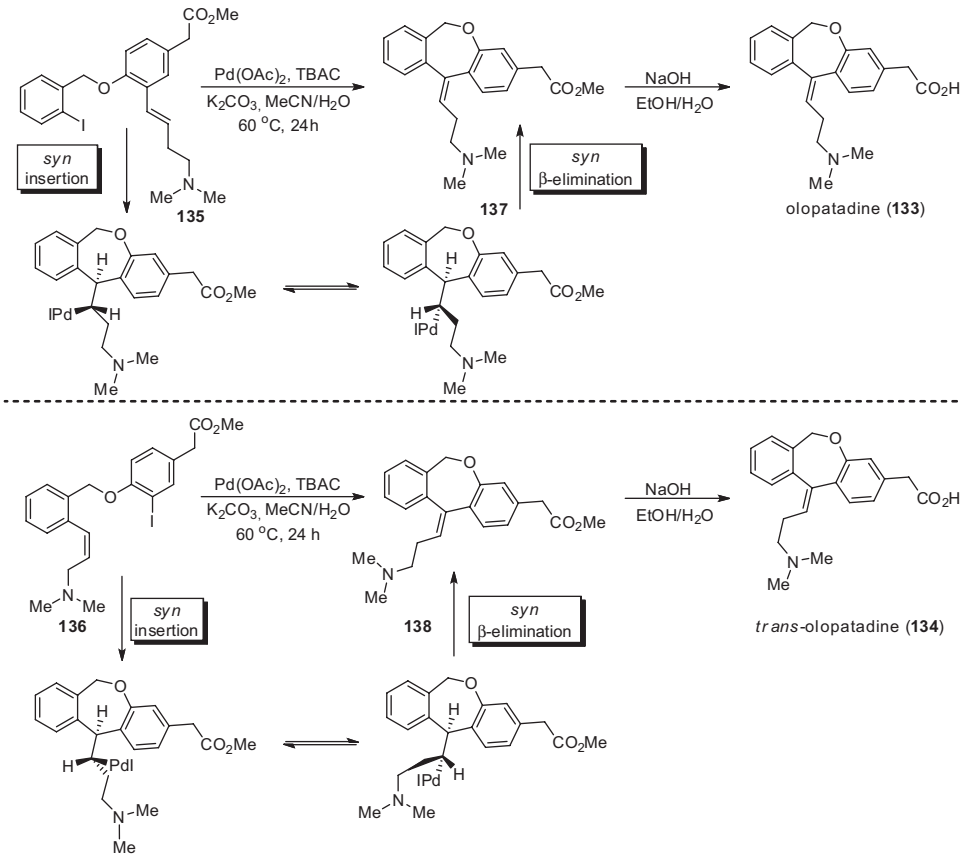
Scheme 35. Synthesis of idebenone (**124**) based on Heck reaction of 2-bromo-3,4,5-trimethoxy-1-methylbenzene with dec-9-en-1-ol under microwave irradiation.

inhibitor, as shown in Scheme 36.[66] Benzoic acid **88** was used as starting material in order to obtain the triflate **130**. This intermediate and the 1-tridecene were employed as coupling partners in the Heck reaction to obtain **131**. The system used was based on $PdCl_2$(dppf) and K_2CO_3, affording the coupling product in 78% yield after 12 h with 3.2 mol% of palladium. An alternative pathway to link the alkyl and aryl fragments was also tested: the coupling was performed in the presence of 9-borabicyclo(3,3,1)-nonane (9-BBN) to generate an alkylborane *in situ* from olefin **132** and achieve Suzuki coupling. However, this methodology was not productive. Once the Heck reaction was performed, **128** was obtained with 34% overall yield after the reduction of the double bond and the hydrolysis of the acetal protecting group.

