Chapter 4
Pharmaceuticals

Jiao Jiao and Yasushi Nishihara

Abstract This chapter describes the design and development of biologically active compounds using cross-coupling reactions as key steps. These biologically active compounds are of both academic and industrial importance. Drug candidates can be prepared from easily available substrates in a few steps through cross-coupling—underscoring the versatility, effectiveness, functional group tolerance, and mild reaction conditions of the cross-coupling methods. Due to these advantages, palladium-catalyzed cross-coupling reactions are being utilized in the industrial production of pharmaceuticals.

Keywords Pharmaceutical · Large-scale synthesis · Functional group tolerance

4.1 Introduction

Owing to many pioneering chemists' unremitting efforts, recent innovations have replaced earlier protocols to achieve milder, broader, and more efficient catalytic methods for carbon–carbon bond formations [1–11]. The cross-coupling protocols are appropriately considered to be the cornerstones for the synthesis of pharmaceuticals. These reactions provide new entries into pharmaceutical ingredients of continuously increasing complexity. Transition-metal catalysts such as Ni, Cu, Rh, and Ru have been substantially developed in the synthesis of drugs or their precursors [12–16]; however, Pd catalysis, with its high activity and mild reaction conditions, has considerable potential in large-scale applications for pharmaceuticals.

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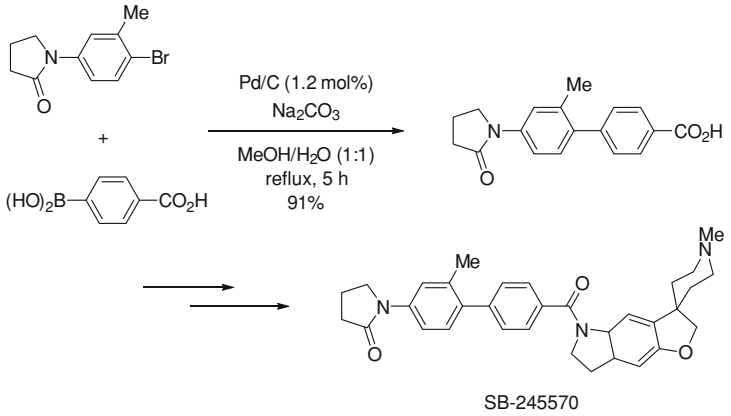
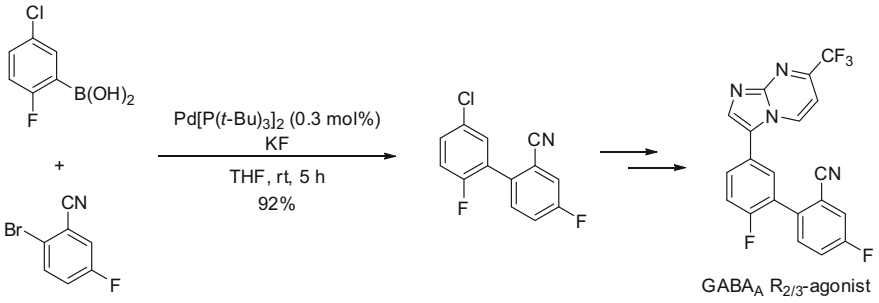
4.2 Suzuki–Miyaura Coupling

The most representative coupling for the synthesis of pharmaceuticals is the Suzuki–Miyaura coupling, which has been widely studied in the past decade. One of the earliest examples of industrial-scale Suzuki–Miyaura coupling in pharmaceuticals was reported in 1999 [17], which described the synthetic pathway of SB-245570, a candidate for the treatment of depression (Scheme 4.1). This synthesis was efficient and inexpensive. The Pd/C-catalyzed Suzuki–Miyaura coupling provided access to the desired product, and reaction in MeOH/H_2O gave an improved product yield with a residual Pd level of <6 ppm.



Scheme 4.1 A synthetic route to SB-245570

Cameron et al. published the preparation of a $GABA_A$ $R_{2/3}$ agonist for the treatment of generalized anxiety disorder (Scheme 4.2) [18]. The biaryl system was assembled from the palladium-catalyzed Suzuki–Miyaura coupling of an aryl bromide with an arylboronic acid. The arylboronic acid was prepared via *ortho*-lithiation of 4-chlorofluorobenzene with lithium 2,2,6,6-tetramethylpiperidine, followed by a B[O(*i*-Pr)]$_3$ quench and acidic workup [19, 20].



Scheme 4.2 A synthetic route to a $GABA_A$ $R_{2/3}$-agonist

3-Amino-2-phenylpiperidines are important pharmacophores because of their role as potent, non-peptidic NK1 receptor antagonists such as CP-99,994 and GR203040 (Fig. 4.1).

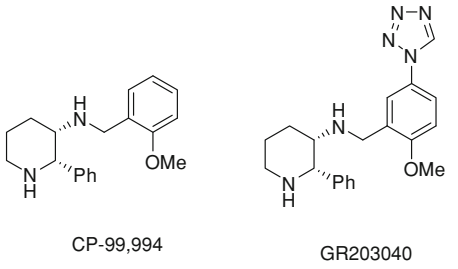
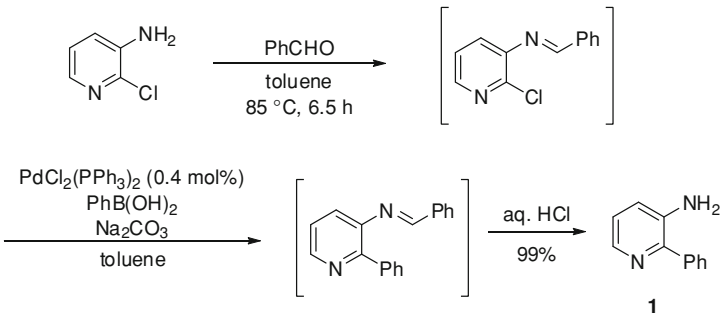


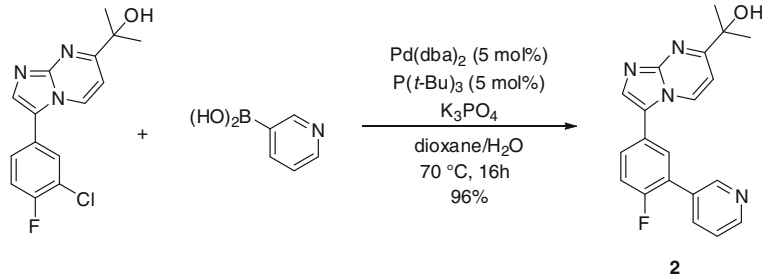
Fig. 4.1 3-Amino-2-phenylpiperidine derivatives

Caron and co-workers have reported Suzuki–Miyaura coupling to prepare 3-amino-2-phenylpyridine, a key intermediate in the preparation of 3-amino-2-phenylpiperidine [21]. The in situ protection of 3-amino-2-chloropyridine with benzaldehyde, followed by Suzuki–Miyaura coupling with phenylboronic acid and the subsequent acidic hydrolysis provides 3-amino-2-phenylpyridine (**1**) in a single, high-yielding step from inexpensive and commercially available starting materials (Scheme 4.3).



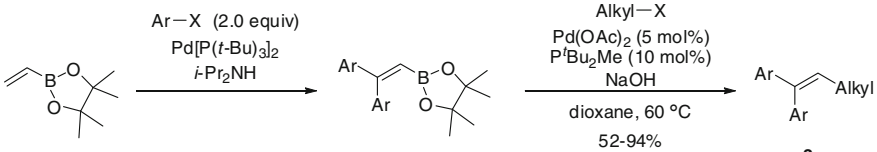
Scheme 4.3 Synthesis of 3-amino-2-phenylpyridine (**1**)

Jensen has described the synthesis of a $GABA_A$ $R_{2,3}$-selective allosteric modulator **2**, a potential treatment for central nervous system conditions, in high yield by Suzuki–Miyaura coupling of imidazopyrimidine with 3-pyridylboronic acid (Scheme 4.4) [22]. This synthetic method highlights the versatility of Pd-catalyzed Suzuki–Miyaura coupling.



