

Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals

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CONTENTS

1. Introduction	2177	3.3. Oxidative Wacker-type Cyclization (C—O Bond Formation)	2236
2. Carbon—Carbon Bond Formation	2178	3.4. Migita Thioether Synthesis (C—S Bond Formation)	2237
2.1. Suzuki—Miyaura Coupling	2178	4. Addendum	2238
2.1.1. Boronic Acid and Aryl Chloride Coupling	2178	5. Conclusions	2239
2.1.2. Boronic Acid and Aryl Bromide Coupling	2180	Author Information	2239
2.1.3. Boronic Acid and Aryl Iodide Coupling	2185	Biographies	2240
2.1.4. Boronic Acid and Alkenyl Triflate Coupling	2187	Acknowledgment	2240
2.1.5. Borane and Aryl Halide Coupling	2189	Abbreviations	2240
2.1.6. Borane and Alkyl Halide Coupling	2190	References	2241
2.1.7. Boronic Ester and Aryl Halide Coupling	2190		
2.1.8. Boronic Ester and Alkyl Halide Coupling	2191		
2.1.9. Borate Complexes	2192		
2.2. Negishi Coupling	2193		
2.3. Kumada—Corriu Coupling	2195		
2.4. Stille Coupling	2197		
2.5. Enolate Arylation	2198		
2.6. Sonogashira Coupling	2199		
2.7. Heck Reaction	2204		
2.7.1. Intermolecular Heck Reaction	2204		
2.7.2. Intramolecular Heck Reaction	2211		
2.8. Hayashi—Miyaura Coupling	2212		
2.9. Tsuji—Trost Allylation	2213		
2.10. Carbonylation	2214		
2.11. Cyanation	2217		
2.12. Olefin Metathesis	2221		
2.13. Pauson—Khand Reaction	2224		
2.14. Cyclopropanation	2225		
2.15. Nozaki—Hiyama—Kishi Reaction	2226		
2.16. Other Transition Metal-Mediated Couplings for C—C Bond Formation	2227		
2.16.1. Reformatsky Reaction	2227		
2.16.2. Blaise Reaction	2229		
2.16.3. Noyori Aldehyde Alkylation	2229		
2.16.4. Wurtz Coupling	2229		
2.16.5. Cuprate Addition	2230		
3. Carbon—Heteroatom Bond Formation	2230		
3.1. Buchwald—Hartwig Amination (C—N Bond Formation)	2230		
3.2. Ullmann Ether Synthesis (C—O Bond Formation)	2234		

1. INTRODUCTION

Research in the mid 1960s to early 1970s sparked an evolution in the approach of synthetic chemists toward the assembly of molecules. Inspired by known Wacker-type processes in which oxygen nucleophiles (i.e., water or hydroxide ion) react with olefin—palladium complexes to form a carbon—oxygen bond, Tsuji considered the application of carbon nucleophiles in similar processes that would lead to carbon—carbon bonds; accordingly, in 1965 he reported the reaction of π -allylpalladium chloride and malonate (or acetoacetate) to give allylmalonate (or allylacetate).¹ A few years later, Heck² and Mizoroki et al.³ independently reported the coupling of aryl halides and olefinic compounds mediated by catalytic palladium. Further breakthroughs by chemists such as Yamamoto and co-workers,^{4a} Tamura and Kochi,^{4b} Corriu and Masse,^{4c} and Kumada and co-workers^{4d,e} in the field of nucleophilic substitution-type cross-couplings of organometallic reagents and aryl or alkenyl halides continued the advancement of organic synthesis.⁵ Since these pioneering efforts, more recent developments have replaced earlier protocols with milder, broader, and more efficient catalytic technologies for carbon—carbon bond formation.⁶ In addition, Buchwald and Hartwig, among others, expanded the versatility of transition metal catalysis with vastly improved and contemporary methods for carbon—heteroatom bond formation, which have supplanted the relatively harsh Ullmann conditions of the early twentieth century.^{7,8a,8b}

As a result, transition metal-catalyzed couplings have become a reliable and indispensable tool for the synthesis of pharmaceuticals over the last two decades. These reactions provide new entries into pharmaceutical ingredients of continuously

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increasing complexity, and catalysis with metals such as Pd, Ni, Cu, Zn, Co, Rh, Ru, and Mo have streamlined the syntheses of many marketed drugs or drug candidates under current development in laboratories around the world.^{8,9} In particular, Pd has emerged as the metal of choice for several transition metal-catalyzed applications, despite its high cost relative to other nonprecious metals such as Cu, Ni, or Fe, due to several factors: (a) Pd can promote the couplings of low reactivity substrates (e.g., aryl chlorides); (b) Pd generally allows for reactions at lower temperatures; (c) Pd catalysts often provide high turnover numbers (TONs), which is of primary importance in large-scale applications where cost is the driving force.^{9a}

The application of transition metal catalysis to large-scale synthesis requires technologies that are safe, robust, and scalable.¹⁰ In the pharmaceutical industry, synthetic processes must also provide drug ingredients with very high purity. A consequence of implementing transition metal couplings is the need to purge residual metals from API (active pharmaceutical ingredient) to meet the stringent specifications for materials subjected to clinical testing. To this end, much research has been devoted to solving this problem, and process chemists currently have a wide array of options for the efficient scavenging of most metals.^{11–13}

This review is intended to give a comprehensive picture of the *large-scale* applications of transition metal-catalyzed coupling reactions for the manufacture of drug components in the pharmaceutical industry through the end of August, 2010. In addition to showcasing bond-forming chemistries, this review focuses on reaction workups and purifications that purge metal catalysts to provide material of sufficient purity. Most of the examples presented here originated in process chemistry groups in pharmaceutical companies and have been selected based on two criteria: (a) the transformation has been realized on a large scale (at least 100 mmol); (b) the article contains a detailed experimental procedure. A list of publications that report coupling reactions for the large-scale synthesis of pharmaceuticals but do not provide experimental procedures is also included.¹⁴

Finally, examples found exclusively in the patent literature have not been covered in this review because, in our opinion, the most significant cases have been reported in the mainstream literature. Furthermore, patented coupling technologies have been recently reviewed.¹⁵

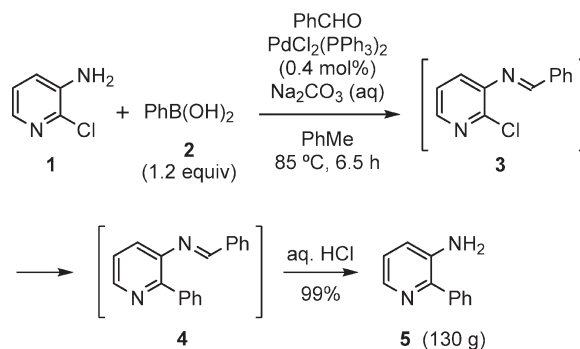
2. CARBON–CARBON BOND FORMATION

2.1. Suzuki–Miyaura Coupling

The Suzuki–Miyaura reaction is the Pd-catalyzed cross-coupling of an organoboron reagent and an organo halide or sulfonate.¹⁶ Since its initial reports in 1979,¹⁷ the Suzuki reaction has become arguably the most efficient method for aryl–aryl bond formation. The mild reaction conditions, wide functional group compatibility, and commercial availability of many boronic acids make this coupling ideal for the preparation of highly functionalized molecules. On the other hand, the reaction can be very sensitive to the presence of oxygen, and thorough degassing is often needed to avoid the formation of homocoupling and deboronation byproducts.

As the following examples illustrate, the Suzuki reaction is routinely used in the pharmaceutical industry for the assembly of biaryl synthetic targets, and this transformation is overwhelmingly the most common Pd-catalyzed coupling for the large-scale synthesis of drug candidates. Besides palladium, nickel can

Scheme 1

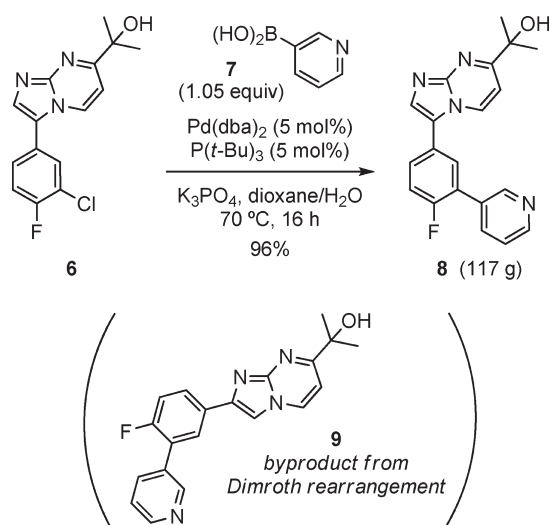


also be employed as the catalyst, although this is much less common.¹⁸ The synthetic,¹⁶ mechanistic,¹⁹ and green²⁰ aspects of the Suzuki reaction have been previously reviewed.

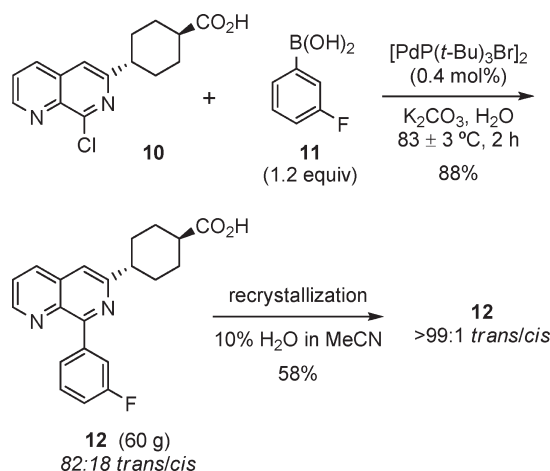
2.1.1. Boronic Acid and Aryl Chloride Coupling. Caron and co-workers at Pfizer have reported the preparation of 3-amino-2-phenylpyridine (**5**), an important pharmacophore present in potent, nonpeptidic NK1 receptor antagonists (Scheme 1).²¹ In an original three-step synthesis, the amino functionality was protected as the acetamide²² prior to the subsequent Suzuki coupling to introduce the phenyl group. With the goal of finding a shorter route, the researchers temporarily protected the amine as an imine. Thus, amine **1** was converted to imine **3** with benzaldehyde in high yield after heating to reflux in toluene under Dean–Stark conditions (analogous imine formation from benzophenone was sluggish). Because imine formation was fast, a one-pot protocol was developed in which amine **1**, benzaldehyde, and phenylboronic acid (**2**) were premixed in toluene at rt for 10 min, followed by treatment with PdCl₂(PPh₃)₂ and aqueous Na₂CO₃. The Suzuki coupling was complete after heating to 85 °C for 6.5 h, and the imine was hydrolyzed by quenching with 3 N HCl. Coupling product **5** was isolated in quantitative yield as an oil that crystallized upon standing. Other Pd catalysts were tested, but PdCl₂(PPh₃)₂ was chosen because of its robustness under the reaction conditions.

Researchers at Merck described the preparation of GABA_A α_{2/3}-selective allosteric modulator **8**, a potential treatment of central nervous system conditions, via the Suzuki–Miyaura coupling of aryl chloride **6** and 3-pyridylboronic acid (**7**) (Scheme 2).²³ Because of the cost and limited commercial availability of boronic acid **7**, this material was prepared via lithiation of 3-bromopyridine followed by quench with triisopropyl borate and extractive workup.²⁴ With **7** on hand, the Suzuki coupling was first attempted with Pd₂(dba)₃, P(*t*-Bu)₃, and KF in THF under anhydrous conditions,²⁵ but no desired **8** was obtained. Alternative solvents such as dioxane and additives such as Cs₂CO₃, CsF, or K₃PO₄ did not promote the coupling either. After it was discovered that water could facilitate Suzuki reactions,²⁶ the coupling of chloride **6** and boronic acid **7** was accomplished with Pd₂(dba)₃, P(*t*-Bu)₃, and Na₂CO₃ in THF/H₂O. In addition to the desired **8**, however, these conditions generated byproduct **9** via Dimroth rearrangement.²⁷ A thorough study of reaction conditions revealed that the undesired Dimroth rearrangement was fast in DMAc, MeCN, and EtOH, but relatively slow in 1,4-dioxane, THF, and 2-MeTHF. In the latter three solvents, desired product **8** crystallized from solution to prevent the rearrangement. The amount of water was also critical, as too much promoted byproduct formation but too little lowered the

Scheme 2



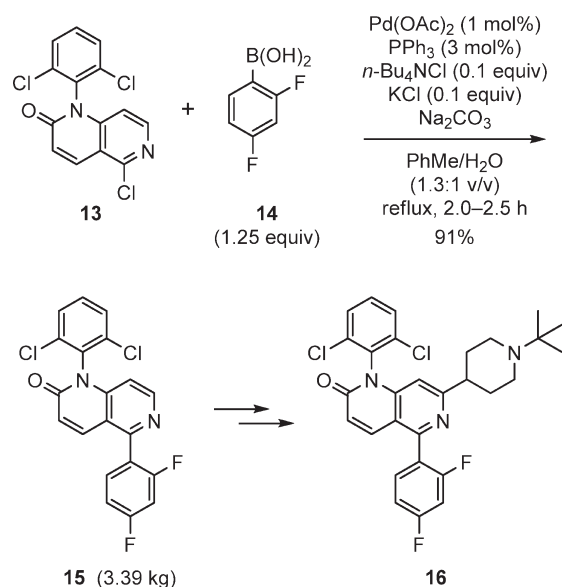
Scheme 3



reaction rate. The final conditions included preforming the catalyst system by mixing $\text{Pd}(\text{dba})_2$ and $\text{P}(\text{t-Bu})_3$ in 1,4-dioxane, adding this solution to a mixture of chloride **6**, boronic acid **7**, and K_3PO_4 in 1,4-dioxane/ H_2O (3:1 v/v), and heating to 70 °C for 16 h. Coupling product **8** was obtained in excellent yield but with high levels of residual Pd (ca. 4000 ppm). Metal removal was accomplished during subsequent HCl salt formation by treating with $\text{BH}_3 \cdot \text{NMe}_3$ complex followed by a polishing step with Darco to provide API with <3 ppm Pd.