An intramolecular Heck-based cyclization was used as a key step for commendable synthesis of the antihistaminic drug olopatadine (**133**) and its *trans* isomer (**134**).[67] Besides the Heck reaction, another vital step in this route was a stereoselective Wittig olefination using a non-stabilized phosphorus ylide that afforded the olefins **135** and **136** (*E*:*Z* ratio = 9:1 for **135**, for instance). Concerning the Heck reaction, $Pd(OAc)_2$, K_2CO_3, and NBu_4Cl (TBAC) were allowed to react with **135** and **136** at 60 °C during 24 h, providing the cyclic adducts **137** and **138** with reasonable 60% and 55% yields, respectively. However, it is important to note that in catalytic terms, the results were not encouraging, considering that 20 mol% of palladium was used and a disappointing turnover number (TON) of 3 was observed (Scheme 37).



Scheme 36. Synthesis of the ginkgolic acid based on the Heck reaction of aryl triflate **130**.



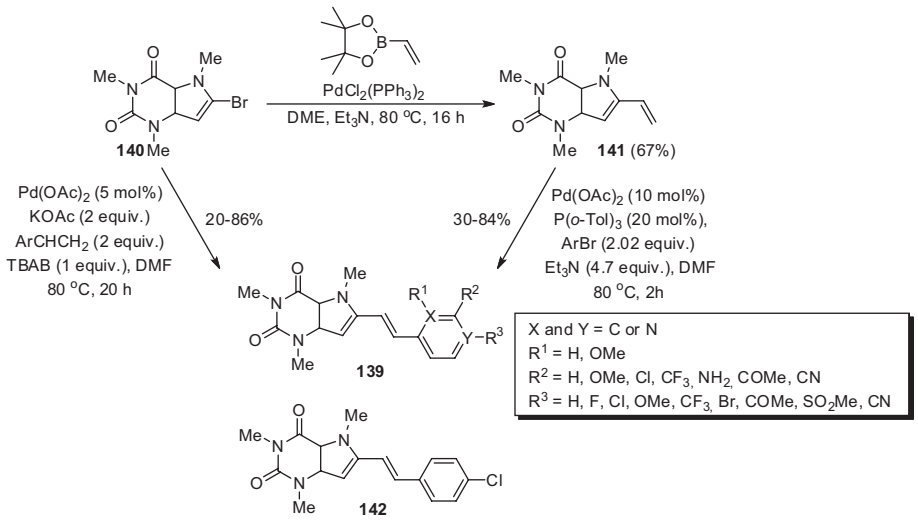
Scheme 37. Heck reaction in synthesis of olopatadine (**133**) and *trans*-olopatadine (**134**).

In relation to the stereochemistry of the Heck products, the above results were not surprising since they were consistent with a *syn*-insertion of the arylpalladium intermediate (provided by oxidative addition step) at the olefinic moiety followed by a *syn* β-elimination that afforded the product with the ascribed stereochemistry. Finally, with the cyclic products in hands, the syntheses were completed by alkaline hydrolysis of methyl esters that afforded the target olapatadine and *trans*-olapatadine.

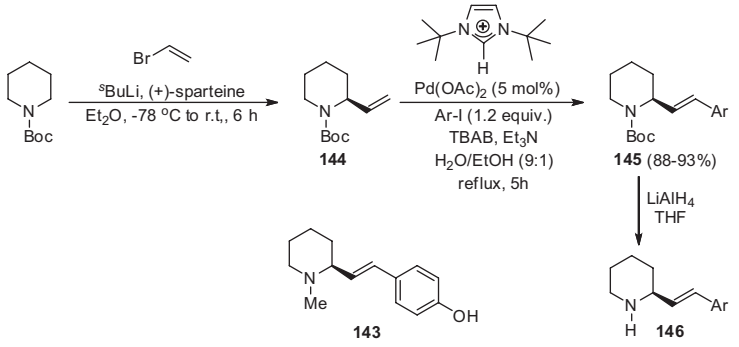
Two Heck-based strategies were applied in the synthesis of caffeine-styryl compounds (**139**) with dual A_{2A} antagonist/MAO-B inhibition properties and potential application in Parkinson's disease (Scheme 38).[68] In the first approach, the bromide **140** was submitted to a Suzuki cross-coupling with vinylboronic acid pinacol ester affording the vinyl-caffeine intermediate **141** in 67% yield. This intermediate was used as substrate in the Heck reaction with various aryl bromides in a system composed of $Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N and DMF. Accordingly, the caffeine-styryl analogues **139** were obtained with yields ranging from 30 to 84% in 2 h of reaction at 80 °C, with 10 mol% of palladium. In the second approach, the organic bromide **140** was used directly under Heck conditions in combination with styrene derivatives, DMF, NBu_4Br (TBAB) and $Pd(OAc)_2$. With this strategy, the target compounds **139** obtained with 20 to 86% yield in 20 h of reaction with 5 mol% of catalytic precursor. In terms of biological activities, the compound that exhibited the best results was **142**, the structure of which is shown at the bottom of Scheme 38.