Scheme 4.4 Synthesis of a $GABA_A$ $R_{2,3}$-selective allosteric modulator **2**

Itami and Yoshida have described a sequence of double Mizoroki–Heck reactions of the vinylboronate pinacol ester with aryl halides, followed by Suzuki–Miyaura coupling of the generated β,β-diarylvinylboronates with alkyl halides (Scheme 4.5) [23], to very efficiently produce pharmaceutically important 1,1-diaryl-1-alkenes **3** (Fig. 4.2). In the Pd-catalyzed Suzuki–Miyaura coupling step, the use of bulky electron-rich ligands such as P^tBu_2Me and PCy^t_2Bu was found to be very effective.



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 1-naphthyl.
Alkyl = $^nC_4H_8Ph$, $^nC_6H_{12}OH$, $^nC_6H_{12}OPiv$, $C_2H_4SiMe_3$, $^nC_6H_{12}CN$, $^nC_6H_{12}$-$OSiEt_3$, C_3H_6Ph, $^nC_4H_8NPhth$, 1-hexen-6-yl

Scheme 4.5 Synthesis of 1,1-diaryl-1-alkenes **3**

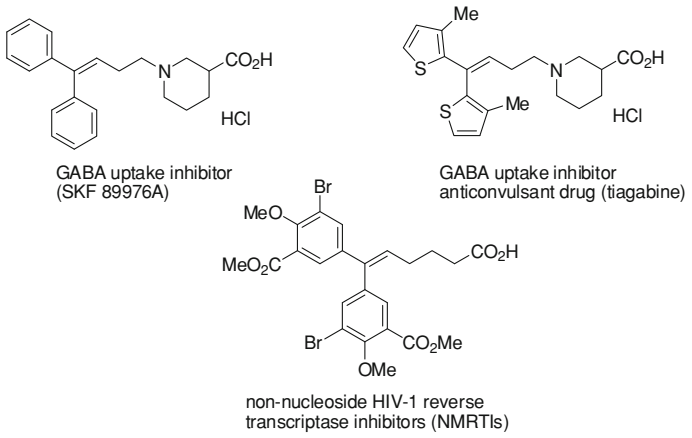
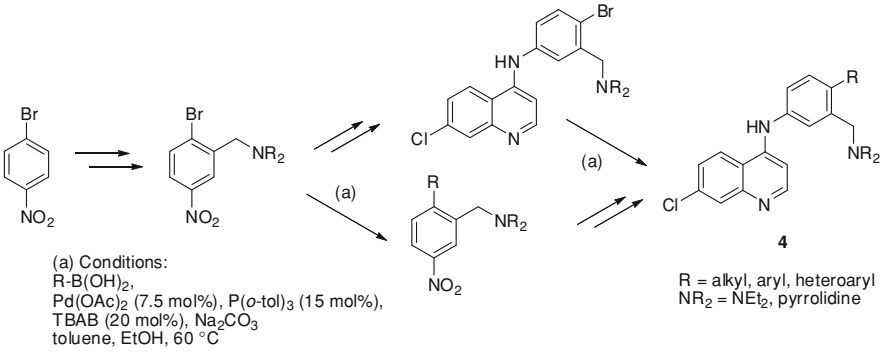


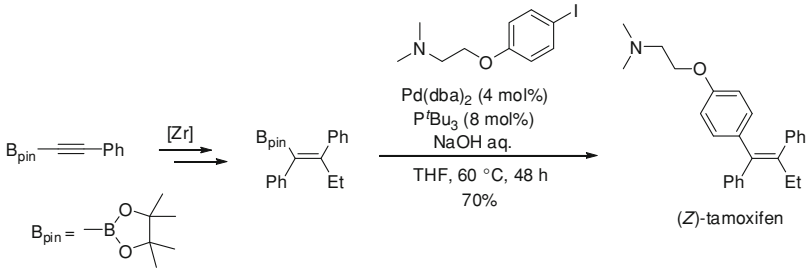
Fig. 4.2 Examples of pharmaceutically important 1,1-diaryl-1-alkenes

A versatile methodology for the synthesis of 4-aminoquinoline derivatives **4** (antimalarial drugs) using $C(sp^2)$-$C(sp^2)$ Suzuki–Miyaura cross-coupling reactions as key steps is presented in Scheme 4.6 [24]. These methodologies provided the novel synthesis of a variety of aryl- and alkyl-substituted 4-aminoquinoline analogs by a general protocol, which allowed the convenient introduction of diversity using Suzuki–Miyaura couplings between aryl bromides and commercially available arylboronic acids.



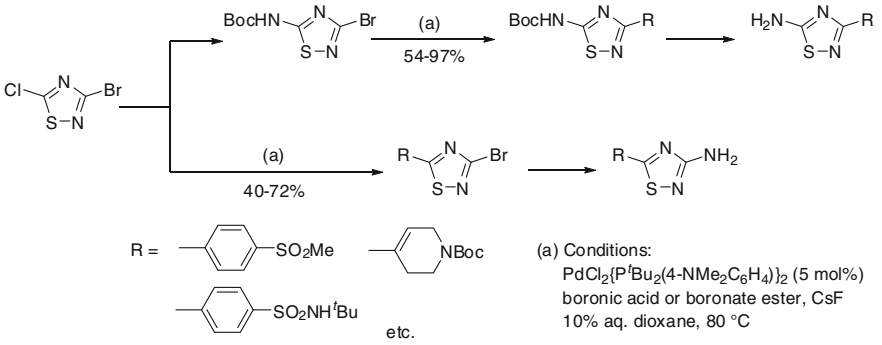
Scheme 4.6 Synthesis of 4-aminoquinoline derivatives **4**

A versatile and direct synthesis of multi-substituted olefins has been developed by the regioselective formation of zirconacyclopentenes, followed by Pd-catalyzed cross-coupling and sequential Suzuki–Miyaura coupling with various aryl iodides (Scheme 4.7) [25]. (*Z*)-Tamoxifen, a widely used treatment for all stages of breast cancer, can be successfully synthesized via this methodology with high regio- and stereoselectivities (>99 %).



Scheme 4.7 Synthesis of (Z)-tamoxifen

Wehn has demonstrated a novel approach to the synthesis of the substituted 5-amino- and 3-amino-1,2,4-thiadiazoles beginning from a common precursor (Scheme 4.8). Derivatization by palladium-catalyzed Suzuki–Miyaura coupling enables an efficient supply of analogs around this pharmaceutically relevant core (Fig. 4.3) [26].



Scheme 4.8 Synthesis of the substituted 5-amino- and 3-amino-1,2,4-thiadiazoles

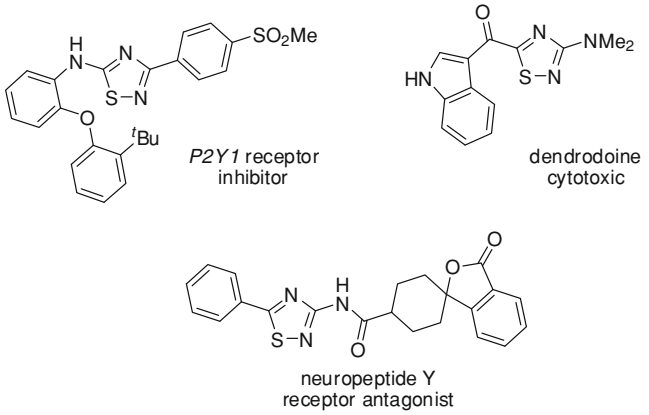
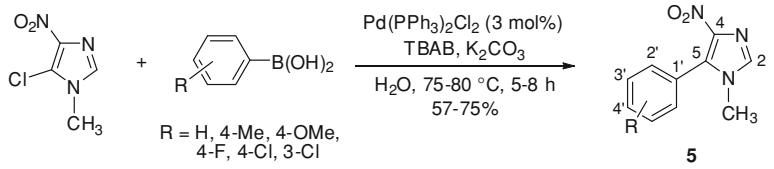