Jiang and Prasad and co-workers at Novartis have described the synthesis of phosphodiesterase-4 inhibitor **12** for the treatment of chronic obstructive pulmonary disease and asthma (Scheme 3).²⁸ The last step of the synthesis required the coupling of chloride **10** and boronic acid **11** under Suzuki–Miyaura conditions. Several screened Pd catalysts ($\text{Pd}(\text{OAc})_2$, POPd, POPd1, POPd2, PS-Pd, FiberCat-1001, and FiberCat-1000-D7)²⁹ with loadings as high as 10 mol% either provided **12** in low yield or gave no desired product. The catalyst of choice was found to be the Pd(I) dimer $[\text{PdP}(\text{t-Bu})_3\text{Br}]_2$, which carried out this transformation in water at 83 °C in 2 h. The residual Pd

Scheme 4

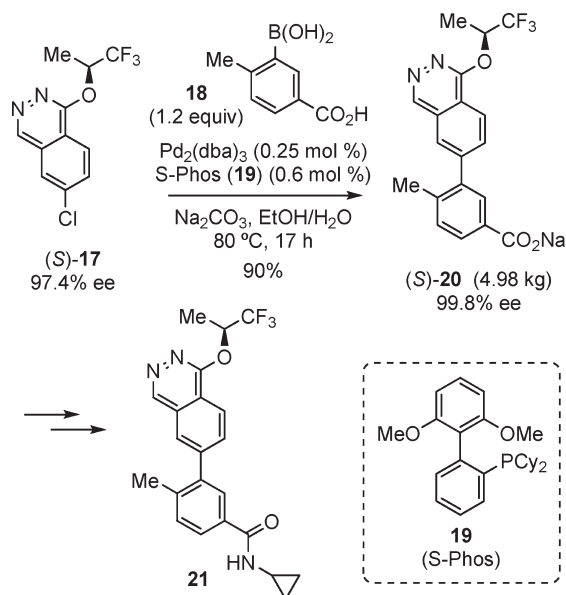


in the crude isolated product was lowered by treating with Smopex 110 at 60 °C for 1 h and filtering through activated carbon and Celite. Smopex 110 performed better than Smopex 112 under aqueous, acidic media to give crude **12** with ≤1 ppm of Pd as a 82:18 *trans/cis* mixture, which was upgraded to >99:1 after recrystallization from 10% H_2O in MeCN.

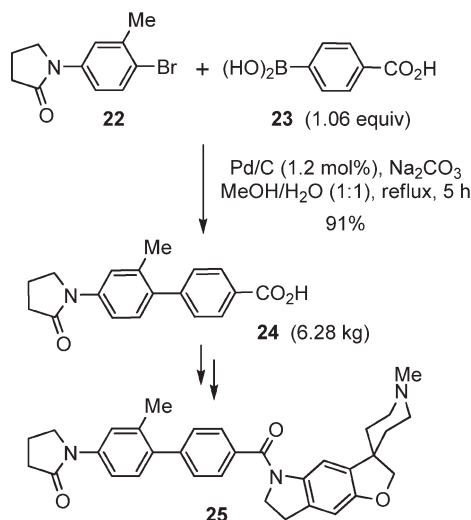
Chung and co-workers at Merck described the preparation of naphthyridinone **16**, a p38 MAP kinase inhibitor drug candidate for the treatment of rheumatoid arthritis and psoriasis (Scheme 4).³⁰ Initial Suzuki couplings of chloronaphthyridinone **13** and 2,4-difluorophenylboronic acid (**14**) using $\text{PdCl}_2(\text{dppf})$ in toluene at reflux required 2.0–2.5 equiv of boronic acid to achieve reaction completion. Process development reduced the boronic acid to 1.25 equiv for coupling in a biphasic system of aqueous Na_2CO_3 and toluene with $\text{Pd}(\text{OAc})_2$ (1 mol%), PPh_3 (3 mol%), KCl (0.1 equiv), and $n\text{-Bu}_4\text{NCl}$ (0.1 equiv). Under these biphasic conditions at 90 °C, the coupling proceeded to completion within 2.0–2.5 h and provided product **15** in 91% yield after recrystallization from EtOAc. The boronic acid was prepared from triisopropyl borate, and residual byproduct *i*-PrOH increased the rate of the Suzuki coupling; thus, an improved procedure was later implemented using only 1.1 equiv of boronic acid with $\text{Pd}(\text{OAc})_2$ (1 mol%), PPh_3 (2 mol%), and Na_2CO_3 in *i*-PrOH.

Thiel and co-workers at Amgen reported the multikilogram preparation of phthalazine **21**, a p38 MAP kinase inhibitor for the treatment of inflammatory conditions such as rheumatoid arthritis, Crohn's disease, and psoriasis (Scheme 5).³¹ Initial conditions for the coupling of chloride **17** and boronic acid **18** followed literature procedures using $\text{Pd}_2(\text{dba})_3/\text{S-Phos}$ (**19**) and K_3PO_4 in dioxane at reflux.²⁶ A preliminary base and solvent screen was conducted to reduce *p*-toluic acid byproduct formation (from protodeboronation) and to replace carcinogenic dioxane. Dicyclohexylamine and EtOH/ H_2O (4:1 v/v) emerged as the preferred base and solvent system, and these conditions with $\text{Pd}_2(\text{dba})_3/\text{S-Phos}$ effected complete coupling at 80 °C after 4 h with <1% protodeboronation byproduct. Unfortunately, these conditions complicated the reaction workup and product isolation, and had to be replaced. A more extensive base and

Scheme 5



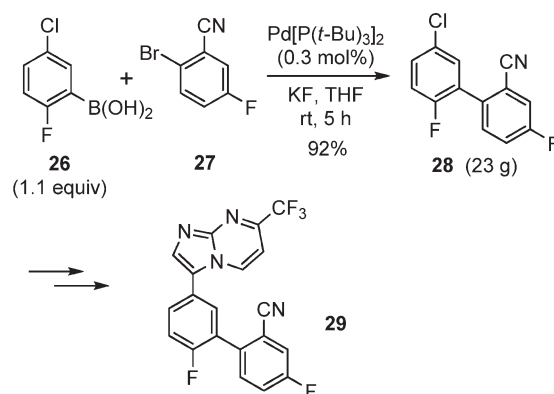
Scheme 6



solvent screen with the $\text{Pd}_2(\text{dba})_3$ /S-Phos catalyst system revealed the easiest product isolation from Na_2CO_3 in aqueous EtOH (but at the expense of producing up to 15% of *p*-toluic acid as byproduct). Using this new base and solvent system, (S)-20 was crystallized directly from the reaction mixture by diluting with water, which purged *p*-toluic acid and Pd and upgraded the chiral purity of the drug intermediate. Unreacted chloride 17 was not efficiently removed from this crystallization; thus, high reaction conversions were required to isolate (S)-20 with acceptable purity.

2.1.2. Boronic Acid and Aryl Bromide Coupling. One of the earliest examples of large-scale Suzuki coupling was reported by researchers at SmithKline Beecham Pharmaceuticals, who have described the multikilogram preparation of 25, a candidate for the treatment of depression (Scheme 6).³² The carboxylic acid moiety of the molecule had been previously prepared via the coupling of aryl bromide 22 and boronic acid 23 using typical conditions with $\text{Pd}(\text{PPh}_3)_4$ as catalyst.³³ Although this method

Scheme 7



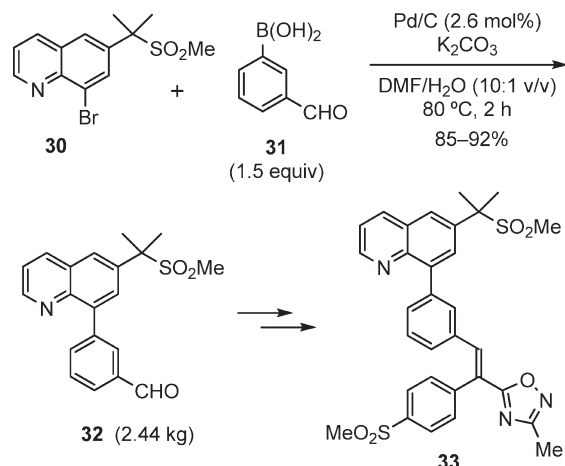
worked well up to 4-mol scale, the catalyst was expensive, air-sensitive, and difficult to purge from the drug intermediate 24 (40–80 ppm of Pd). Alternatively, Pd supported on charcoal (Pd/C) was chosen for further development. This heterogeneous catalyst³⁴ is inexpensive, readily available, and can be removed via filtration, which has the potential to minimize Pd contamination in 24. Another advantage is that Pd/C can be used without additional ligand, which avoids possible ligand contamination in isolated product. On the other hand, the potential for Pd leaching from the carbon support should be closely monitored.³⁵ In addition, the Pd/C dispersion, distribution, oxidation, and water content can affect the reaction outcome and catalyst screening may be necessary.³⁵

Optimized conditions coupled 22 and 23 using Pd/C (1.2 mol%) and Na_2CO_3 in 1:1 MeOH/ H_2O at reflux. After removing the catalyst by filtration, acidification of the reaction mixture with concentrated HCl followed by a hot IMS slurry³⁶ provided 24 in excellent yield and purity. The source of Pd/C was important for the outcome of the reaction. Thus, type 58 catalyst (eggshell from Johnson Matthey), with Pd metal distributed entirely on the carbon surface, proved much more efficient than intermediate catalyst 487 (Johnson Matthey), with Pd distributed both in the pores and on the surface. The choice of solvent was also crucial, as the reaction failed in EtOH/ H_2O and DME/ H_2O .

Cameron and co-workers at Merck published the preparation of GABA α_2/γ -agonist 29 for the treatment of generalized anxiety disorder (Scheme 7).³⁷ The biaryl system was assembled from the Suzuki coupling of commercially available 2-bromo-5-fluorobenzonitrile (27) and boronic acid 26, with the latter prepared via *ortho*-lithiation of 4-chlorofluorobenzene with lithium 2,2,6,6-tetramethylpiperidine³⁸ followed by $\text{B}[\text{O}(i\text{-Pr})]_3$ quench and acidic workup. $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ (0.3 mol%) was the catalyst of choice, and the coupling was carried out at rt in THF. The reaction mixture was filtered through silica, and a heptane slurry provided biaryl 28 in excellent yield.

Researchers at Merck have described the preparation of 33, a PDE4 inhibitor with potential application in inflammatory diseases such as asthma and chronic obstructive pulmonary disease (Scheme 8).^{39,40} Key intermediate 32 was prepared through a Suzuki–Miyaura reaction of bromoquinoline 30 and commercially available boronic acid 31. Although initial couplings catalyzed by $\text{PdCl}_2(\text{dppf})$ performed very well, the isolated 32 contained high levels of Pd (3500 ppm) and iron (1160 ppm) from the dppf ligand. Because of concerns with residual metals at those levels, heterogeneous Pd/C was investigated as a ligand-free

Scheme 8

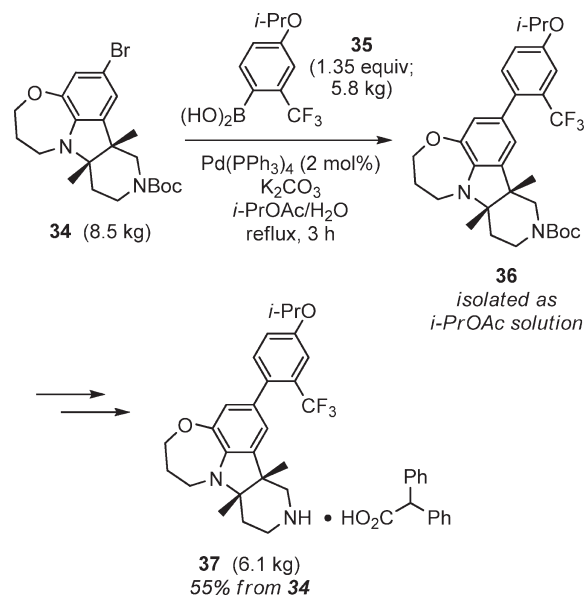


catalyst that should facilitate product purification.³⁴ The screening of Pd catalysts (dry 5% Pd/C [C6064] from Engelhard; water-wet 5% Pd/C [A405023-5] and 10% Pd/C [A402032-10] from Johnson Matthey) identified nonreduced Pd distributed on the activated carbon surface (eggshell dispersion) as the preferred form. Both dry and water-wet catalysts gave satisfactory results. Further optimization of the reaction conditions led to the use of 2.6 mol% Pd/C and extra fine K_2CO_3 in a 10:1 (v/v) DMF/ H_2O mixture at 80°C , which gave reproducible yields of **32** (85–92%) with 18–80 ppm of Pd. KF in place of K_2CO_3 afforded similar yields, but the Pd level varied from 90 to 3180 ppm, comparable to the original levels obtained from $\text{PdCl}_2(\text{dppf})$. Degassing the reaction mixture was necessary to suppress the homocoupling of boronic acid⁴¹ and minimize residual Pd levels in isolated **32**. Further processing allowed for the reduction of the metal content below 10 ppm.