A facile synthesis of styryl analogues of piperidine alkaloids was developed recently using *N*-Boc-piperidine as starting material (Scheme 39).[69] These alkaloids, including the (+)-caulophyllumine B (**143**), display high anti-cancer activity *in vitro*.[69] The first step of the synthesis was an enantioselective vinylation of the starting material affording the intermediate **144** that was used as substrate for Heck reactions with aryl iodides. In order to perform this Heck reaction, palladium acetate (5 mol%) was used as a pre-catalyst, in combination with an *N*-heterocyclic carbene (NHC) precursor and the phase transfer reagent TBAB. Under these conditions, styryl-piperidine adducts **145** were produced in excellent yields (88-93%). Finally, the target structures **146** were obtained by the reductive removal of the Boc protective group of compounds **145**. Compound **143** could be prepared after methylation of the appropriate precursor **146**.

Recently, Pfizer researchers described an efficient Heck- and Migita-based multi-kilogram process for the



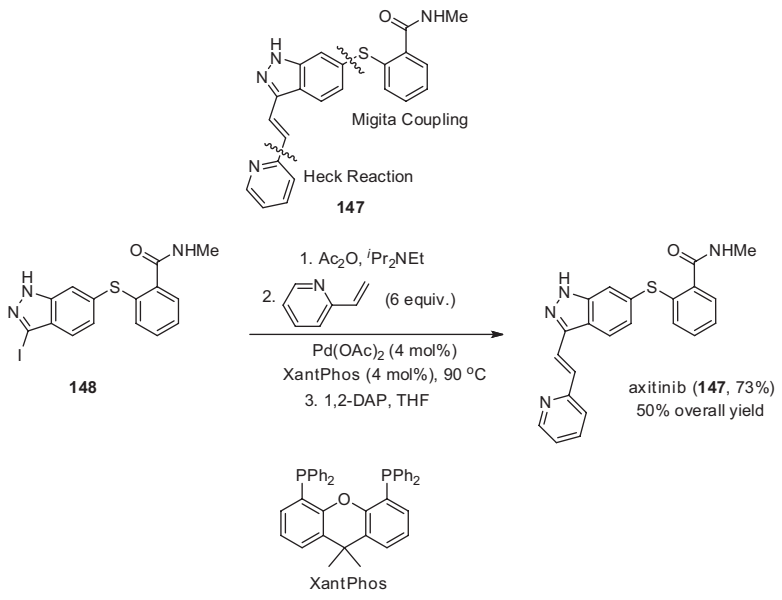
Scheme 38. Two Heck-based approaches employed in the synthesis of caffeine-styryl derivatives.