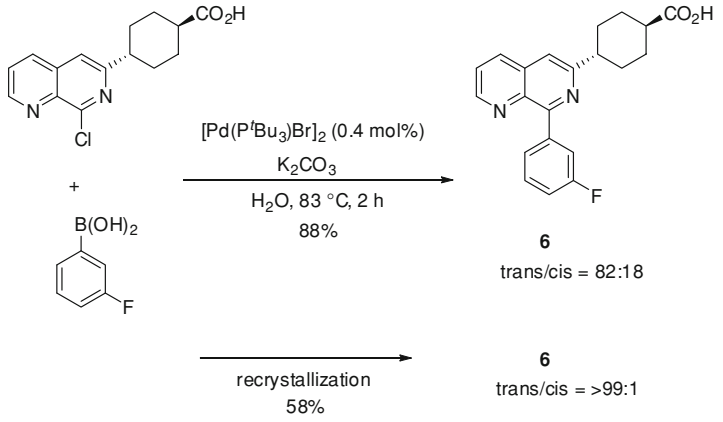
Fig. 4.3 Representative amino-1,2,3-thiadiazoles in natural products and potential pharmaceuticals

Saadeh has reported a one-pot synthesis of several 5-aryl-1-methyl-4-nitroimidazoles **5**, which exhibit potent lethality against Entamoeba histolytica and Giardia intestinalis, through Suzuki–Miyaura coupling between 5-chloro-1-methyl-4-nitroimidazole and a variety of arylboronic acids (Scheme 4.9) [27].



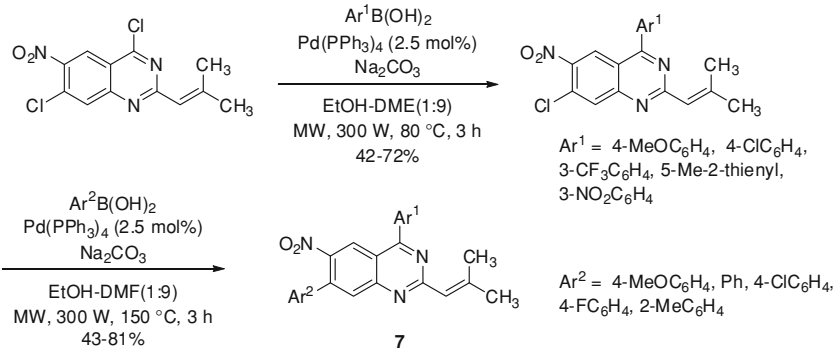
Scheme 4.9 A one-pot synthesis of 5-aryl-1-methyl-4-nitroimidazoles **5**

Jiang and Prasad have used this methodology in the synthesis of a phosphodiesterase-4 inhibitor **6** for the treatment of chronic obstructive pulmonary disease and asthma (Scheme 4.10) [28]. The desired drug substance **6** was obtained in 58 % yield. After recrystallization using 10 % water in acetonitrile, less than 1 % of the *cis*-isomer remained. The remaining 1 % of undesired *cis*-isomer was largely isomerized to the *trans*-isomer using phosphorus oxychloride at 110 °C.



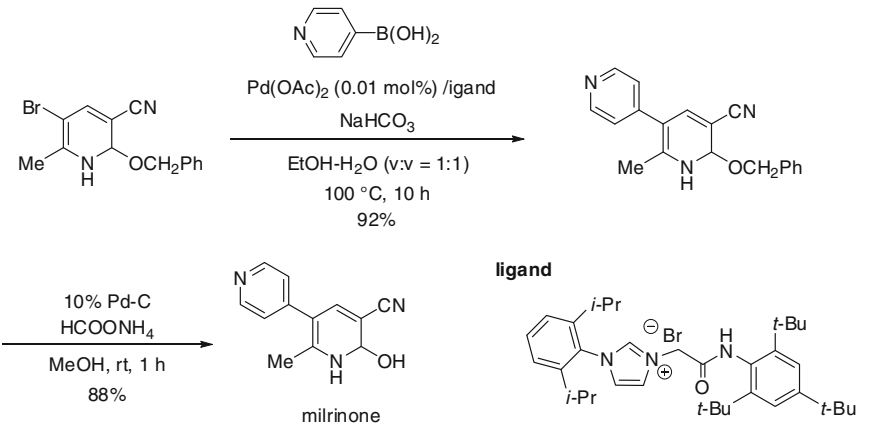
Scheme 4.10 Synthesis of a phosphodiesterase-4 inhibitor **6**

Vanelle has reported a synthetic pathway for diarylquinazolines **7**, which display significant pharmaceutical potential, starting from 4,7-dichloro 2-(2-methylprop-1-enyl)-6-nitroquinazoline and using microwave-promoted chemoselective Suzuki–Miyaura cross-coupling reactions (Scheme 4.11) [29].



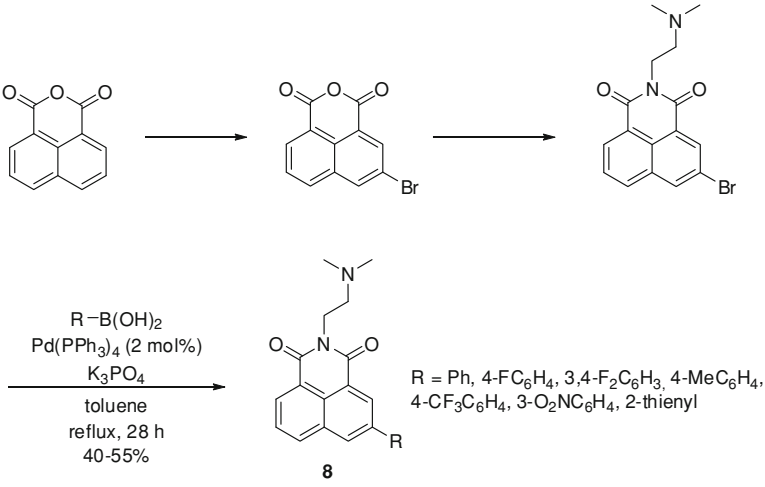
Scheme 4.11 A synthetic route to diarylquinazolines **7**

Very recently, Lee investigated a new catalytic system based on the palladium-amido-*N*-heterocyclic carbenes for Suzuki–Miyaura coupling reactions of heteroaryl bromides and chlorides with 4-pyridylboronic acids to produce a precursor of milrinone (Scheme 4.12) [30].



Scheme 4.12 A synthetic route to a precursor of milrinone

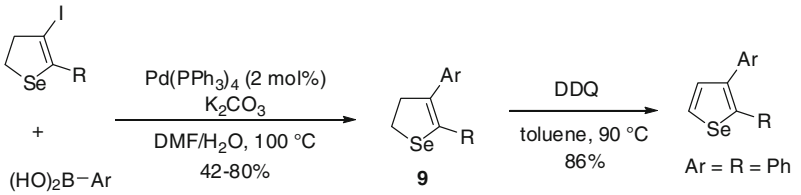
Also, Qian recently designed and synthesized a series of 5 non-amino aromatic-substituted naphthalimides **8** from naphthalic anhydride by three steps, including bromination, amination, and $Pd(PPh_3)_4$-catalyzed Suzuki–Miyaura coupling (Scheme 4.13) [31]. Compared with the current state-of-the-art antitumor agent, amonafide, these new naphthalimide derivatives not only exhibited better antitumor activity against HeLa and P388D1 cancer cell lines in vitro, but they also may have fewer side effects.