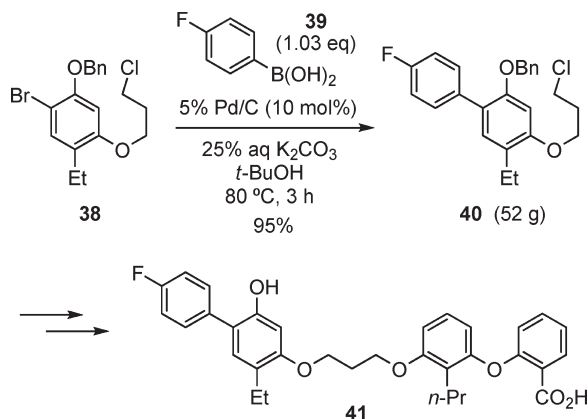
Researchers at Bristol–Myers Squibb have described the large-scale preparation of diphenylacetic acid salt **37**, a $5\text{HT}_{2\text{C}}$ receptor agonist candidate for the treatment of obesity (Scheme 9).⁴² The biaryl moiety was assembled through a Suzuki coupling of aryl bromide **34** and commercially available boronic acid **35**. The original conditions developed by the medicinal chemistry group at BMS employed $\text{Pd}(\text{PPh}_3)_4$ (2.5 mol%) and $\text{Ba}(\text{OH})_2$ in a DME/ H_2O mixture. After 3 h, the reaction was complete but coupling product **36** could not be isolated as a solid and contained high levels of Pd (2500–3500 ppm). Treatment with Picachem carbon⁴³ or washing the organic phase with a solution of tris(hydroxymethyl)aminomethane did not reduce the Pd content to satisfactory levels. On the other hand, sequential treatments with 2,4,6-trimercaptotriazine¹³ and Picachem carbon 80PN did decrease the Pd level below 100 ppm. Although this procedure performed well up to 1-kg scale, the filtration of solids from the trimercaptotriazine treatment was slow and required the use of Celite. Further optimization decreased the catalyst loading to 2 mol% and replaced $\text{Ba}(\text{OH})_2/\text{DME}$ with $\text{K}_2\text{CO}_3/i\text{-PrOAc}$. This solvent change allowed for a more efficient process, as the subsequent Boc-deprotection and final salt formation could be carried out in $i\text{-PrOAc}$. In addition, a single treatment with Picachem carbon 80PN (10% wt/wt) at 50°C for 2 h followed by Boc-deprotection with MsOH lowered Pd to below 50 ppm in product **37**.

Yates and co-workers at Eli Lilly reported the preparation of the multipotent eicosanoid pathway modulator **41**, which has

Scheme 9

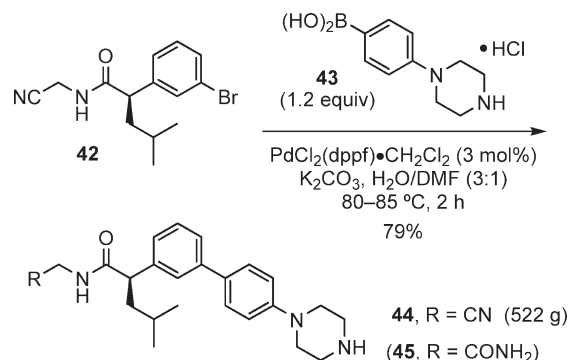


Scheme 10

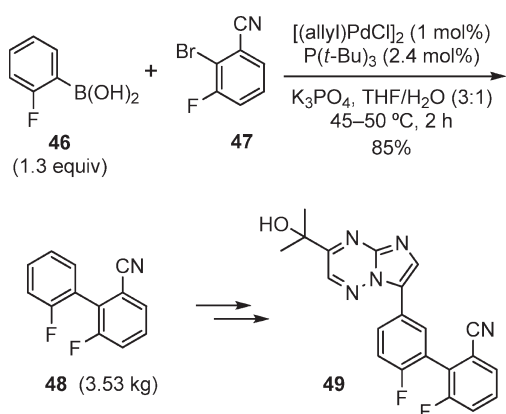


shown antiproliferative activity against several tumor cell lines (Scheme 10).⁴⁴ To prepare key intermediate **40**, initial conditions for a Suzuki–Miyaura coupling of aryl bromide **38** and boronic acid **39** employed $\text{Pd}(\text{OAc})_2$ and PPh_3 as the catalyst system, but the reaction outcome was not reproducible and varied with the quality of bromide **38**. In addition, controlling the residual metal from $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ was also difficult, with isolated products having Pd levels varying from 20 to >1000 ppm. The researchers then turned to heterogeneous catalysis³⁴ and found that 5% Pd/C performed well in this reaction, with Pd levels below 20 ppm in the isolated coupling product **40**. Several Pd/C catalysts were screened (5% JM, 5% JM Type 58, 5% PMC, 10% PMC, 5% Degussa, 10% Degussa), and both standard and eggshell dispersion catalysts were successful in this transformation. Interestingly, a higher Pd loading (10% versus 5%) had no effect on the rate of reaction, which suggests that catalysis is a quasi-heterogeneous process.^{40,45} Degassing the reaction mixture prior to heating suppressed the homocoupling of aryl bromide (<0.5%), and even though the reaction worked equally well in EtOH, $n\text{-PrOH}$, and $n\text{-BuOH}$, aqueous $t\text{-BuOH}$ was chosen as solvent for easy isolation of **40**.

Scheme 11



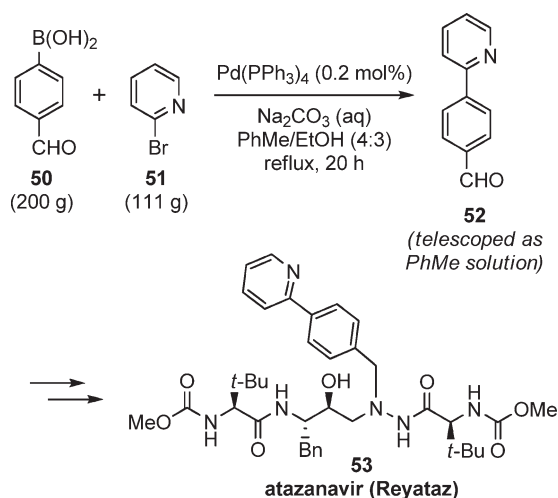
Scheme 12



Researchers at Merck used a Suzuki coupling to complete the synthesis of **44**, a potent, selective, and reversible inhibitor of cathepsin K with potential applications for the treatment of conditions characterized by excessive bone loss such as osteoporosis (Scheme 11).⁴⁶ The coupling of aryl bromide **42** and boronic acid **43** was initially carried out with the Boc-protected boronic acid, 5 mol% $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$, and aqueous Na_2CO_3 in DMF at 90 °C, but the subsequent Boc-deprotection step proved difficult and a considerable amount of amide **45** was obtained from nitrile hydrolysis. A screen of several Pd catalysts ($\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{OAc})_2$, $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$), phosphine ligands, bases, and solvents revealed that unprotected boronic acid **43** could be coupled using 3 mol% $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ and K_2CO_3 in aqueous DMF at 80 °C. These conditions provided crude product with 8000 ppm of Pd and Fe that could not be purged by chromatography or simple treatment with $\text{P}(n\text{-Bu})_3$.⁴⁷ Alternatively, the isolated **44** was treated with 20 mol% PBU_3 in EtOAc and then protonated with aqueous lactic acid. The resulting water-soluble lactic acid salt of **44** was extracted into the aqueous layer (without nitrile hydrolysis), whereas the PBU_3 helped to solubilize the Pd and Fe in the organic phase. After salt breaking with Na_2CO_3 and extraction of the free base into EtOAc, the API was crystallized from toluene with <50 ppm of Pd and Fe.

Gauthier and co-workers at Merck used a Suzuki coupling in their synthetic route to **49**, an orally active $\alpha_{2/3}$ -selective GABA_A agonist candidate for the treatment of central nervous system conditions such as anxiety, convulsions, and cognitive disorders (Scheme 12).⁴⁸ The biaryl moiety was assembled from the

Scheme 13

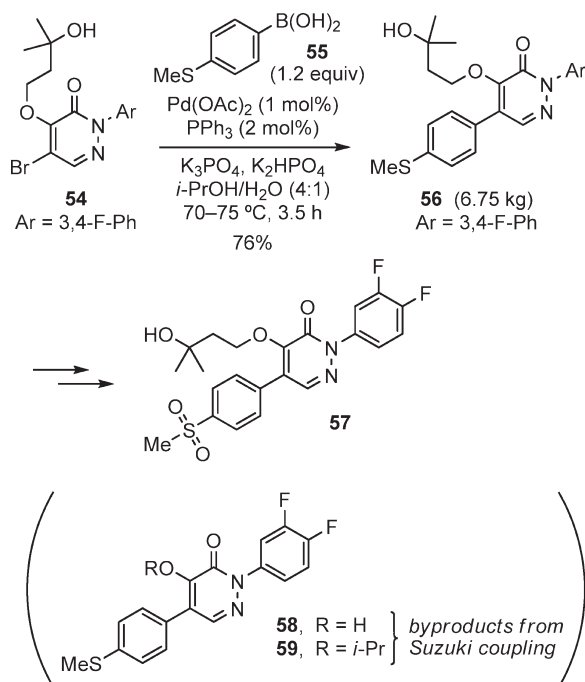


coupling of 2-fluorophenylboronic acid (**46**) and aryl bromide **47** in the presence of 1.0 mol% allylpalladium chloride dimer and 2.4 mol% $\text{P}(t\text{-Bu})_3$ (10% in hexane). After heating at 45–50 °C for 2 h, the biaryl **48** was crystallized from water/*i*-PrOH in 85% yield and 96.3% purity (high-performance liquid chromatography (HPLC)).

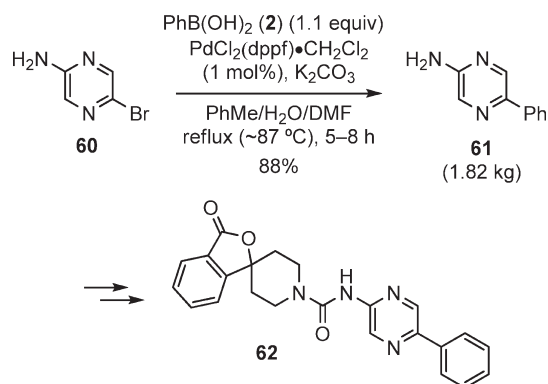
Xu and co-workers at Bristol–Myers Squibb incorporated the Suzuki coupling of boronic acid **50** and 2-bromopyridine (**51**) into the synthesis of acyclic azapeptidomimetic **53** (trade name Reyataz), a potent human immunodeficiency virus protease inhibitor (Scheme 13).⁴⁹ The coupling was accomplished using only 0.2 mol% of $\text{Pd}(\text{PPh}_3)_4$. Low catalyst loading was necessary to isolate the coupling product **52** with acceptable levels of residual Pd (5–50 ppm). The choice of solvent was also key; 4:3 toluene/ethanol provided a homogeneous solution from which **52** was obtained in good yield. During the early stages of development, **52** was recrystallized from 1:1 toluene/heptane and recovered in 80% yield, but it was later found that this intermediate could be telescoped as a toluene solution into the next step without further purification.

Researchers at Abbott have described the synthesis of **57**, a potent and highly selective COX-2 inhibitor candidate for the treatment of rheumatoid arthritis and osteoarthritis (Scheme 14).⁵⁰ The synthetic route to **57** contains the coupling of aryl bromide **54** and commercially available 4-(methylthio)phenylboronic acid (**55**). This Suzuki reaction was effected by $\text{Pd}(\text{OAc})_2$, PPh_3 , and a mixture of K_3PO_4 (1 equiv) and K_2HPO_4 (2 equiv) in 4:1 *i*-PrOH/ H_2O at 70–75 °C. Suzuki product **56** was obtained in 76% yield after passing the crude product through a silica cartridge filter and crystallizing from 4:1 heptane/EtOAc. The filtration through silica reduced the amount of Pd considerably and also purged black, amorphous impurities that could not be separated by recrystallization or Celite filtration. It was necessary to sparge the reaction mixture with nitrogen before heating to obtain high yields. Also, the $\text{K}_3\text{PO}_4/\text{K}_2\text{HPO}_4$ mixture performed better than K_3PO_4 or K_2HPO_4 alone, and this buffered system decreased the amount of hydrolytic products **58** and **59**. The reaction proceeded to completion with only 0.1 mol% of $\text{Pd}(\text{OAc})_2$ in combination with $\text{P}(o\text{-tolyl})_3$ ligand but at the expense of a longer reaction time and higher temperature (17 h at 80 °C). Other Pd catalysts were tested, and it was found that $\text{PdCl}_2(\text{PPh}_3)_2$ gave

Scheme 14



Scheme 15

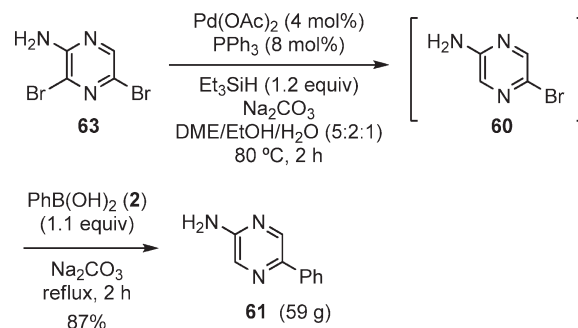


comparable yields whereas Pd/C provided lower yields of the coupling product.