Scheme 39. Synthesis of piperidine analogues by Heck reactions.

vascular endothelial growth factor (VEGF) inhibitor axitinib (**147**) (Scheme 40).[70] A Migita coupling was used in the first step of the synthesis in order to assemble the mercaptobenzamide moiety of **147**. In the last step of the route, a Heck reaction between **148** and 2-vinyl-piridine was designed. However, the free NH of **148** impaired the reaction. Therefore, the authors decided to acylate the indazole for both protecting the NH group and rendering the oxidative addition to palladium easier. The protection was achieved *in situ* with Ac_2O and when no more than 2% of **148** was present, the Heck reaction was started using 4 mol% of $Pd(OAc)_2$, 4 mol% of XantPhos and six equivalents of 2-vinyl-pyridine. When the reaction was completed, 1,2-diaminopropane (DAP) was added in THF for removal of the protective group and to chelate the palladium before product crystallization. With this strategy, 29 kg of axitinib could be obtained with 50% overall yield in a six steps route.

A variation of the Heck reaction that has attracted considerable attention in recent years is the so-called Heck-Matsuda arylation, which is based on the use of aryldiazonium salts as electrophiles.[71] These compounds have the advantages of lower cost and improved reactivity in comparison to more traditional electrophiles like aryl halides.[18] As an example, a Heck-Matsuda based strategy via aryl-coumarins was used in the synthesis of (*R*)-tolterodine (**149**), a drug that is employed in urinary incontinence treatment.[72] The coupling was employed in the first step of the route between the *ortho*-substituted cinnamate **150** and the 4-bromo substituted arenediazonium salt **151**, using 10 mol% of $Pd(OAc)_2$ as a pre-catalyst and $CaCO_3$ as base. It is important to note that the target molecule tolterodine contains no bromine substituents, for this reason, after completion of the Heck reaction, the product was not isolated, being directly submitted to debromination under H_2 atmosphere and subsequently isolated as **152** with 63% over two steps (Scheme 41). The employment of the bromo-substituted aryldiazonium salt instead of phenyldiazonium salt was justified by the lower yield of the Heck reaction using PhN_2BF_4 (only 41% yield). Nonetheless, compound **152** had already been synthesized via a Heck reaction with 77% yield without requirement of the debromination step.[73] With the desired coumarin **152** in hands, the synthesis was accomplished by

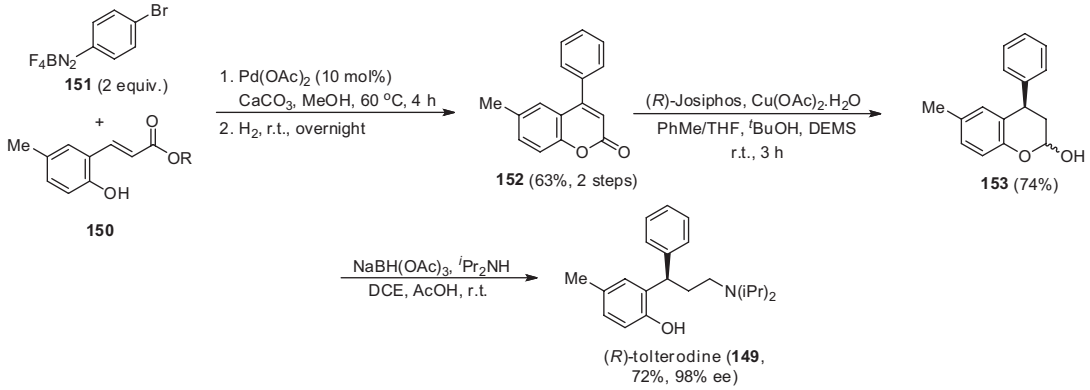


Scheme 40. Process for axitinib based on palladium catalyzed Migita C-S coupling and Heck reaction.