Scheme 4.13 A synthetic route to substituted naphthalimides **8**

Zeni has reported the palladium-catalyzed Suzuki–Miyaura coupling reactions of a variety of arylboronic acids with 4-iodo-2,3-dihydroselenophene derivatives

to afford 4,5-diaryl-2,3-dihydroselenophenes **9** (Scheme 4.14) [32]. The subsequent dehydrogenation of these 4,5-diaryl-2,3-dihydroselenophenes **9** were activated by DDQ, and the corresponding 2,3-diarylselenophenes were obtained in good yields. The 2,3-diarylselenophenes were found to be effective in counteracting lipid and protein oxidation as well as scavenging 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) radicals. These findings indicate that 2,3-diarylselenophenes are prototypes for future drug development programs to treat disorders involving reactive oxygen species.

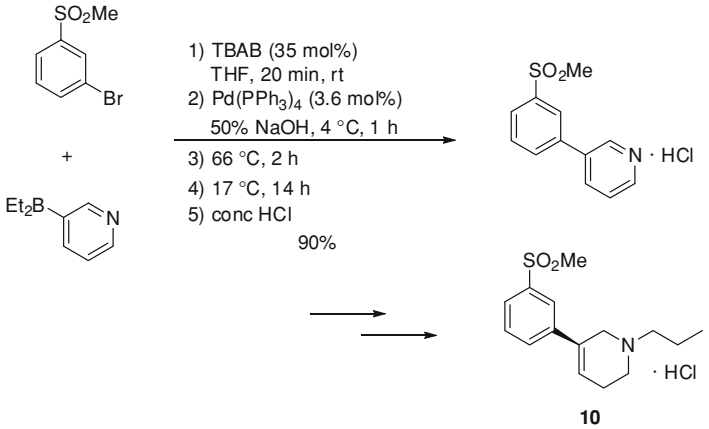


R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *sec*-Bu, SCH_3, $CH(OH)C_5H_{11}$, H

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, 3-$MeCOC_6H_4$

Scheme 4.14 4,5-Diaryl-2,3-dihydroselenophenes **9**

Boranes and boronic esters can also be efficiently employed, rather than the boronic acids, as the coupling partners with aryl or alkyl halides [33–38]. Lipton has reported the large-scale synthesis of **10**, a potential central nervous system drug candidate. The key step was the Suzuki–Miyaura coupling reaction of methyl-3-bromophenylsulfone and diethyl-3-pyridylborane (Scheme 4.15) [39].

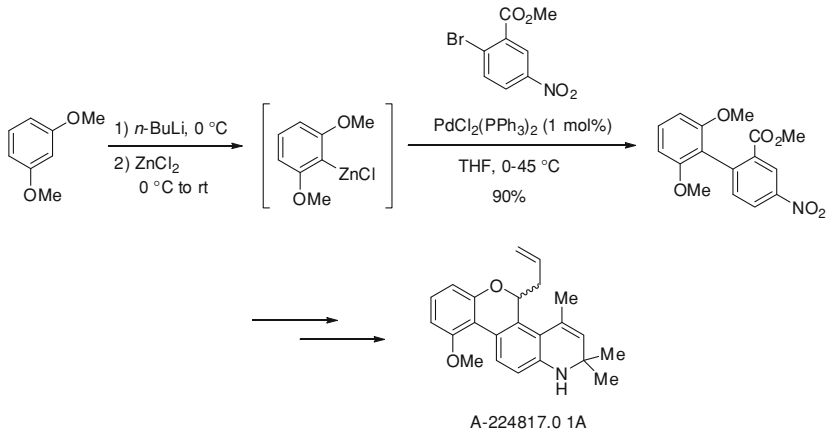


Scheme 4.15 Suzuki-Miyaura coupling reaction of methyl-3-bromophenylsulfone and diethyl-3-pyridylborane

4.3 Negishi Coupling

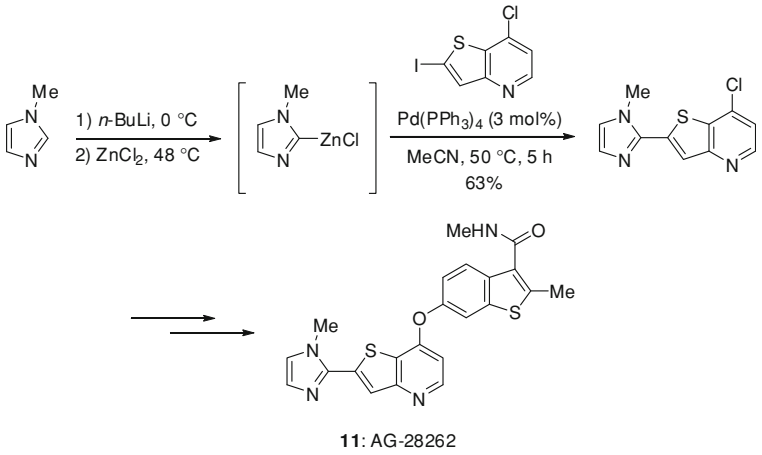
Negishi coupling, another widely applied synthetic pathway for building carbon–carbon bonds in pharmaceuticals, has also undergone extensive advancements in the past decade [40–42]. Chemists such as Knochel [43] and Uchiyama [44, 45] have developed milder reaction conditions for the preparation of organozinc reagents bearing sensitive functional groups such as alcohols and aldehydes. These new methods should find broad applications in the synthesis of complex molecules.

Ku and coworkers incorporated Negishi coupling in the scalable synthesis of A-224817.0 1A, a non-steroidal ligand for the glucocorticoid receptor, which can be used for the treatment of inflammatory diseases and with fewer side effects than the preceding therapeutic agents. The synthesis was accomplished in a few steps, starting from 1,3-dimethoxybenzene. The biaryl intermediate was prepared by an optimized high-yield and high-throughput Negishi protocol (Scheme 4.16) [46].



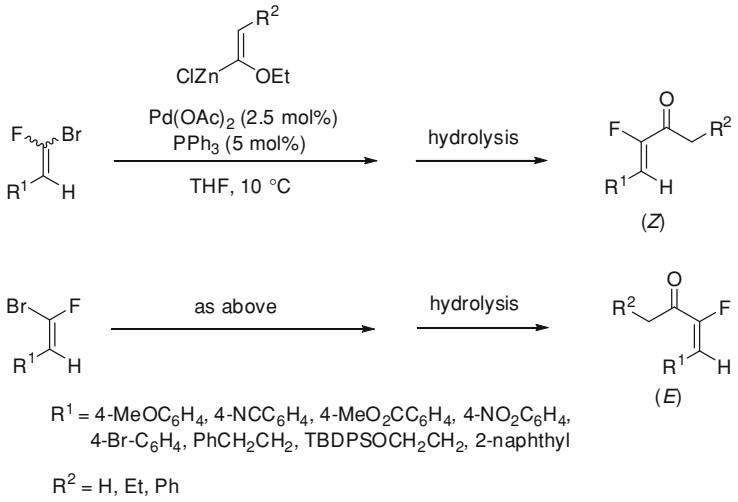
Scheme 4.16 A synthetic route to A-224817.0 1A

Scott has described the synthesis of AG-28262 **11**, a promising VEGFR kinase inhibitor (Scheme 4.17) [47]. The precursor of this molecule was achieved via Pd-catalyzed Negishi coupling. This procedure was repeated for a total of seven batches; the crude product was purified to provide a total of 1.5 kg of **11** with >95 % purity in a 63 % overall yield.