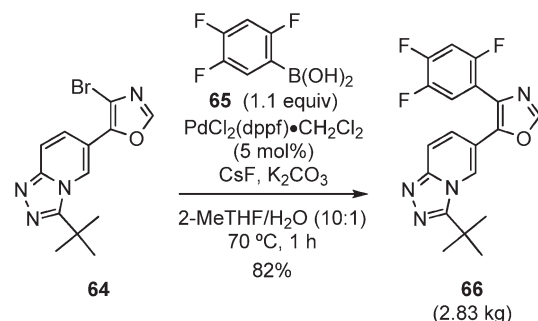
Scientists at Banyu Pharmaceutical and Merck reported the preparation of **62**, a highly selective NPY-5 receptor antagonist for the treatment of obesity.⁵¹ Two different approaches were developed for the preparation of key intermediate **61**. Scheme 15 outlines the first approach in which bromopyrazine **60** and PhB(OH)₂ (**2**) were coupled in the presence of PdCl₂(dppf)·CH₂Cl₂ (1 mol%) using toluene/H₂O/DMF as the solvent system. After a Darco/Na₂SO₄ treatment and crystallization from heptane/toluene, the desired 2-amino-5-phenylpyrazine (**61**) was obtained in 88% yield.

The bromopyrazine **60** used in this coupling was prepared from the selective debromination of dibromopyrazine **63**. The researchers developed an alternative, one-pot process to prepare **60** and telescope the monobromide directly into Suzuki coupling with PhB(OH)₂. As outlined in Scheme 16, dibromopyrazine **63** was treated with Et₃SiH, Pd(OAc)₂, PPh₃, and Na₂CO₃ in DME/EtOH/H₂O at 80 °C to generate the requisite

Scheme 16



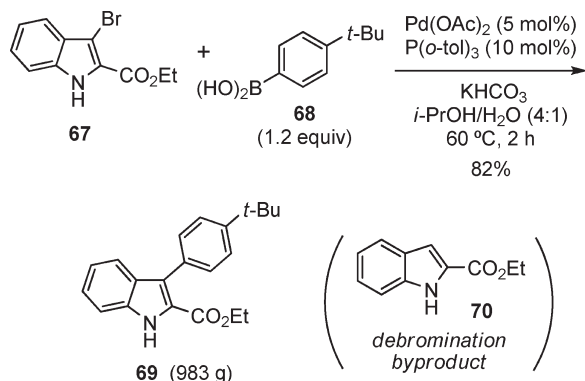
Scheme 17



monobromopyrazine **60**. The presence of Na₂CO₃ in the reduction allowed for a lower excess of Et₃SiH (1.2 equiv) to be used. After cooling, phenylboronic acid and Na₂CO₃ were added and the mixture was reheated to 80 °C for 2 h. Following a similar Darco/Na₂SO₄ treatment and crystallization from heptane/toluene, biaryl **61** was isolated in 87% yield for the two steps combined. Pd(PPh₃)₄ also performed well for the debromination step, but the less expensive Pd(OAc)₂/PPh₃ was chosen for development. Other catalyst systems such as PdCl₂/PPh₃ or Pd/C were much less effective.

Li and co-workers at Pfizer implemented a Suzuki–Miyaura coupling for the synthesis of 4,5-disubstituted oxazole **66** (Scheme 17), a potent and selective inhibitor of the stress-activated kinase p38α with potentially the same attributes of currently commercialized rheumatoid arthritis therapies (such as cyclooxygenase-II (COX-II) inhibitors) and antitumor necrosis factor biological agents.⁵² Bromide **64**, prepared by regioselective oxazole bromination (LHMDS, NBS), underwent a Suzuki reaction with commercially available 2,4,5-trifluorophenylboronic acid (**65**) in the presence of PdCl₂(dppf)·CH₂Cl₂, CsF, and K₂CO₃ in a 2-MeTHF/H₂O mixture at 70 °C. Cesium fluoride was employed as an additive to minimize the competitive protodeboronation of **65**, a degradation commonly associated with polyfluorophenylboronic acids.⁵³ The isolated Suzuki product **66** was contaminated with high levels of Pd (2100 ppm) and Fe (3200 ppm) from the catalyst. Because it was assumed that Pd was chelating to the weakly basic triazole moiety, the researchers employed a more basic amine such as Et₃N with the goal of displacing Pd through competitive binding. Thus, **66** was treated with a mixture of Et₃N and *i*-PrOH, heated to reflux for 2–3 h, and precipitated from solution with the addition of water. After repeating this protocol a second time, **66** was isolated with excellent purity (99.74% by HPLC) and Pd and Fe levels both below 10 ppm.

Scheme 18

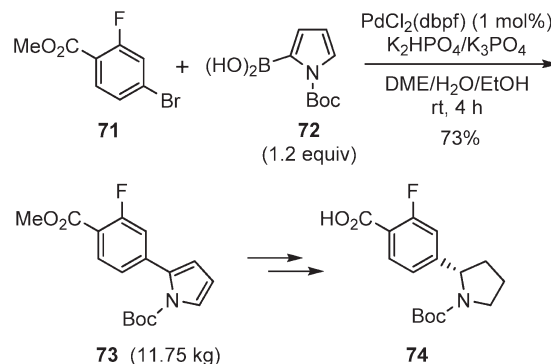


Researchers at GlaxoSmithKline optimized a Suzuki reaction for the preparation of 3-arylindole **69** (Scheme 18).⁵⁴ Original conditions coupled bromoindole **67** and boronic acid **68**, both commercially available, using $\text{Pd}(\text{OAc})_2$ (5 mol%), dppf (5 mol%), and Et_3N in a 6:1 $\text{DMAc}/\text{H}_2\text{O}$ mixture at 85 °C for 2–3 h. Product **69** was obtained in 66% yield on 2.36-kg scale; however, the process provided isolated material with high Pd and Fe (3675 and 471 ppm, respectively) and led to varying amounts of reduced indole byproduct **70**. A D-Optimal DoE (design of experiment) study⁵⁵ that included ligand, solvent, and base as variables was performed with the goal of improving the reaction outcome. The researchers tested a number of monodentate, large and small bite angle bidentate, electron-neutral, and electron-rich ligands together with organic and inorganic bases and several solvents that usually performed well in Suzuki couplings. Using DoE-identified conditions, initial gram-scale experiments with $\text{P}(\text{o-tolyl})_3/\text{KHCO}_3/n\text{-BuOH}$ at 60 °C led to complete conversion of bromide **67** in 3 h with <2% of desbromo byproduct **70**. The Suzuki product **69** was precipitated from solution in 90% yield by adding water, but the material was contaminated with 12000 ppm of Pd. Alternative MTBE extraction and crystallization from heptane gave lower yields (40–60%). When *i*-PrOH was used as solvent, the MTBE workup provided **69** in higher yield (87%) but with 8000 ppm Pd.

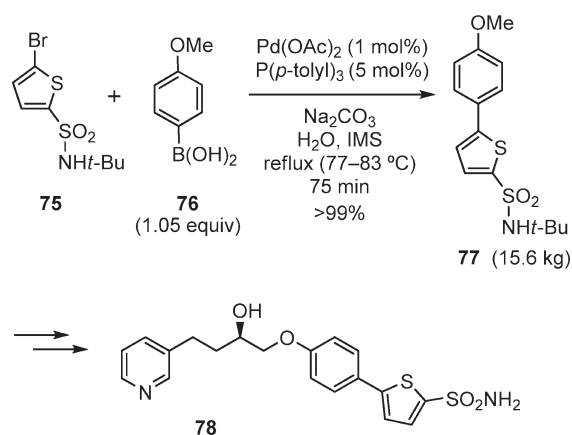
The researchers then focused on developing an efficient method to remove Pd to acceptable levels. Several solid-phase treatments were tested (Smopex-110, activated carbon, phosphotungstic acid-modified alumina, phosphotungstic acid-modified carbon, ethylene diamine-modified silica, mercaptopropyl-modified silica, triamine-derived silica), but only triamine-derived silica afforded a Pd level below 300 ppm. Because of cost and long cycle times, however, triamine-derived silica was ruled out. As an alternative to solid-phase treatments, the Suzuki product **69** was extracted into toluene and washed with an aqueous 20% NaHSO_3 solution at 60 °C for 1 h, which precipitated Pd solids from solution. After filtration of the toluene layer, heptane was added to crystallize desired **69** in 82% yield with <0.1% of byproduct **70** and only 100 ppm of Pd.

Researchers at Abbott incorporated a Suzuki coupling into the synthesis of optically pure benzoic acid **74** (Scheme 19).⁵⁶ 2-Arylpyrrole intermediate **73** was prepared via the coupling of commercially available bromide **71** and Boc-pyrrole-2-boronic acid (**72**)⁵⁷ in the presence of $\text{PdCl}_2(1,1'\text{-di-tert-butylphosphinoferrocene})$ and a combination of K_2HPO_4 and K_3PO_4 in $\text{DME}/\text{H}_2\text{O}/\text{EtOH}$ at rt for 4 h. The mild conditions, including ambient temperature and phosphate buffer, likely

Scheme 19



Scheme 20

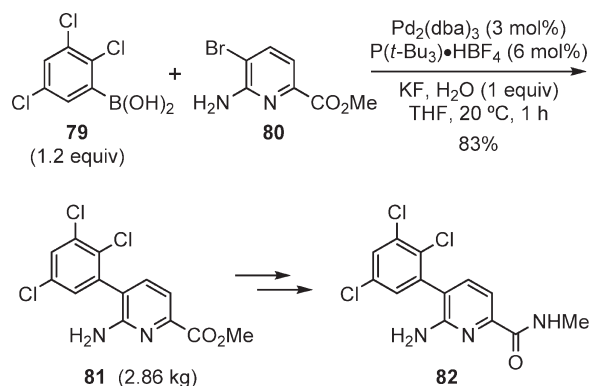


minimized decomposition of the boronic acid. Following an aqueous workup, 2-arylpyrrole **73** was isolated after crystallization from MeOH in 73% yield.

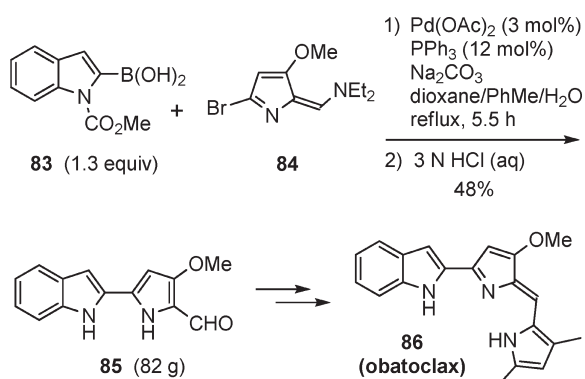
Merifield and co-workers at AstraZeneca in the United Kingdom incorporated a Suzuki coupling into the synthesis of **78**, a candidate for the treatment of inflammatory and allergic conditions such as asthma and rhinitis (Scheme 20).⁵⁸ Original conditions employed by the medicinal chemistry group coupled bromothiophene **75** and boronic acid **76** with $\text{Pd}(\text{PPh}_3)_4$ and Na_2CO_3 in aqueous ethanol. With the goal of preparing the catalyst system in situ immediately before coupling, commercially available phosphine ligands were screened with $\text{Pd}(\text{OAc})_2$ and it was found that the combination $\text{Pd}(\text{OAc})_2/\text{P}(\text{p-tolyl})_3$ gave the best results. Ethanol, methanol, or IMS³⁶ performed well as solvents, and thorough degassing was required to suppress homocoupling of the boronic acid. The final protocol preformed the catalyst by stirring a mixture of 1 mol% $\text{Pd}(\text{OAc})_2$ and 5 mol% $\text{P}(\text{p-tolyl})_3$ in IMS for 3–5 h at rt and added it to a mixture of boronic acid, bromothiophene, and aqueous base in IMS before heating to reflux. When the reaction was complete, the addition of water precipitated coupling product **77** for isolation by filtration in quantitative yield. The level of homocoupling product was kept below 1% on laboratory scale and was even lower on pilot plant scale. The residual Pd content in **77** was 2000–3000 ppm but reduced to acceptable levels downstream.

Fray and co-workers at Pfizer have reported the kilogram-scale preparation of **82**, a $\text{Na}_V1.8$ sodium channel modulator for the

Scheme 21



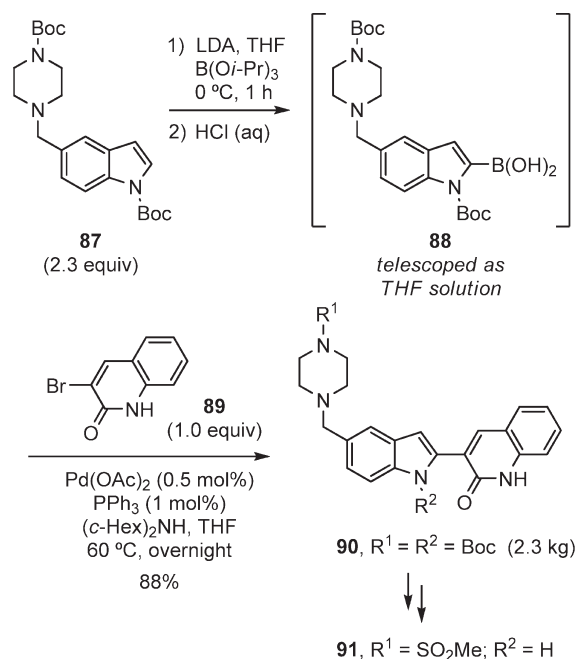
Scheme 22



treatment of pain (Scheme 21).⁵⁹ Key intermediate **81** was assembled via Suzuki–Miyaura coupling of boronic acid **79** and bromopyridine **80**. Original conditions with $\text{Pd}(\text{PPh}_3)_4$, aqueous solvent, and high temperature resulted in low yields, presumably due to ester hydrolysis. Taking advantage of progress made by Fu and co-workers,^{25,60} Hartwig and co-workers,⁶¹ and Buchwald and co-workers,^{62,63} using electron-rich, sterically hindered alkylphosphine ligands for Pd catalysis,^{6c} Fray and co-workers developed a set of Suzuki conditions for **79** and **80** employing $\text{Pd}_2(\text{dba})_3$, $\text{P}(t\text{-Bu})_3 \cdot \text{HBF}_4$, and KF in aqueous THF at 20°C for 1 h. Using KF as the activator likely minimized ester hydrolysis and decomposition of the trichlorophenylboronic acid. After filtration through Arbolcel filter aid and two recrystallizations from EtOAc, the coupling product **81** was isolated in 83% yield with 257 ppm Pd.