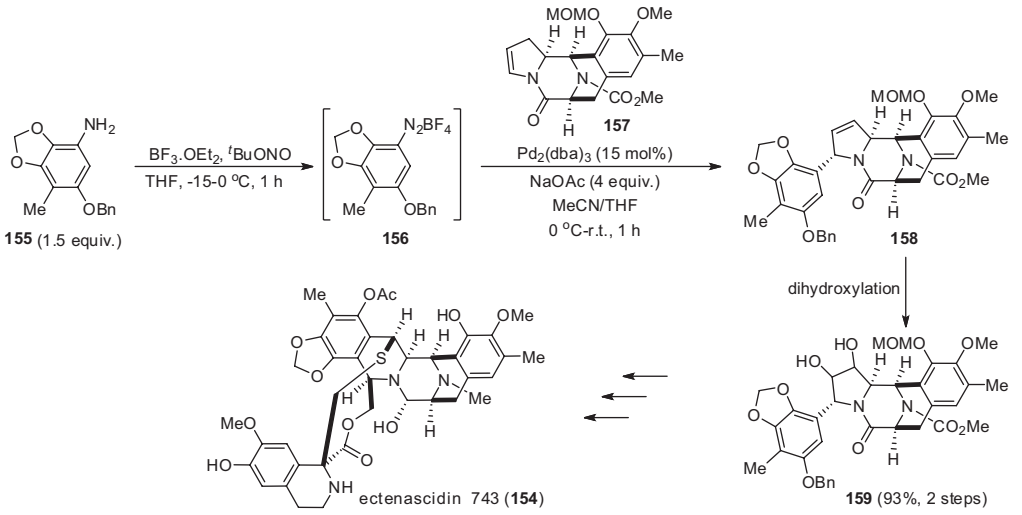
a copper-catalyzed enantioselective conjugate reduction, furnishing **153**, followed by reductive amination. With this methodology, (*R*)-tolterodine was obtained in 30% overall yield and 98% ee after four steps.

A Heck-Matsuda methodology was applied in the synthesis of the anti-cancer tetrahydroisoquinoline alkaloid ectenascidin 743 (**154**).[74] The diazonium salt **156** was generated *in situ* by the treatment of **155** with $BF_3.OEt_2$ and ^{t}BuONO and reacted with the enamide intermediate **157** in the presence of $Pd_2(dba)_3$ (15 mol%) and NaOAc. In this way, the reaction occurred exclusively in the less hindered face of the olefin, affording **158** with regio- and stereocontrol. It is important to mention that **158** was roughly purified and employed for subsequent dihydroxylation, leading to **159** in 93% yield for the two steps in a 2.15 gram scale, which is a significant amount given the complexity of the targets (Scheme 42).

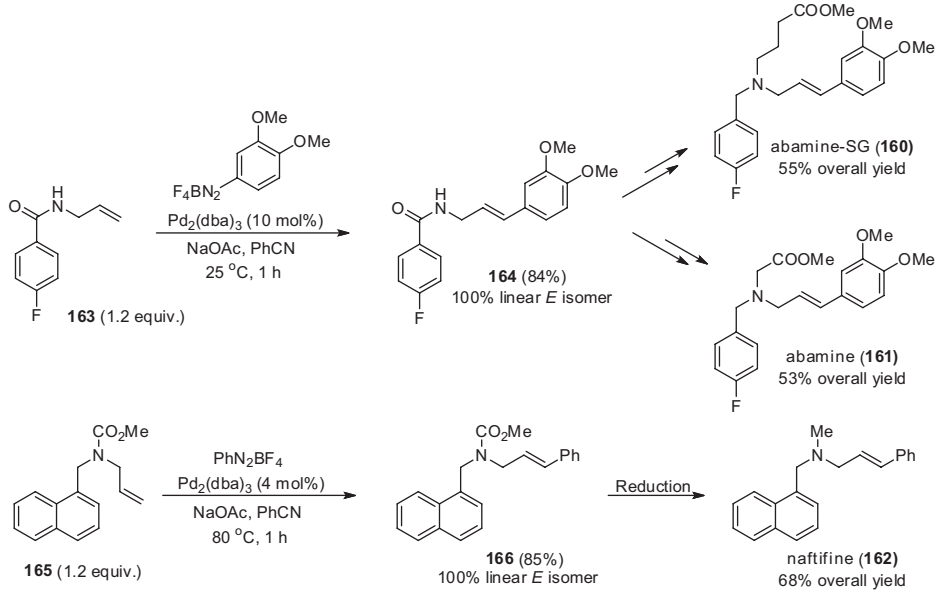
Heck-Matsuda reactions of substituted allylamines were employed as key steps in the synthesis of the bioactive compounds abamine-SG (**160**), abamine (**161**) and naftifine (**162**) (Scheme 43).[75] Concerning the abamines, the reaction between the allylamine **163** and the corresponding diazonium salt in the presence of 10 mol% of $Pd_2(dba)_3$ afforded the adduct **164** with 84% yield and no detection of the undesired branched product. With the coupling product in hands, the syntheses were accomplished with 55% and 53% overall yields. With respect to naftifine, 4 mol% of the pre-catalyst were employed in the coupling of PhN_2BF_4 with the allylamine **165**, leading to the intermediate **166** with 85% yield and total regio- and stereocontrol. The authors believe that this excellent selectivity arises from a substrate-directed reaction: in complexing with both the olefin and carbonyl moieties of the substrate, the cationic arylpalladium intermediate takes part in a stable six-membered ring that favourably delivers the desired product. After the Heck reaction, a simple ester reduction was necessary to provide the target molecule in 68% yield.