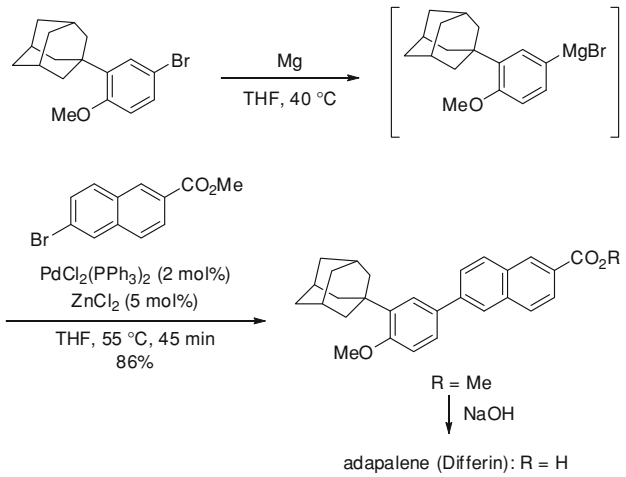
Scheme 4.17 A synthetic route to AG-28262

Pannecoucke has developed a highly stereo-specific synthesis of (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated ketones via a kinetically controlled Negishi coupling, providing easy and general access to valuable fluorinated intermediates for pharmaceuticals and peptide mimics (Scheme 4.18) [48].



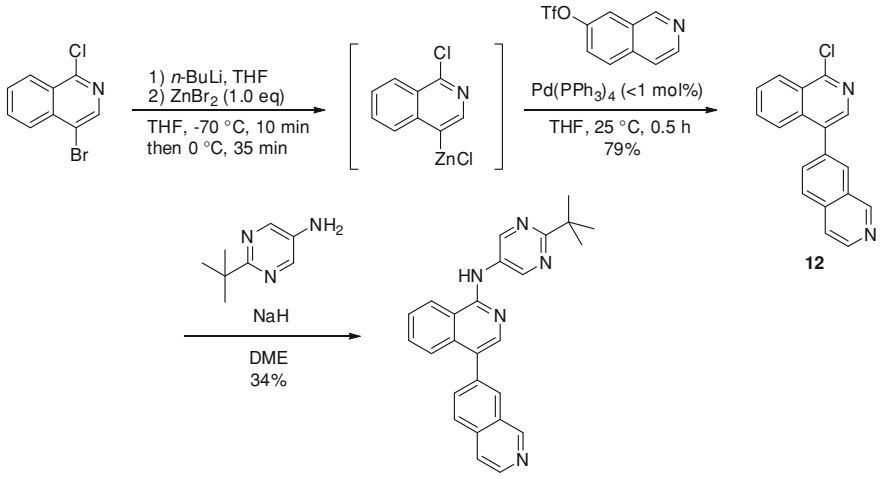
Scheme 4.18 Synthesis of (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated ketones

Liu and Xiang assembled adapalene (Differin®), a synthetic retinoid for the topical treatment of acne, psoriasis, and photoaging, via the $ZnCl_2$-mediated Negishi coupling of a Grignard reagent and an aryl bromide (Scheme 4.19) [49].



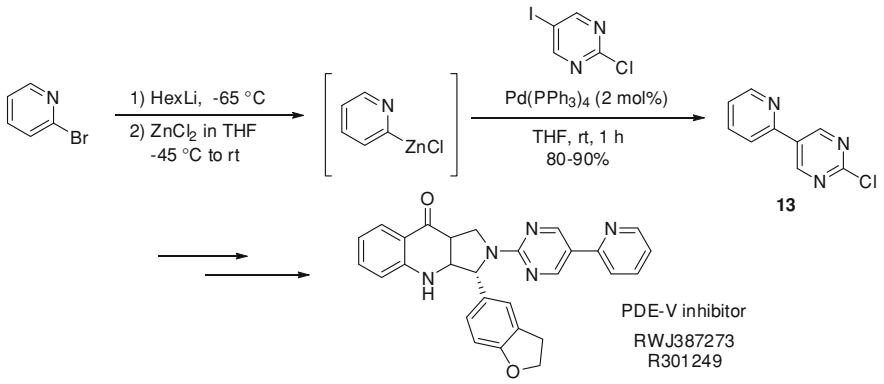
Scheme 4.19 A synthetic route to adapalene (Differin®)

A scalable synthetic route to [4,7′]bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine, an inhibitor of B-Raf kinase, was described by Bänziger and Yusuff (Scheme 4.20) [50]. The key step in this synthesis is the Pd-catalyzed Negishi coupling of 4-bromo-1-chloroisoquinoline with trifluoromethanesulfonic acid isoquinoline-7-yl ester to yield the molecule **12**. This cross-coupled intermediate was transformed to the desired drug by an amination reaction with 2-*tert*-butyl-5-aminopyrimidine in the presence of NaH. Special care had to be taken to ensure complete removal of traces of Zn and Pd from the final drug substance.



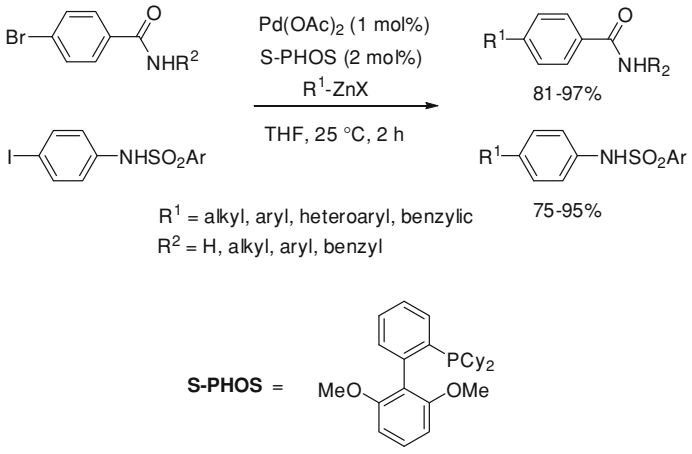
Scheme 4.20 A synthetic route to [4,7’]bis-isoquinolinyl-1-yl- (2-*tert*-butyl-pyrimidine-5-yl)amine

Pérez-Balado has developed a practical and scalable synthesis of 2-chloro-5-(pyridin-2-yl)pyrimidine **13**, an intermediate to a selective PDE-V inhibitor (Scheme 4.21) [51]. Negishi cross-coupling between the in situ prepared 2-pyridylzinc chloride and 5-iodo-2-chloropyrimidine, catalyzed by $Pd(PPh_3)_4$, can afford the product **13** in one step.



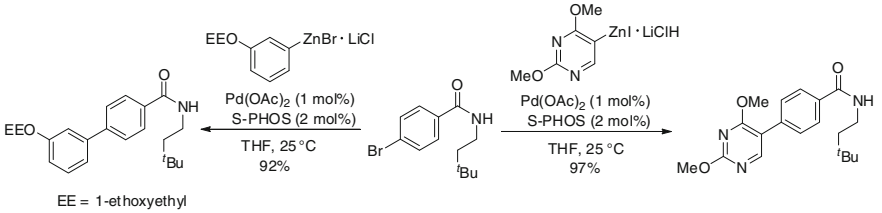
Scheme 4.21 Synthesis of 2-chloro-5-(pyridin-2-yl)pyrimidine **13**

Knochel has demonstrated that the acidic hydrogens of amines, alcohols, and phenols are compatible with Negishi cross-coupling conditions and do not require the use of protecting groups (Scheme 4.22) [52]. The reaction conditions use Buchwald's S-PHOS, which allows general Pd-catalyzed Negishi cross-coupling of functionalized alkyl, aryl, heteroaryl, and benzylic zinc reagents with aryl halides bearing amide or sulfonamide functionalities in spite of their acidic hydrogens.



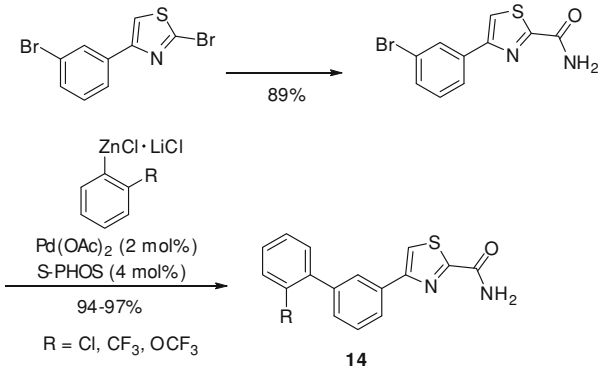
Scheme 4.22 Negishi cross-coupling compatible with acidic hydrogens

Furthermore, many antiarrhythmic agents (Bristol–Myers Squibb) have been prepared by Knochel et al. in 92–97 % yields by the direct Negishi coupling of aromatic and heteroaromatic zinc reagents under standard conditions (Scheme 4.23).