Dairi and co-workers at Gemin X Biotechnologies in Canada have reported the synthesis of obatoxax (**86**), a novel indolyl-prodigiosin derivative with potent anticancer activity in several animal tumor models from the antagonism of multiple members of the B-cell lymphoma family of antiapoptotic proteins (Scheme 22).⁶⁴ The Suzuki coupling of boronic acid **83** and bromide **84** formed key intermediate **85**. Methoxycarbonyl-protected **83** was a cheaper alternative to the commercially available Boc-protected analogue⁶⁵ and provided **85** with higher yield and purity. The coupling was catalyzed by $\text{Pd}(\text{OAc})_2$ (3 mol%) and PPh_3 (12 mol%) with Na_2CO_3 as base in a mixture of 1,4-dioxane/toluene/ H_2O . This solvent system and rapid heating helped to minimize boronic acid decomposition. Once the reaction reached completion, the mixture was treated with $\text{P}(n\text{-Bu})_3$ ⁴⁷ to scavenge Pd and minimize residual metal in

Scheme 23



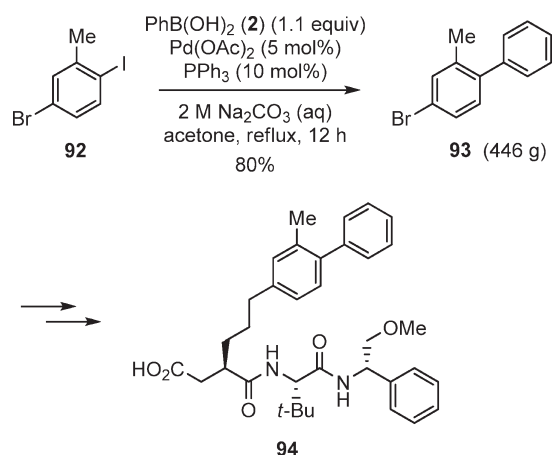
isolated **85** from 0.5–2.7% to <10 ppm (after enamine hydrolysis and carbamate cleavage with aqueous 3 N HCl).

Payack and co-workers at Merck have reported the preparation of **91**, a novel antiangiogenic tyrosine kinase inhibitor with application in oncology (Scheme 23).⁶⁶ A highly convergent route was implemented that culminated in the Suzuki–Miyaura coupling of advanced intermediates boronic acid **88** and 3-bromoquinolin-2(1H)-one (**89**) to generate **90**. Boronic acid **88** was prepared from indole **87** (LDA, $\text{B}(\text{O}i\text{-Pr})_3$, then aqueous HCl) and telescoped into the Suzuki coupling in THF solution. $\text{Pd}(\text{OAc})_2$ and PPh_3 were employed as the catalyst system. Basic aqueous conditions promoted the deboronation of **88**, and the researchers found an anhydrous alternative that employed dicyclohexylamine as an activator for Suzuki coupling. Deboronation was also prevented by adding the boronic acid solution slowly to a mixture of the catalyst and bromoquinoline. Once the reaction was complete, a carbon treatment followed by crystallization from hexanes/THF provided material contaminated with salts. A second carbon treatment in water and crystallization gave analytically pure material with low Pd levels.

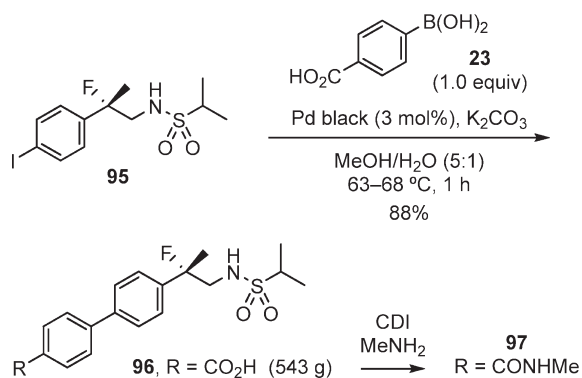
2.1.3. Boronic Acid and Aryl Iodide Coupling. Thomson and co-workers at Pfizer incorporated a Suzuki coupling into their synthesis of **94**, a matrix metalloprotease-3 (MMP-3) inhibitor for the treatment of pathological conditions involving tissue destruction as in venous and diabetic ulcers (Scheme 24).⁶⁷ Intermediate biaryl **93** was prepared via the chemoselective coupling of 5-bromo-2-iodotoluene (**92**) and $\text{PhB}(\text{OH})_2$ (**2**) and isolated in 80% yield from high-vacuum distillation. The same biaryl **93** had been previously prepared by a different group through the Suzuki coupling of $\text{PhB}(\text{OH})_2$ and 4-bromo-2-methylphenyldiazonium tetrafluoroborate, but only in 48% yield.⁶⁸

Magnus and co-workers at Eli Lilly have reported the synthesis of **97**, a candidate for the treatment of Parkinson's disease (Scheme 25).⁶⁹ The biaryl functionality was introduced via Suzuki coupling of iodide **95** and boronic acid **23**. Initially, this

Scheme 24



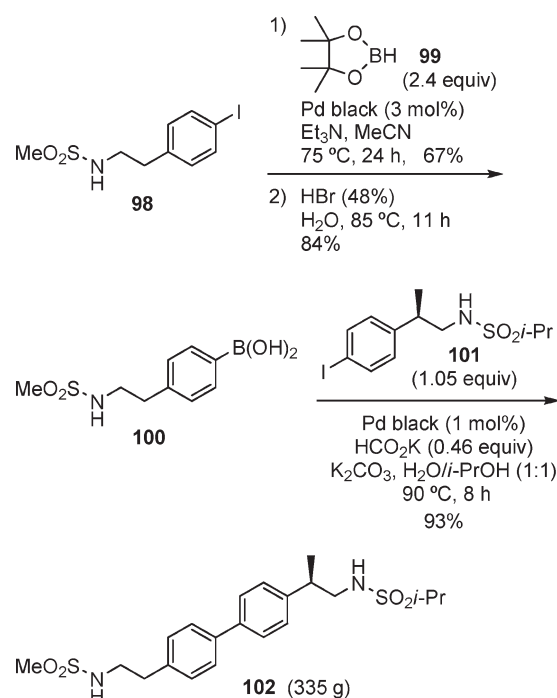
Scheme 25



transformation was effected with $\text{Pd(OAc)}_2/\text{PPh}_3$ and Na_2CO_3 in aqueous *i*-PrOH at reflux for 3 h. These conditions provided biaryl **96** as a slow-filtering solid in 70% yield but with <95% purity. Because this group had experience using Pd black for similar Suzuki couplings, they applied these conditions (Pd black, K_2CO_3 , MeOH/ H_2O 5:1 v/v) to **95** and **23** for the synthesis of **96**. The biaryl product was isolated in 88% yield (99% purity, <10 ppm Pd) after crystallization from *i*-PrOH/ H_2O /AcOH. These modified crystallization conditions provided **96** as a rapid-filtering drug intermediate.

Miller and co-workers at Eli Lilly completed the synthesis of **102**, an AMPA potentiator for the treatment of cognitive deficits associated with Alzheimer's disease, with the Suzuki coupling of boronic acid **100** and aryl iodide **101** (Scheme 26).⁷⁰ Boronic acid **100** was prepared from the Pd black-catalyzed reaction of iodide **98** and pinacolborane (**99**) followed by hydrolysis with aqueous HBr. With **100** in hand, the Suzuki coupling with iodide **101** required some optimization to suppress the homocoupling of boronic acid. Thus, in agreement with published literature,⁴¹ the exclusion of oxygen through vacuum degassing and nitrogen backfill, and the use of 5% Pd/C as Pd(0) rather than Pd(OAc)_2 as Pd(II), produced lower levels of homocoupled byproduct (0.5% versus 1.5–4.1%). Pd black further reduced the homocoupled byproduct to 0.3%, and potassium formate was added as a mild reducing agent to reduce any Pd(II) that was generated in situ. The final protocol executed the Suzuki coupling of

Scheme 26

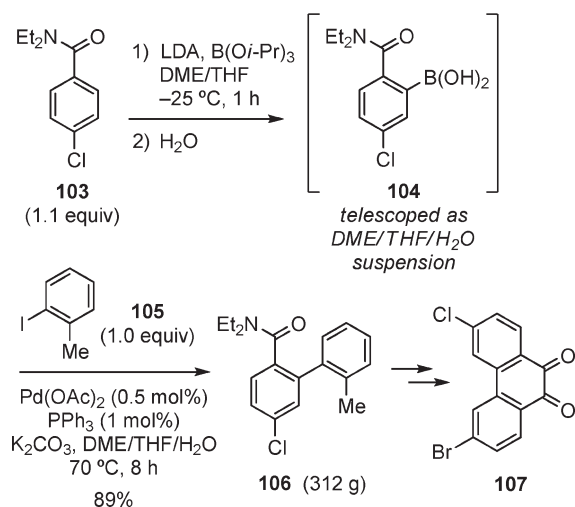


boronic acid **100** and iodide **101** in the presence of 1 mol% Pd black and 0.46 equiv of potassium formate in a 1:1 $\text{H}_2\text{O}/i\text{-PrOH}$ mixture. After sparging the vessel with nitrogen via subsurface addition for 30 min, the Pd catalyst was added and the deoxygenation procedure was continued for an additional 15 min until O_2 in the exit gas was below 0.5 ppm. The mixture was then heated to 90 °C for 8 h. As a result of these improvements, homocoupling was suppressed to <0.05%, and **102** was crystallized from acetone/ H_2O to provide API in excellent 93% yield.

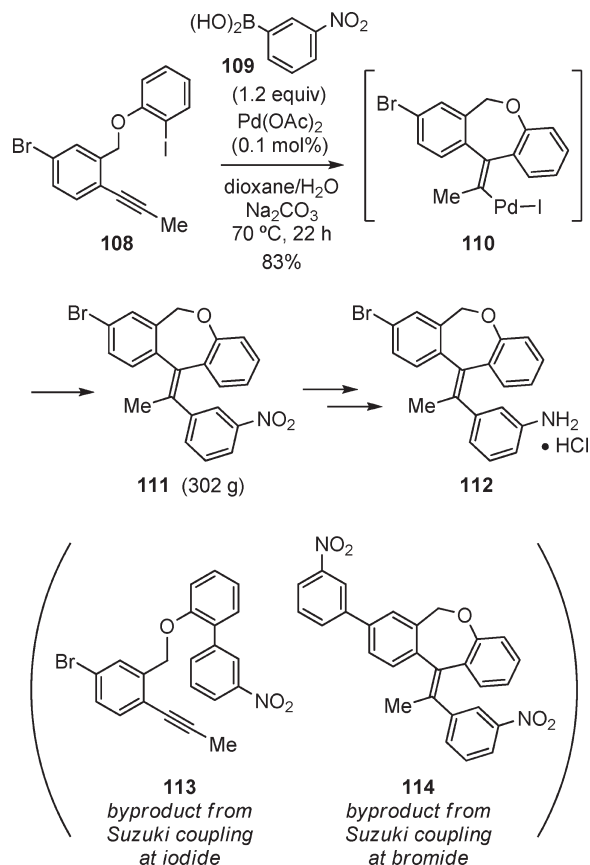
Limanto and co-workers at Merck described the synthesis of phenanthredione **107**, a useful building block for the preparation of other modularly derivatized phenanthrenequinones or pharmaceutically important phenanthreneimidazoles (Scheme 27).⁷¹ Biaryl intermediate **106** was synthesized from the Suzuki–Miyaura reaction of boronic acid **104**, prepared as a suspension in DME/THF/ H_2O via *ortho*-metalation of amide **103**,⁷² and 2-iodotoluene (**105**). The Suzuki coupling was effected by 0.5 mol% Pd(OAc)_2 and 1 mol% PPh_3 in a biphasic mixture of DME, THF, and H_2O at 70 °C for 8 h. After an aqueous workup, biaryl **106** was isolated as a yellow oil and carried forward without further purification.

Richey and Yu at Eli Lilly have reported the synthesis of HCl salt **112**, an important intermediate in the preparation of a selective nuclear hormone receptor modulator (Scheme 28).⁷³ The key transformation was a Pd-catalyzed intramolecular carbometalation of alkyne **108** to construct the dibenzoxapine core, which was claimed to be the first application of this reaction on large-scale. Dibenzoxapine synthesis involves the cyclization of Ar-Pd-I (from **108**) onto the methylacetylene to generate intermediate **110**; subsequent coupling of **110** with boronic acid **109** provides desired dibenzoxapine **111**. Alternatively, the direct coupling of **108** and **109** without cyclization leads to the undesired **113**. An extensive ligand screen (using desbromo-**108** as a model substrate) revealed that the desired dibenzoxapine formation was favored in the absence of

Scheme 27

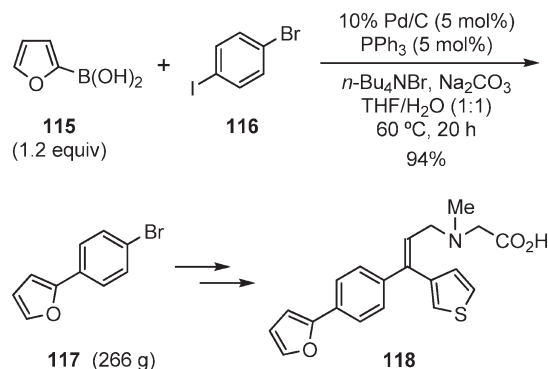


Scheme 28



ligand.⁷⁴ In addition, water had a critical role as cosolvent to reduce the amount of polymeric byproducts that were formed presumably from slow couplings of the alkenylpalladium intermediate and boronic acid. The final conditions for the preparation of dibenzoxapine from the desbromo variant of **108** used 2 mol% Pd(OAc)₂, 1.2 equiv of boronic acid, and 3 equiv of Na₂CO₃ at 70 °C. This model study afforded dibenzoxapine (desbromo-**111**) in 89% after chromatographic purification.