Scheme 41. Synthesis of (*R*)-tolterodine based on a Heck-Matsuda reaction and enantioselective reduction of compound **152**.



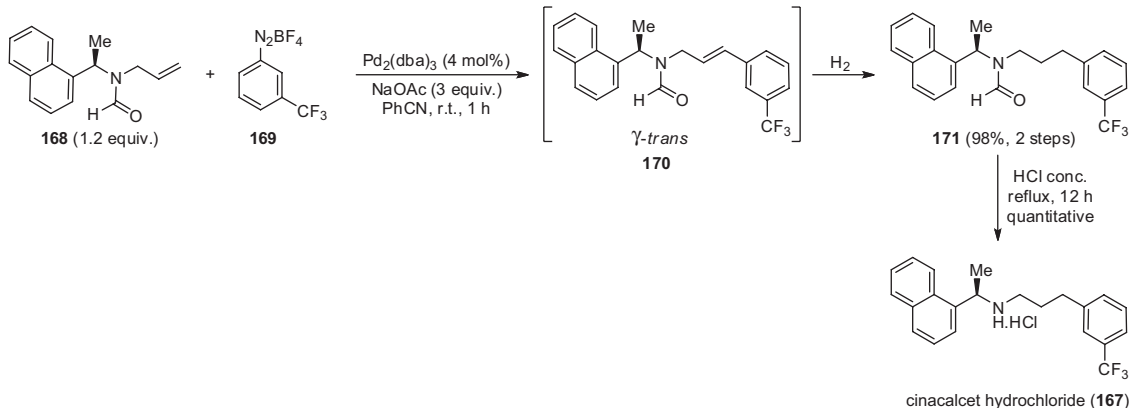
Scheme 42. Heck-Matsuda reaction applied in the synthesis of **158**, an intermediate in the synthesis of **154**.



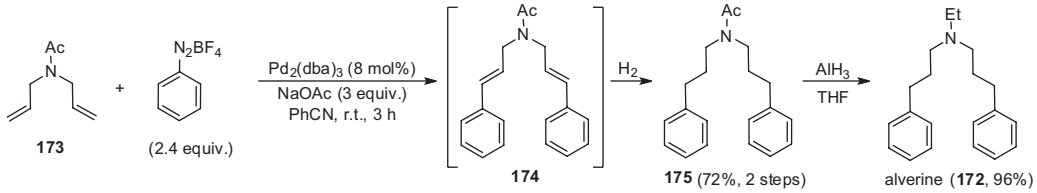
Scheme 43. Heck-Matsuda as key step in the syntheses of abamine SG, abamine and naftifine.