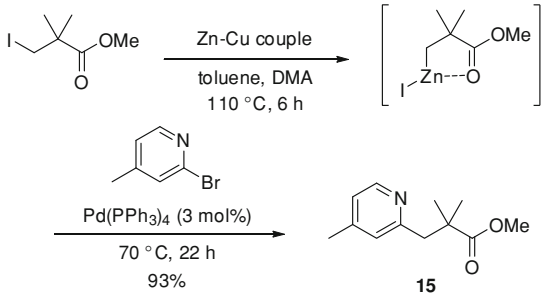
Scheme 4.23 A synthetic route to antiarrhythmic agents (Bristol–Myers Squibb)

In addition, sodium channel blockers **14** (Merck) were synthesized from the corresponding primary amide and zinc reagents in 94–97 % yield (Scheme 4.24).



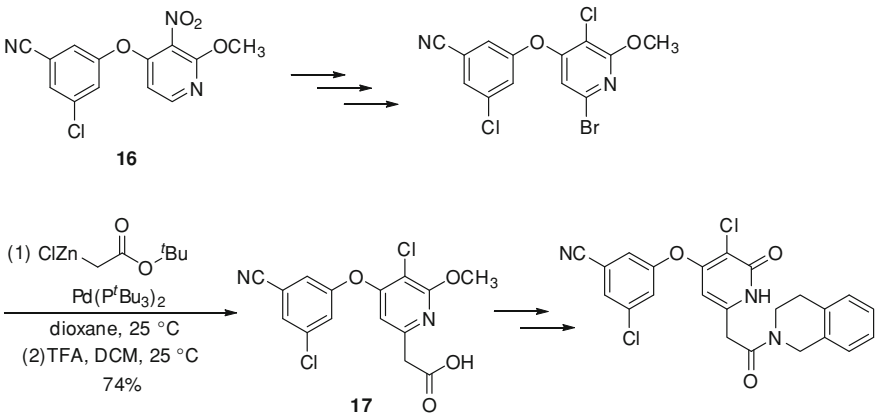
Scheme 4.24 A synthetic route to sodium channel blockers **14**

Kwak has developed an efficient and convenient Negishi coupling protocol for the preparation of 3-aryl-2,2-dimethylpropanoates **15**, providing easy access to key pharmaceutical intermediates that would otherwise require multi-step syntheses using conventional enolate chemistry (Scheme 4.25) [53].



Scheme 4.25 A synthetic route to 3-aryl-2,2-dimethylpropanoates **15**

Kennedy-Smith and Sweeney have reported the synthesis of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are important components of antiretroviral therapy for the treatment of HIV infection [54]. A pyridone compound, which was found to strongly inhibit the polymerase activity of wild-type HIV reverse transcriptase, was successfully synthesized from compound **16** (Scheme 4.26). Negishi coupling was involved as one of the key steps to install the acetic acid functionality, giving rise to intermediate **17**.

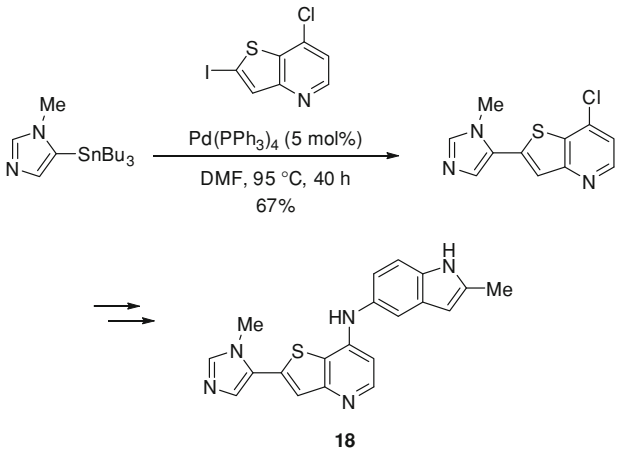


Scheme 4.26 A synthetic route to an HIV reverse transcriptase

4.4 Migita-Kosugi-Stille Coupling

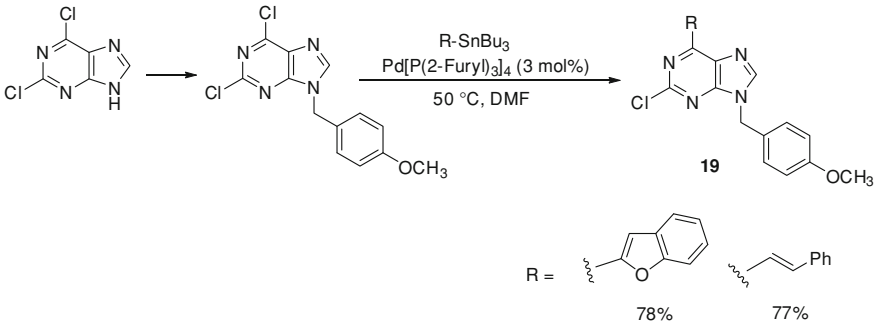
The Migita-Kosugi-Stille Coupling has not been widely used in the large-scale manufacturing of pharmaceuticals. This is mainly due to the toxicity of the organotin reagents and the difficulty of purging tin-containing by-products from drug intermediates and active pharmaceutical ingredients. Despite these issues, many organotin reagents used for Migita-Kosugi-Stille Coupling are widely available, stable to air and moisture, and compatible with a variety of functional groups.

Ragan has incorporated the Migita-Kosugi-Stille Coupling of imidazolylstannane and iodothienopyridine into the synthesis of a VEGFR kinase inhibitor **18**, a compound with promising antitumor activity (Scheme 4.27) [55]. An exhaustive survey of coupling reactions revealed this Migita–Kosugi–Stille approach to be the only robust and scalable method for the coupling of the imidazole and thienopyridine rings.



Scheme 4.27 A synthetic route to a VEGFR kinase inhibitor **18**

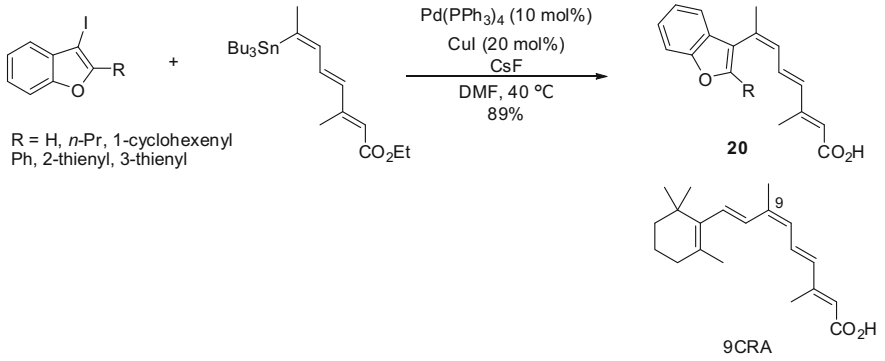
Gundersen has reported the synthesis of 6-benzofuryl- and styrylpurines **19**, in which Migita-Kosugi-Stille coupling was involved as a synthetic strategy to achieve the target molecules with regioselectivity (Scheme 4.28) [56]. Several of these compounds displayed profound antimycobacterial activity with low toxicity toward mammalian cells.