Scheme 29



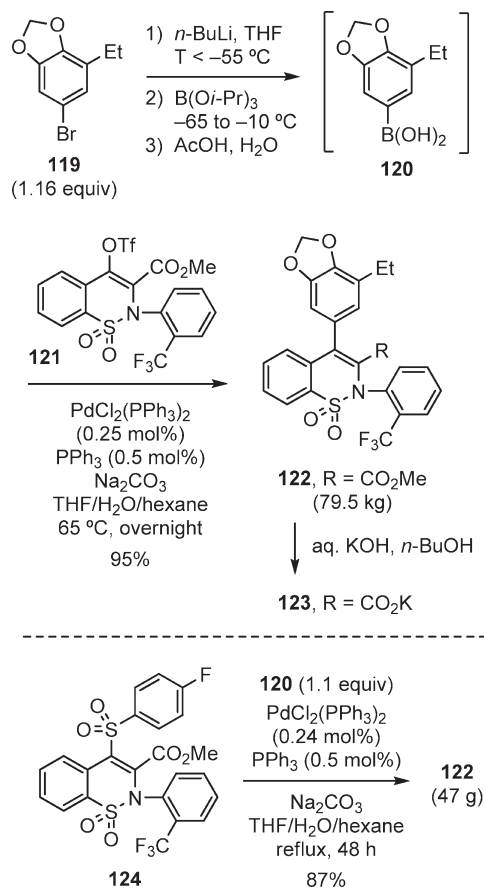
The application of model conditions (from desbromo-**108**) to actual substrates **108** and **109** led to incomplete conversion as well as impurities **114** and dimer from homocoupled boronic acid (Scheme 28). The dimer from boronic acid homocoupling was reduced from 5% to 1.4% by sparging the reaction mixture with nitrogen prior to the addition of the Pd catalyst. An excess of boronic acid (1.2 equiv) was employed to fully consume the iodide; however, about 4% of unreacted iodide **108** remained after 12 h at 70 °C, and higher temperatures increased the formation of impurity **114**. Fortunately, unreacted iodide could be purged via crystallization, and so it was not necessary to force the reaction to completion.

As mentioned previously, a major problem was the presence of polymeric byproducts stemming from the alkenylpalladium intermediate **110**. These impurities were difficult to detect by quantitative HPLC, resulting in discrepancies between in situ HPLC yields and isolated yields. For example, initial experiments with higher Pd catalyst loadings (2 mol%) provided only 70% isolated yield even though the in situ HPLC yield was 87%. When Pd loading was reduced to only 0.1 mol%, the isolated and in situ yields were 83% and 89%, respectively. Alternatively, with 10 mol% Pd(OAc)₂ the isolated and in situ yields were 61% and 86%, respectively. To explain this trend, Richey and Yu postulated that the desired intramolecular cascade reaction might be first order in Pd whereas the formation of polymeric byproducts might be higher order in Pd.

Researchers at Johnson & Johnson PRD in Belgium and Solvias A.G. in Switzerland collaborated to prepare drug candidate **118** (Scheme 29).⁷⁵ The first step of the synthesis required the chemoselective Suzuki–Miyaura coupling of 2-furanboronic acid (**115**) and 1-bromo-4-iodobenzene (**116**). This transformation was accomplished with excellent results using 10% Pd/C³⁴ (5 mol%) in an aqueous THF mixture, and a portion of PPh₃ was added to increase the rate of reaction.⁷⁶ The researchers did not comment on the selectivity for monocoupling over biscoupling of **116**; however, after Dicalite filtration, the monocoupled product 2-(4-bromophenyl)furan (**117**) was crystallized by the slow addition of water in very high yield (94%) with >99% purity and <10 ppm Pd.

2.1.4. Boronic Acid and Alkenyl Triflate Coupling. Jacks and co-workers at Pfizer reported the kilogram-scale synthesis of potassium salt **123**, an endothelin receptor antagonist for the treatment of primary pulmonary hypertension and congestive heart failure (Scheme 30).⁷⁷ The Suzuki coupling of boronic acid **120** and triflate **121** was developed for the preparation of intermediate **122**. Boronic acid **120** was prepared from bromide

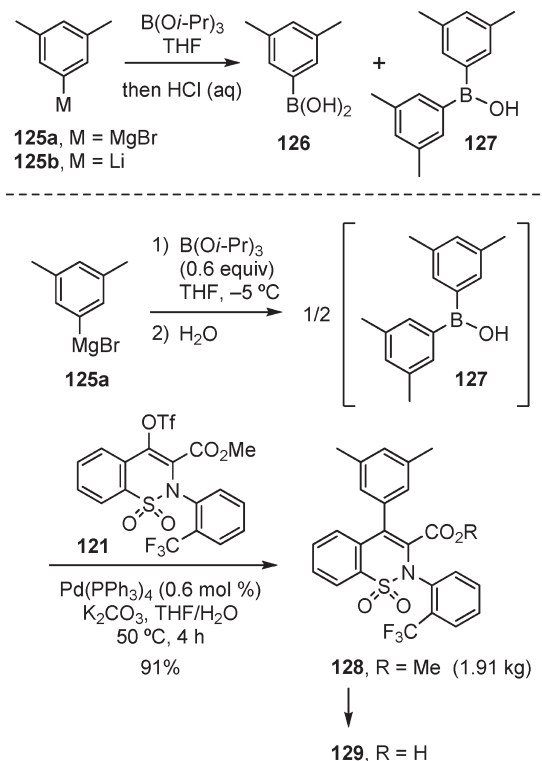
Scheme 30



119 ($n\text{-BuLi}$, B(Oi-Pr)_3 , then aqueous AcOH)⁷⁸ and carried into subsequent coupling without isolation. The subsequent Suzuki coupling was effected by $\text{PdCl}_2(\text{PPh}_3)_2/2\text{ PPh}_3$, a robust system that required a very low catalyst loading (0.25 mol%) for reaction completion. Several other catalyst systems were evaluated but did not perform as well. After reaction completion, 2,4,6-trimercaptotriazine¹³ was incorporated into the workup to scavenge Pd from the drug intermediate. These conditions performed well on a very large scale to provide 79.5 kg of **122** for an excellent 95% yield with <10 ppm Pd.

Jacks and co-workers at Pfizer investigated different coupling partners as alternatives to triflate **121**, which was prepared from expensive triflic anhydride.⁷⁷ Several substrates were prepared (mesylate, tosylate, phosphate, benzenesulfonate, 4-fluorobenzenesulfonate, 4-chlorobenzenesulfonate) and coupled with boronic acid **120** with different catalyst/ligand combinations. Of these alternative coupling partners, the most reliable and consistent yields were obtained from 4-fluorobenzenesulfonate **124** (Scheme 30), which proved more stable than the mesylate and phosphate under basic conditions and more reactive than the benzenesulfonate and tosylate. (Interestingly, the 4-chlorobenzenesulfonate led to substantial side coupling at the 4-chloro position.) Using the same $\text{PdCl}_2(\text{PPh}_3)_2/2\text{ PPh}_3$ system employed for the coupling of triflate **121**, 4-fluorobenzenesulfonate **124** was converted to **122** in 87% yield on a 50-g scale, although the reaction time was longer compared to triflate coupling. Because of project termination, this alternative approach was not tested on pilot plant scale.

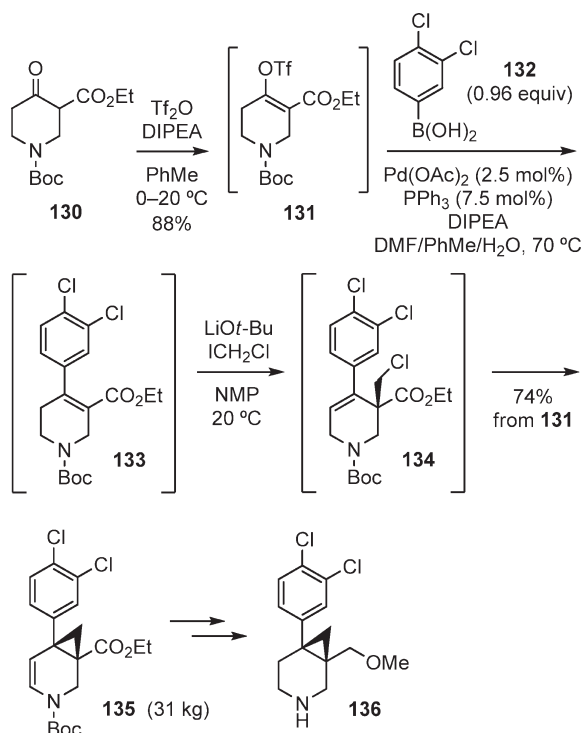
Scheme 31



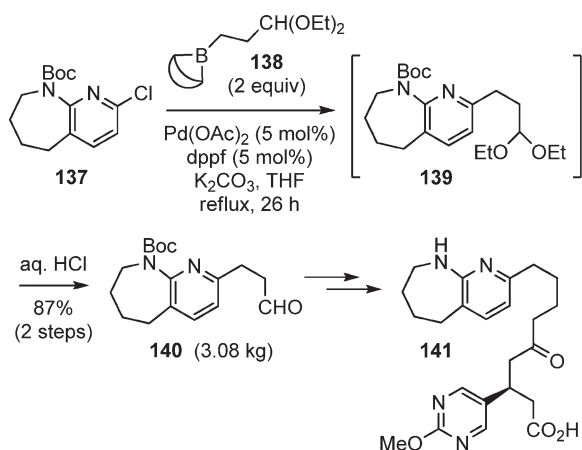
Winkle and Schaab at Pfizer coupled triflate **121** with a different boronic acid for the synthesis of intermediate **128** en route to alternative endothelin A antagonist **129**, a potential treatment of pulmonary hypertension (Scheme 31).⁷⁹ Because of the high cost of 3,5-dimethylphenylboronic acid (**126**), the researchers decided to prepare **126** in-house by treating organomagnesium bromide **125a** or organolithium **125b** with B(Oi-Pr)_3 ; however, considerable amounts of diarylboronic acid **127** were formed regardless of reaction temperature (-70 to $-5\text{ }^{\circ}\text{C}$) or excess of B(Oi-Pr)_3 (up to 2 equiv). On the other hand, reducing the B(Oi-Pr)_3 to only 0.6 equiv led to the exclusive formation of diarylboronic acid **127**. Because of the difficulties associated with crystallizing this type of diarylboronic acid,⁸⁰ the reagent was carried directly into Pd-catalyzed coupling with triflate **121** to afford the Suzuki product **128** in 91% yield. Prior to workup, the reaction mixture was treated with 2,4,6-trimercaptotriazine to remove residual palladium.¹³ This large-scale coupling of **127** expands the scope of the Suzuki reaction in the literature, as diarylboronic acids have received less attention than boronic acids for this type of transformation.

Sharp and co-workers at GlaxoSmithKline incorporated a Suzuki–Miyaura reaction into the pilot plant-scale synthesis of **136**, a potent serotonin, noradrenaline, and dopamine reuptake (triple reuptake) inhibitor for the treatment of major depressive disorder (Scheme 32).⁸¹ Key intermediate **135** was isolated from a sequence of Suzuki reaction, alkylation with ICH_2Cl , and cyclopropanation. One concern for the Suzuki coupling of triflate **131** and boronic acid **132** was the potential production of tetrachlorobiphenyl, a highly controlled compound, from the homocoupling of boronic acid. Indeed, the homocoupling of boronic acid proved to be a problem for the reaction of **131** and **132**; using Pd(OAc)_2 (2.5 mol%), PPh_3 (7.5 mol%), and DIPEA at $70\text{ }^{\circ}\text{C}$ provided the Suzuki product **133** with 1–5%

Scheme 32



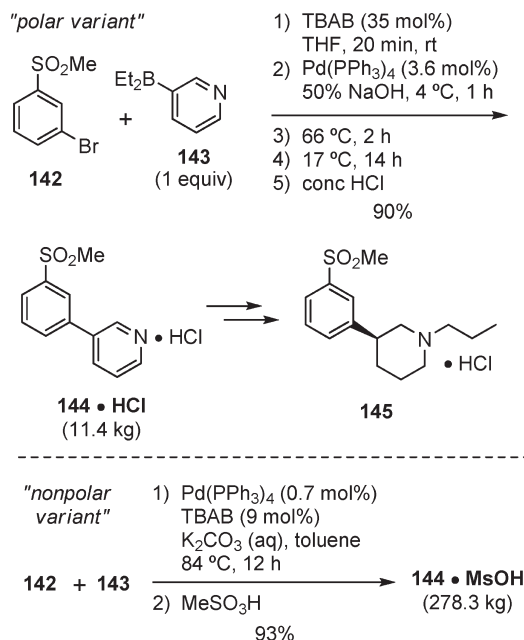
Scheme 33



tetrachlorobiphenyl. As Pd(II) is known to promote the homocoupling of boronic acids,^{41,82} the Pd(0) catalyst was preformed by mixing Pd(OAc)₂, PPh₃, and DIPEA in DMF/toluene/H₂O at 70 °C to ensure the full reduction of precatalyst to the active Pd(0) species. In addition, the amount of boronic acid was reduced to 0.96 equiv to avoid excess reagent that might be used for homocoupling. When these modifications were applied on a large scale, the observed level of tetrachlorobiphenyl was below 30 ppm and could be purged to <10 ppm by recrystallizing the downstream intermediate 135 from heptane.