Still exploring the Heck-Matsuda arylation of allylamine derivatives, Correia and co-workers recently reported new and concise synthetic routes for the lab-scale preparation of three other drugs: cinacalcet hydrochloride, alverine and tolpropamine.[76] Cinacalcet hydrochloride (**167**) is a calcimimetic drug commercialized under the trade names Sensipar and Mimpara, which is therapeutically useful for the treatment of secondary hyperthyroidism and also indicated against hypercalcemia in patients with parathyroid carcinoma. In the new synthetic approach, the main carbon skeleton of the final target was assembled through the arylation of allylformamide **168** with diazonium salt **169** leading to the adduct **170**, which was *in situ* reduced, taking advantage of the palladium content from the arylation step, to afford intermediate **171** in excellent yield for the two steps. It is worth noting that the reduced steric volume of the nitrogen formyl protecting group proved to be essential for the observed high reactivity and regioselectivity of the arylation step. The deformylation of **171** under acidic medium with concomitant hydrochloride formation completed the synthesis of **167** (Scheme 44).

Alverine (**172**), a smooth muscle relaxant used for the treatment of gastrointestinal disorders such as diverticulitis and irritable bowel syndrome, was prepared from *N,N*-diallylacetamide **173** by means of a double Heck-Matsuda reaction/hydrogenation: a one-pot sequence furnished **175**, in 72% yield, after reduction of the Heck adduct **174** in a tandem fashion. Acetyl group reduction of **175** with AlH_3 afforded the final target in excellent yield (Scheme 45).



Scheme 44. Synthesis of **167** by means of a Heck-Matsuda reaction.

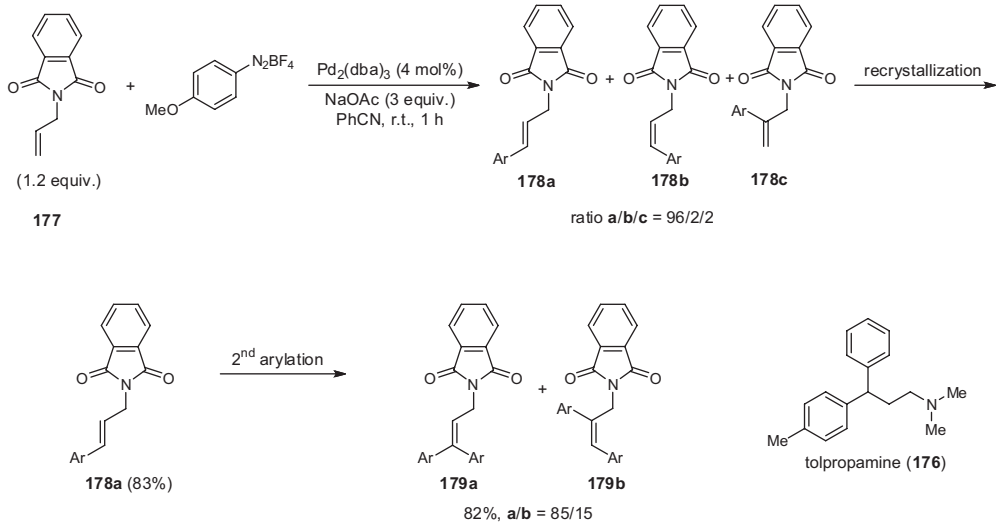


Scheme 45. Double Heck-Matsuda arylation en route to **172**.