Scheme 4.28 Synthesis of 6-benzofuryl- and styrylpurines **19**

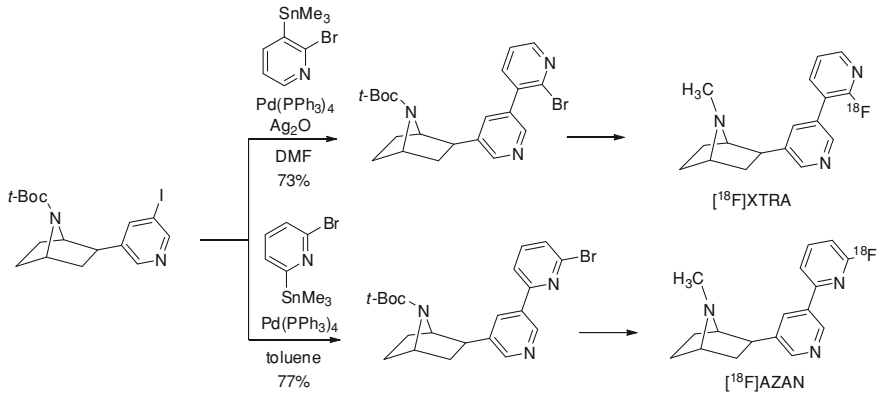
Wada developed cesium-fluoride-promoted Migita-Kosugi-Stille Coupling reactions of vinyl triflates with an alkenylstannane bearing an electron-withdrawing group. These methodologies were then adopted for the preparation of the 9Z-retinoic acid (9CRA) analogs (known metabolites of vitamin A and ligands of the retinoid X receptor) having a 2-substituted benzo[b]furan [57]. Treatment of 2-substituted 3-iodobenzofurans (derived from 2-alkynyl-1-(1-ethoxyethoxy)benzenes) with the alkenylstannane in the presence of cesium fluoride, copper iodide,

and with $Pd(PPh_3)_4$ as the catalyst, afforded the coupled products **20** in good yield without isomerization of the double bonds (Scheme 4.29).



Scheme 4.29 Synthesis of the 9Z-retinoic acid (9CRA) analogs **20**

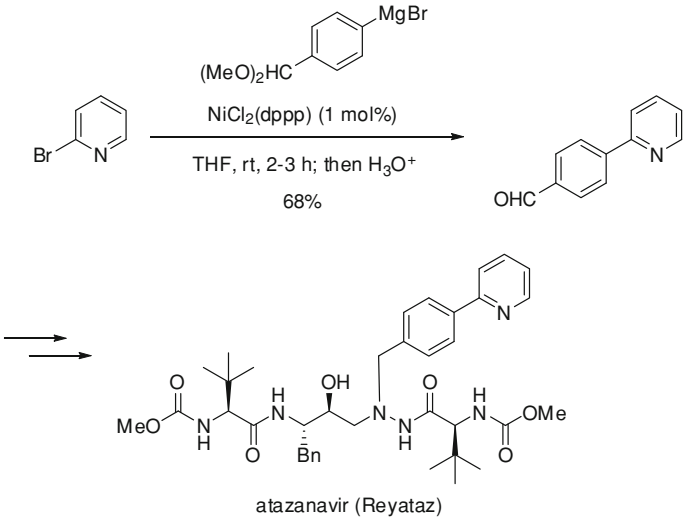
Gao has recently described an improved synthesis of precursors for the positron emission tomography (PET) radioligands [^{18}F]XTRA and [^{18}F]AZAN, involving a key Migita-Kosugi-Stille Coupling step, followed by deprotection of a Boc group and *N*-methylation sequences (Scheme 4.30) [58].



Scheme 4.30 Synthesis of precursors for [^{18}F]XTRA and [^{18}F]AZAN

4.5 Kumada-Tamao-Corriu Coupling

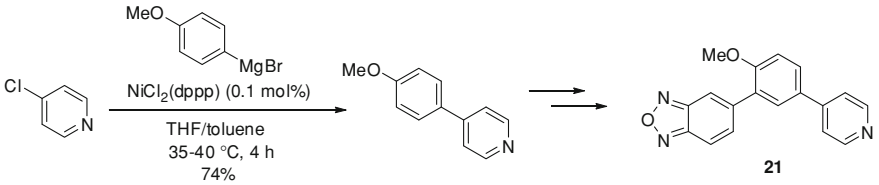
Because of the high reactivity of Grignard reagents relative to other organometallic species, the scope of Kumada-Tamao-Corriu Coupling for the large-scale synthesis of pharmaceuticals has been limited. Long has reported the coupling reaction of 2-bromopyridine and arylmagnesium bromide to prepare a biaryl



Scheme 4.31 A synthetic route to the HIV protease inhibitor atazanavir (Reyataz®)

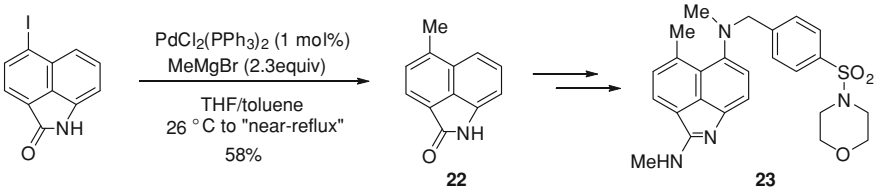
compound, an intermediate in the synthetic route to the HIV protease inhibitor atazanavir (Reyataz®), as shown in Scheme 4.31 [59].

Manley has employed Kumada-Tamao-Corriu Coupling of 4-chloropyridine and arylmagnesium bromide to prepare a biaryl compound, followed by further reactions to prepare compound **21**, an inhibitor of the phosphodiesterase-4D isoenzyme that could potentially be used in the treatment of asthma (Scheme 4.32) [60].



Scheme 4.32 A synthetic route to an inhibitor **21** of the phosphodiesterase 4D isoenzyme

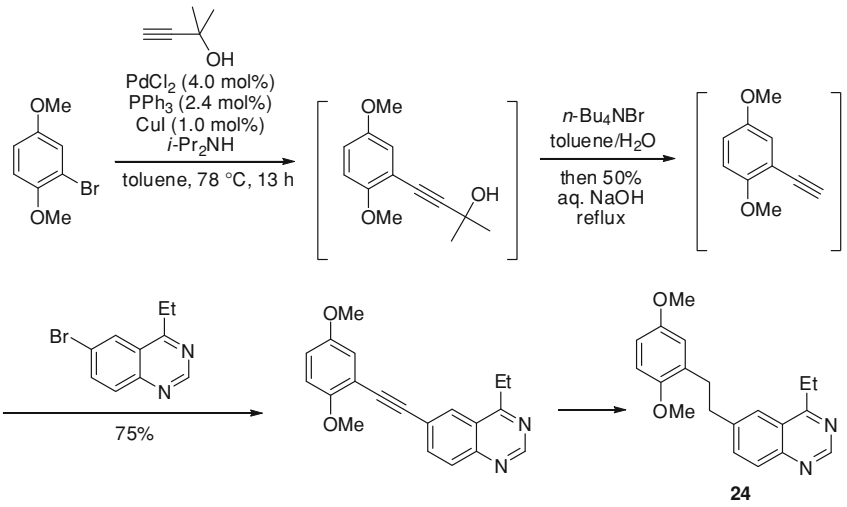
Marzoni and Varney applied the methylation of an aryl iodide under Kumada-Tamao-Corriu Coupling conditions for their improved synthesis of compound **22**. This is an intermediate to a thymidylate synthase inhibitor **23** which has potential for the treatment of cancer (Scheme 4.33) [61].



Scheme 4.33 Synthesis of an intermediate to a thymidylate synthase inhibitor **22**

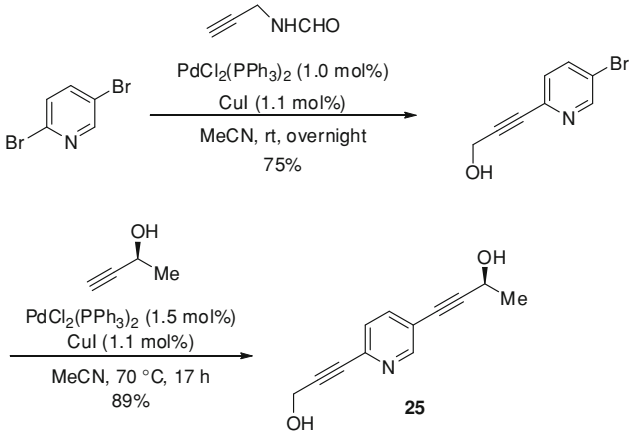
4.6 Sonogashira–Hagihara Coupling

Prasad has developed an elegant process for the one-pot coupling of an aryl bromide and a heteroaryl bromide via stepwise Sonogashira-Hagihara reactions with an acetylene linker masked as 2-methyl-3-butyn-2-ol for the synthesis of an antimitotic agent **24** (Scheme 4.34) [62].