2.1.5. Borane and Aryl Halide Coupling. Keen and co-workers at Merck Sharp & Dohme Research Laboratories in the U.K. have published the synthesis of nonpeptidic $\alpha_v\beta_3$ antagonist 141, a candidate for the treatment of osteoporosis (Scheme 33).⁸³ The propionaldehyde chain in the molecule was introduced via the Suzuki–Miyaura coupling of

Scheme 34

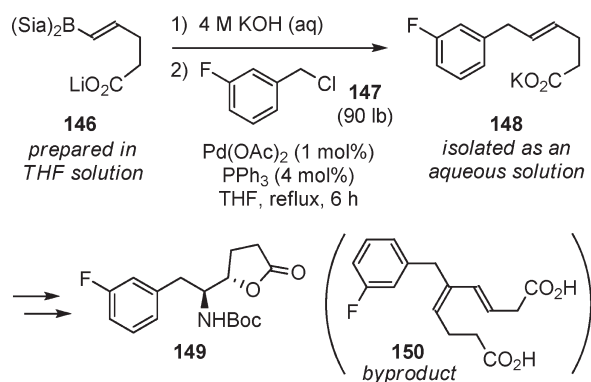


pyridozepine chloride 137 and trialkylborane 138 (prepared from commercially available acrolein diethyl acetal and 9-BBN).⁸⁴ Prior to this publication, the only literature examples in which trialkylboranes derived from acrolein acetal had been coupled under Suzuki–Miyaura conditions involved vinyl triflates as the second coupling partner.^{85,86} The coupling of 137 and 138 was accomplished using Pd(OAc)₂/dppe and K₂CO₃ in THF at reflux. The Suzuki product 139 was treated with aqueous 2 N HCl and isolated as aldehyde 140 in 87% yield on kilogram-scale.

Lipton and co-workers at Pharmacia Corporation reported the very large-scale synthesis of 145, a potential central nervous system (CNS) drug candidate (Scheme 34).⁸⁷ The key step was the Suzuki reaction of methyl-3-bromophenylsulfone (142) and diethyl-3-pyridylborane (143), and two different experimental protocols were developed. The "polar variant" employed Pd(PPh₃)₄ as catalyst and aqueous 50% NaOH/THF mixture.⁸⁸ These conditions employed 35 mol% of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst to obtain satisfactory conversions; however, crystallized coupling product was initially contaminated with phase-transfer catalyst from the high TBAB loading. A simple acid–base extractive workup purged the phase-transfer catalyst, and the Suzuki product 144 was cleanly precipitated as the hydrochloride salt from MeOH/EtOAc via addition of 1 equiv of concentrated HCl.

A "nonpolar variant" of this Suzuki coupling employed a biphasic mixture of water and toluene and used K₂CO₃ as base at a higher temperature (83–87 °C) than the polar variant (Scheme 34).⁸⁷ Compared to the polar variant, the "nonpolar" protocol reduced the catalyst loading (from 3.6 mol% to 0.7 mol%) and TBAB (from 35 mol% to 9 mol%), and the yield improved slightly from 90% to 93%. The researchers attributed this small yield improvement to less water degradation of reagents (including catalyst), which remained mostly in the toluene phase. By comparison, the polar variant was a more homogeneous mixture from the miscibility of water and THF, and the reagents and catalyst were exposed to a stronger base. In

Scheme 35



the nonpolar variant, Suzuki product **144** was isolated as the methanesulfonic acid salt.

2.1.6. Borane and Alkyl Halide Coupling. Ager and co-workers at DSM Pharma Chemicals reported the preparation of chiral lactone **149**, a precursor to compounds for the treatment of HIV, through the application of Shi's epoxidation (not shown) on a large scale for the first time (Scheme 35).⁸⁹ The lactone precursor carboxylate salt **148** was synthesized from the Suzuki coupling of disiamylborane **146** and 3-fluorobenzyl chloride (**147**). Borane **146** was freshly prepared from the hydroboration of the lithium salt of 4-pentynoic acid (43 lb) with Si_2BH , the latter available from isoamylene (88 lb) and 1 M $\text{BH}_3 \cdot \text{THF}$.^{90,91} (High-quality $\text{BH}_3 \cdot \text{THF}$ was necessary to avoid impurity **150**.) The resulting solution of disiamylborane **146** in THF was treated with KOH (vigorous hydrogen evolution, presumably from the quench of excess Si_2BH), followed by benzyl chloride **147** (90 lb) and $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ to generate Suzuki product **148**. This coupling product was carried forward as an aqueous solution without isolation.

2.1.7. Boronic Ester and Aryl Halide Coupling. A collaboration between Urawa and co-workers at Eisai and Ogura and co-workers at Chiba University in Japan led to the kilogram-scale synthesis of **155**, a potent antagonist of $\text{D}_3/\text{D}_2/5\text{-HT}_2$ receptors (Scheme 36).⁹² Key intermediate **153** was prepared by coupling aryl bromide **151** and boronic ester **152** with $\text{PdCl}_2(\text{PPh}_3)_2$ (1 mol%) in toluene at reflux. These conditions provided crude **153** with high levels of Pd (>2000 ppm) which had to be purged to 10 ppm Pd in the pharmaceutical ingredient **155**. A screen of palladium scavengers revealed that activated carbon, activated clay, and 25% aqueous ammonia were all ineffective at purging residual Pd. Alternatively, treating the reaction mixture with ethylenediamine generated an insoluble oil; after removing this oil, the organic solution was treated with (+)-di-*p*-toluoyl-D-tartaric acid (DTTA, **154**) to provide salt **153**·1/2 DTTA with only 11 ppm Pd. Separation of the oil after ethylenediamine treatment was problematic, however, and several commercially available, polymer-supported ethylenediamine derivatives were tested to facilitate the process (Figure 1). All these resins decreased the amount of Pd to 100–300 ppm from the initial 2000–3000 ppm, and DIAION CR20 resin (**159**) was selected for further development because it was commercially available with constant quality and could be used on large scale. The best results were realized when a solution of Suzuki product **153** was treated with 2 weight equiv of DIAION CR20 resin (with respect to starting piperazine) in toluene at 60 °C for 17 h (higher Pd levels in the final product with resin treatment at rt). Also, lower

Scheme 36

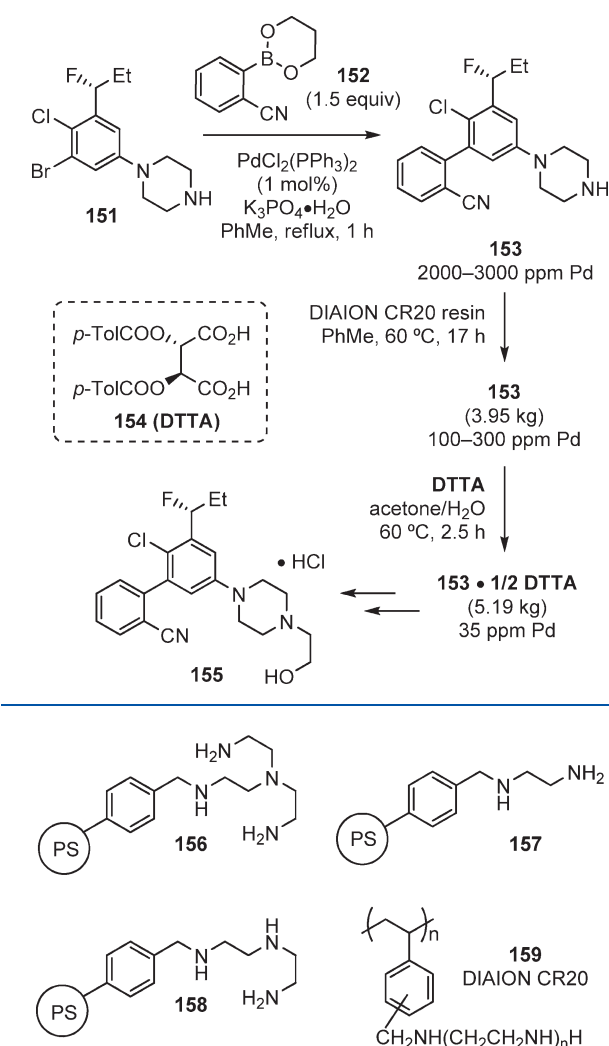
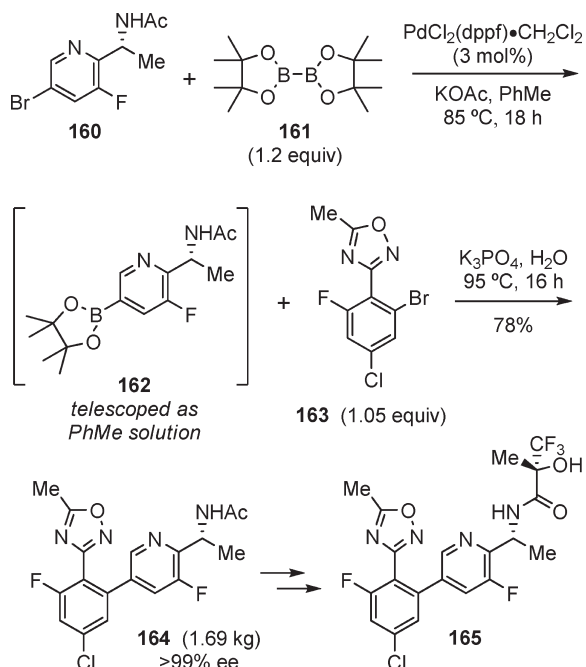


Figure 1

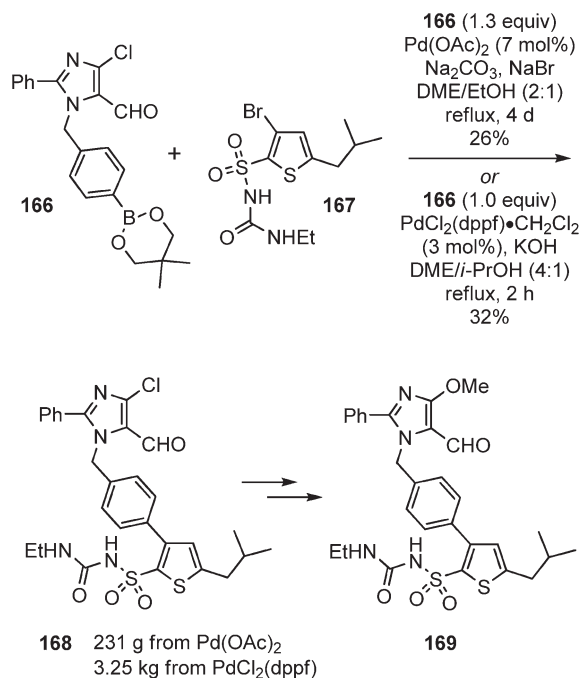
Pd levels were obtained from milled **153**, most likely due to the larger surface area available for Pd scavenging. After removal of the resin by filtration, the filtrates were concentrated and the residue was redissolved in acetone/water. The addition of DTTA precipitated the corresponding tartrate salt with only 35 ppm Pd on 5-kg scale.

Menzel and co-workers at Merck reported the preparation of orally bioavailable and CNS penetrant bradykinin 1 antagonist **165** for the treatment of inflammation and pain (Scheme 37).⁹³ The researchers employed a one-pot, two-step Suzuki–Miyaura coupling to assemble the biaryl core. Chiral pyridine **160**, prepared on kilogram-scale following reported procedures,⁹⁴ was treated with pinacolborane dimer (**161**), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$, and KOAc in nitrogen-sparged toluene at 85 °C to furnish boronic ester **162**, which was carried forward in solution without isolation.⁹⁵ After cooling to 20 °C, aryl bromide **163** and aqueous 1 M K_3PO_4 were added and heating was resumed to generate the Suzuki product **164**. After completion, the reaction mixture was treated with 50 wt% Ecosorb C-941 for 15 h at rt to remove colored impurities and then filtered through Solka-Floc. The filtrate was concentrated and the crude residue was treated with heptane to crystallize **164** in 78% yield.