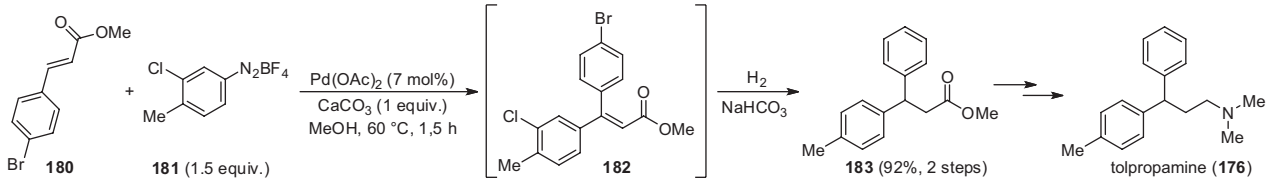
For the preparation of tolpropamine (**176**), an antihistaminic drug used for the treatment of allergies, a synthetic strategy involving a step-by-step bis-arylation of the allylamine derivative **177** was envisioned for the construction of the non-symmetrical diarylmethane fragment present in the final target. However, an initial model study, aiming at the preparation of the simpler symmetrical bis-arylated product, revealed some difficulties: although the terminal mono-arylated adduct **178a** could be isolated in the pure form after the first arylation step, the second arylation reaction showed only moderate regioselectivity, leading to a mixture of the isomeric products **179a** and **179b**, which displayed very difficult separation (Scheme 46).

Thus, a new synthetic strategy featuring the Heck-Matsuda arylation of a methyl cinnamate derivative was proposed. Unfortunately, the appropriate combinations of cinnamate substrates and aryldiazonium salts, which could lead directly to the coupling product with the substitution pattern present in the final target, were found to be unreactive under the studied conditions.

Alternatively, the Heck-Matsuda reaction involving the corresponding halogenated coupling partners **180** and **181** led to the diaryl product **182** in excellent yield. *In situ* double bond hydrogenation and concomitant dehalogenation afforded the properly substituted intermediate **183** in 92% yield for the 2 steps. Ester hydrolysis followed by amidation



Scheme 46. Initial model studies for the synthesis of **176**.



Scheme 47. Synthesis of **176** by means of a modified Heck-Matsuda procedure.

and reduction reactions completed the synthesis of **176** (Scheme 47).

8. Conclusions and Perspectives

The ongoing efforts towards the use of Pd-catalyzed C-C cross-coupling reactions for the synthesis of drug components or drug candidates highlighted in this review demonstrated how powerful these methodologies are. The Suzuki reaction is the most exploited cross-coupling reactions, especially when the creation of a biaryl motif is involved. One of the main advantages of this methodology is the use of air- and water-stable, non-toxic and ease to manipulate organoboronic acid and its derivatives. Heck reactions are also intensely exploited for inter or intramolecular coupling involving Csp^2 double bonds. Despite the success of the coupling reactions, several challenges need to be overcome in order to have an economic, robust and reliable industrial process. Scale-up from the small (medicinal chemistry synthesis) to large scale usually requires new Pd catalyst precursors and several modifications to the reaction parameters. From the economic standpoint, in some cases, the cost of the precious metal palladium, as well as the ligand itself, can be a problem. There is a plethora of palladium catalyst precursors described in the literature that promote the C-C cross-coupling reactions. However, when these reactions need to be applied for the synthesis of complex molecules such as drug components or drug candidates, a few simple catalyst precursors are usually the first choice: $Pd(OAc)_2$, $Pd_2(dba)_3$, Pd/C, $PdCl_2L_2$, $Pd(PPh_3)_4$. For aryl iodides or some very activated aryl bromides, ligand-free Pd catalysts can be used. However, in most of the reactions involving the synthesis of drugs, a phosphine ligand is necessary and triphenylphosphine is the most frequently used ligand. This cheap and stable phosphine is usually used already complexed in the Pd precursor ($PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$) or in association with a simple Pd precursor ($Pd(OAc)_2$ or $Pd_2(dba)_3$). When a bidentated ligand is necessary, dppf or other ferrocenil-based bidentated phosphine ligands are used, with $PdCl_2(dppf)_2$ being the catalyst precursor of choice. Economically more attractive aryl chlorides have been used in some cases due to the development of electron-rich- and steric demanding phosphine ligands. However, the quest for precursor catalyst and ligands that allow high TON and turnover frequency (TOF), that would make the process economically attractive is still a challenge. Another important point that needs to be taken in account is the contamination of the product with palladium and the need for further purification steps. Therefore, practical and feasible catalytic systems that allow the easy recovery of palladium or coupling reactions involving cheaper transition metals are welcomed.

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