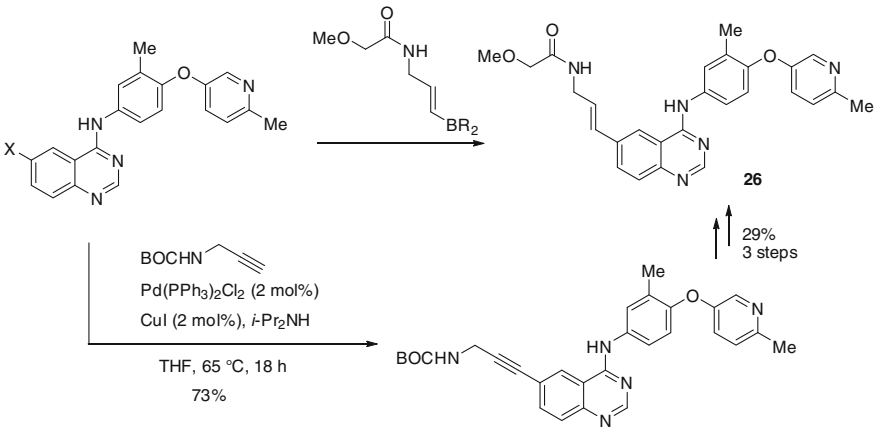
Scheme 4.34 A synthetic route to an antimitotic agent **24**

Hartner developed a series of Sonogashira–Hagihara coupling reactions, in which various alkynes were coupled with 2,5-dibromopyridine at both bromo positions, for the preparation of key intermediates to $\alpha_V\beta_3$ antagonists **25** (Scheme 4.35) [63]. These are potential agents for the treatment for osteoporosis.



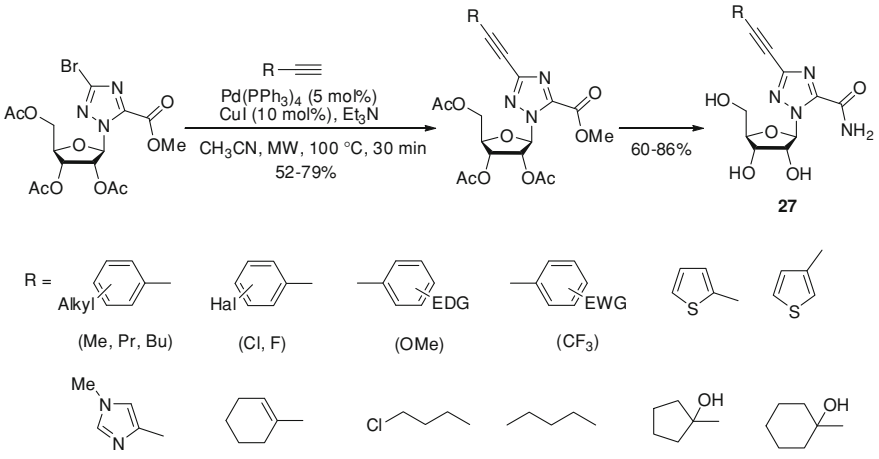
Scheme 4.35 A synthetic route to $\alpha V\beta_3$ antagonists 25

Ripin has described the synthesis of the anti-cancer agent (CP-724, 714) **26** on a multi-kilogram-scale using several different synthetic routes (Scheme 4.36) [64]. Applications of the Sonogashira–Hagihara and Mizoroki–Heck couplings to this synthesis have been investigated, seeking a safe, environmentally benign, and robust process for the production of this drug candidate.



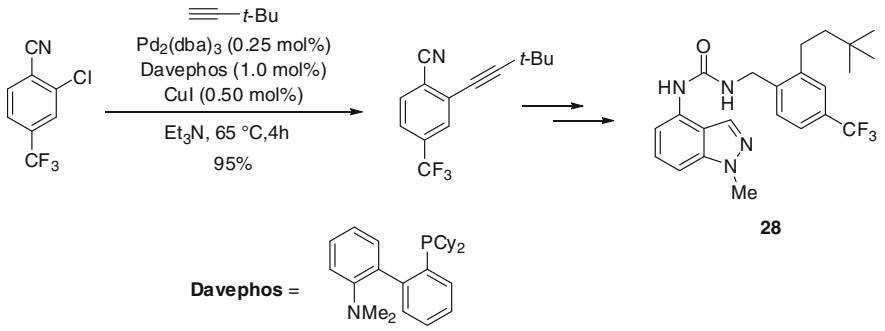
Scheme 4.36 Synthesis of the anti-cancer agent (CP-724,714) **26**

Peng has developed the synthesis of a series of 3-arylethynyltriazolyl ribonucleosides **27** via a microwave-assisted Sonogashira–Hagihara coupling reaction (Scheme 4.37); these products show promise vis-à-vis anti-cancer activity on the drug-resistant pancreatic cancer cell line MiaPaCa-2. The Sonogashira–Hagihara coupling reactions between the 3-bromo-triazole nucleoside and various alkynes were followed by ammonolysis to give the deprotected nucleosides **27** [65].



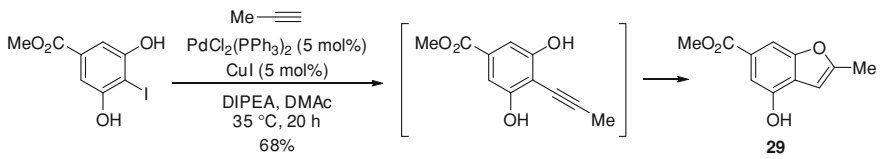
Scheme 4.37 Synthesis of a series of 3-arylethynyltriazolyl ribonucleosides **27**

Yu and coworkers commenced a synthetic route to the TRPV1 receptor antagonist **28** with Sonogashira–Hagihara coupling of an aryl chloride and *tert*-butylacetylene (Scheme 4.38) [66]. In general, aryl chlorides exhibit poor reactivity in the Pd-catalyzed Sonogashira–Hagihara coupling reactions (See Chap. 7); however, an aryl chloride activated by the electron-withdrawing trifluoromethyl and nitrile groups smoothly couples with very low catalyst loading, using the sterically hindered and electron-rich DavePhos as the ligand [67].



Scheme 4.38 A synthetic route to the TRPV1 receptor antagonist **28**

Berliner has developed a Sonogashira–Hagihara reaction of propyne gas and iodoresorcinol for the synthesis of 4-hydroxy-2-methylbenzofuran **29**, a core intermediate to several compounds of pharmaceutical interest (Scheme 4.39) [68].



Scheme 4.39 Synthesis of 4-hydroxy-2-methylbenzofuran **29**;

4.7 Summary

Palladium-catalyzed cross-coupling is clearly a powerful tool to synthesize pharmaceuticals not only for academic research but also for industrial applications. This chapter has demonstrated the versatility of these reactions. In the design and synthesis of biologically active molecules, serious consideration must be given to important factors such as: reactivity of functional groups, stereo- and regioselectivity, toxicity of potential residual contaminants, and efficiency of yield. These are all aspects in which the aforementioned cross-coupling models provide

exceptional and innovative opportunities for the modern process chemist. In addition, considering the myriad of advancements seen in the past decade, many new discoveries should soon offer even more practical and reliable methods of cross-coupling for the large-scale manufacturing of pharmaceuticals.

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