Scheme 37

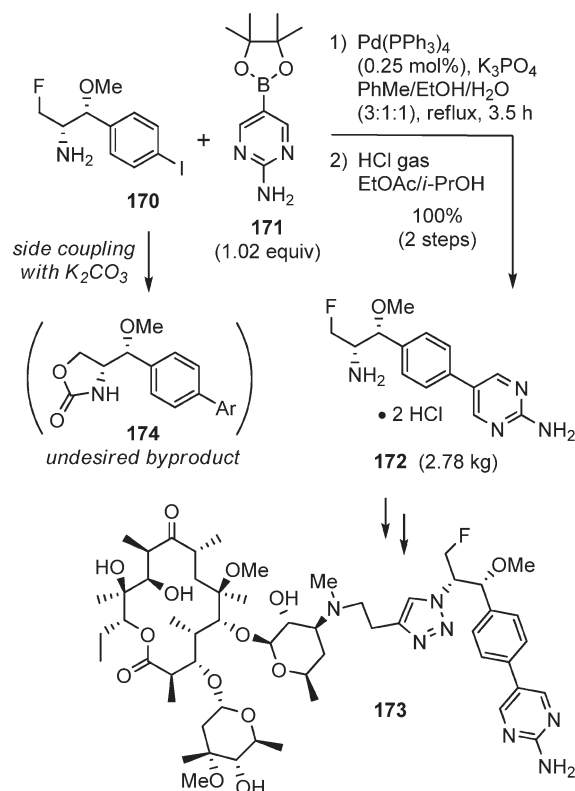


Scheme 38



Scientists at Aventis Pharma Deutschland GmbH have incorporated a Suzuki–Miyaura coupling into the synthesis of angiotensin-(1-7)-receptor agonist **169**, a potential treatment for hypertension, heart hypertrophy, heart failure, and coronary heart diseases such as angina pectoris, myocardial infarct, and endothelial dysfunction (Scheme 38).⁹⁶ The preparation of intermediate **168** from the Suzuki reaction of boronic ester **166** and bromothiophene **167** was the critical step in the synthesis and heavily optimized. Catalysts containing triphenylphosphine,

Scheme 39

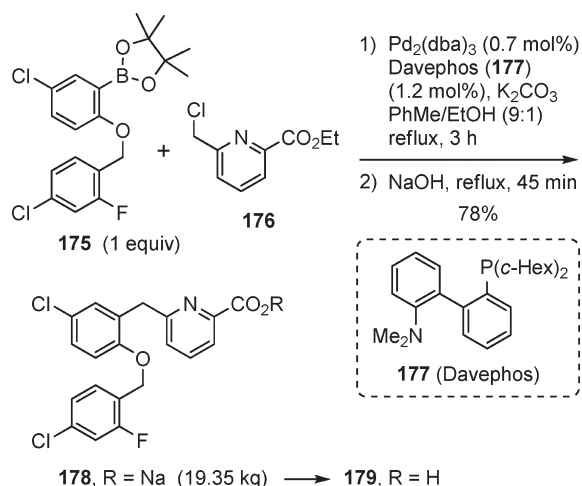


such as Pd(PPh₃)₄ and PdBr₂(PPh₃)₂, provided little or no coupling product **168**, whereas Pd(OAc)₂ in DME/EtOH or PdCl₂(dppf) in DME/*i*-PrOH gave the best results but also led to major impurities from the deboronation or homocoupling of boronic ester. Other solvents had no effect to suppress the formation of these byproducts, and so additives were investigated. NaBr and Ag₂O considerably suppressed the deboronation and homocoupling of **166**, and the less expensive NaBr was chosen in combination with Pd(OAc)₂ and Na₂CO₃ in 2:1 DME/EtOH. These conditions provided the desired **168** in 26% yield after chromatography (along with 12% deboronation and 36% homocoupled byproducts). Alternatively, PdCl₂(dppf) and KOH in DME/*i*-PrOH provided the desired **168** in 32% yield after only 2 h at reflux (but no information was provided about deboronation or homocoupled byproducts). In the same article, the synthesis of ¹⁴C-labeled **169** is also described.

Hanselmann and co-workers at Rib-X Pharmaceuticals reported the synthesis of macrolide **173**, a new candidate for the treatment of bacterial infections (Scheme 39).⁹⁷ The biaryl side chain was assembled via the Suzuki reaction of aryl iodide **170** and boronic ester **171**. Originally, K₂CO₃ was employed as base, but during process development, up to 3% of impurity **174** was detected from the reaction of the amine with CO₂ byproduct. This byproduct was suppressed by replacing K₂CO₃ with K₃PO₄. After Suzuki coupling and workup, the residue was redissolved in an EtOAc/*i*-PrOH mixture and treated with HCl gas to afford bis-HCl salt **172** in quantitative yield.

2.1.8. Boronic Ester and Alkyl Halide Coupling. Wilkinson and co-workers at GlaxoSmithKline in the U.K. incorporated a Suzuki–Miyaura reaction into their synthesis of **179**, an EP₁ antagonist candidate for the treatment of inflammatory pain (Scheme 40).⁹⁸ Expanding on initial efforts by the medicinal

Scheme 40



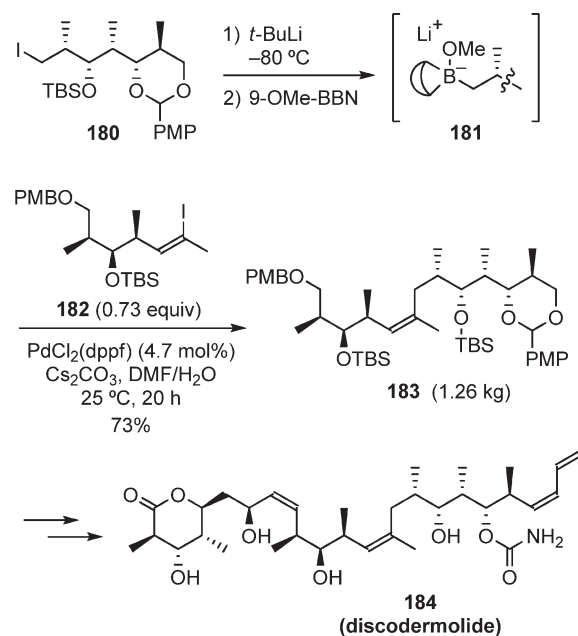
chemistry group, these researchers optimized the coupling of boronic ester **175** and benzyl chloride **176** as an excellent example of selectivity for benzyl chloride over aryl chloride. Whereas the $\text{Pd}(\text{PPh}_3)_4$ conditions from medicinal chemistry gave rise to byproducts from boronic ester homocoupling and deboronation, a catalyst/ligand screen identified 0.5 mol% $\text{Pd}_2(\text{dba})_3$ and 1.0 mol% Davephos (**177**)⁹⁹ for cleaner reactions and reduced catalyst loadings. However, the coupling of **175** and **176** stalled on scale-up due to an unknown impurity in the benzyl chloride, and two additional charges of Pd and ligand (0.1 mol% each per charge) were required for complete conversion. Residual Pd in the coupling product was reduced by treating the reaction mixture with 2,4,6-trimercaptotriazine¹³ at reflux for 3 h. After ester hydrolysis with NaOH , Na salt **178** was obtained in 78% yield with <10 ppm Pd.

2.1.9. Borate Complexes. Researchers at Novartis in Switzerland and the U.S.A. and the University of Cambridge in the U.K. collaborated on the large-scale preparation of (+)-discodermolide (**184**), a structurally complex and potent nontaxane microtubule-stabilizing agent that has shown inhibition of tumor cell growth in vitro, including paclitaxel- and EPO-resistant cells.¹⁰⁰ Scheme 41 outlines the Suzuki coupling of borate **181** and iodide **182** to assemble advanced intermediate **183**. Borate **181** was derived from iodide **180** via $t\text{-BuLi}$ and 9-OMe-BBN¹⁰¹ and carried directly into a same-pot Suzuki coupling with iodide **182**, $\text{PdCl}_2(\text{dppf})$, and aqueous Cs_2CO_3 at 25 °C. Crude product **183** was treated with ethanolamine to remove residual Pd and purified via chromatography. Subsequent crystallization from MeCN/heptane provided 1.26 kg of **183** and purged impurities such as *trans*-**183** (from *trans*-**182**) and desiodo-**182**.

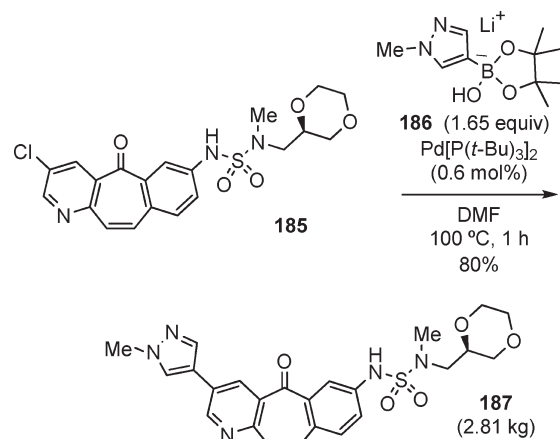
Researchers at Merck in the U.K. and U.S.A. completed the multikilogram synthesis of orally dosed c-Met kinase inhibitor **187**, a potential cancer treatment, with the Suzuki–Miyaura coupling of aryl chloride **185** and pyrazole borate **186** (Scheme 42).¹⁰² The borate complex was prepared from 4-bromo-1-methyl-1*H*-pyrazole via lithiation with *n*-HexLi and quenching with triisopropyl borate followed by reaction with pinacol; the addition of water precipitated **186** as a white solid in 88% yield. This intermediate was much more reactive than the corresponding boronic ester and for this reason was chosen for further development.

Initially, the Suzuki–Miyaura reaction of **185** and **186** was carried out with 5 mol% $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ in DMF at 100 °C

Scheme 41



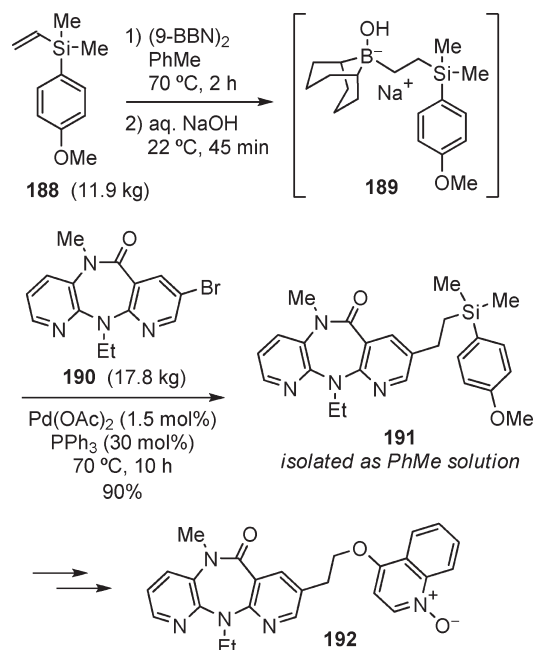
Scheme 42



without base, but the resulting product **187** was contaminated with 14000 ppm Pd. To lower residual metal in the API, the catalyst loading was reduced to 0.6 mol% and the reaction mixture was treated with 2 M aqueous NaOH and EcoSorb C-941 followed by filtration through Solka-Floc. After neutralization with 5 N HCl and crystallization from DMF/ H_2O , **187** was obtained in 80% yield with only 150 ppm Pd. Additional metal was purged by treating a solution of isolated **187** in DME with macroporous polystyrene-2,4,6-trimercaptotriazine (17 wt%) at 20 °C overnight. Resin filtration and crystallization from DMF/ H_2O provided API with 96% recovery and only 7 ppm of Pd.

Busacca and co-workers at Boehringer Ingelheim reported the pilot plant preparation of nevirapine analogue **192**, a non-nucleoside reverse transcriptase inhibitor candidate for the treatment of HIV infection (Scheme 43).¹⁰³ Vinylsilane **188** underwent regiospecific hydroboration with 9-BBN to give the corresponding borane, which was converted to borate complex **189** upon treatment with aqueous NaOH . Without isolation, this

Scheme 43



intermediate was treated with aryl bromide **190**, Pd(OAc)_2 (1.5 mol%), and PPh_3 (30 mol%) and heated at 70°C to provide the Suzuki product **191** in 90% yield as a toluene solution. The combination of nonpolar solvent (i.e., toluene) and high ligand/Pd catalyst ratio minimized the formation of byproduct desbromo-**190** to 4–5%.

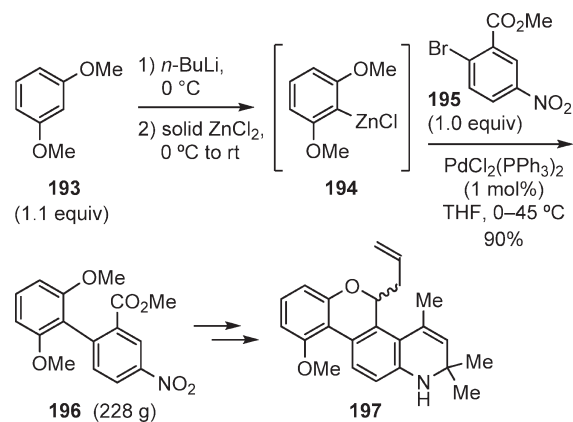
2.2. Negishi Coupling

Although not employed in industry as extensively as the Suzuki reaction, the Pd- or Ni-catalyzed¹⁰⁴ Negishi coupling of organozinc reagents¹⁰⁵ has found its way into the manufacture of pharmaceuticals. The greater ionic character of the C–Zn bond makes organozinc reagents more basic and nucleophilic species than their boron counterparts. Therefore, a fine balance needs to be maintained between reactivity and functional group compatibility. Chemists such as Knochel and co-workers¹⁰⁶ and Uchiyama and co-workers¹⁰⁷ have developed milder reaction conditions for the preparation of organozinc reagents in the presence of sensitive functional groups such as alcohols and aldehydes, and these new methods should find broad applicability for the synthesis of complex molecules.

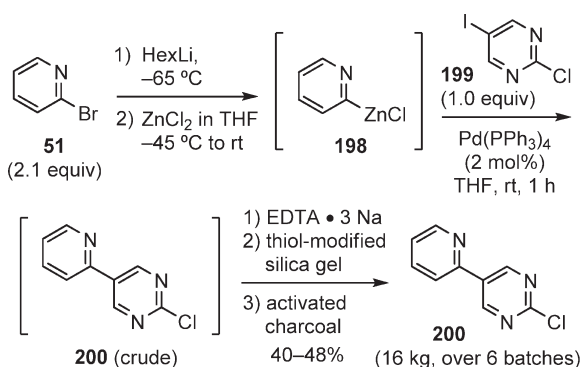
As the following examples illustrate, in most cases the Negishi coupling is carried out in three stages: (1) metalation of an organozinc precursor (ArX , ArH) to the corresponding arylmetal (ArLi , ArMgX); (2) zinc–metal exchange with either ZnCl_2 or ZnBr_2 to provide the ArZnX species; (3) Pd(0) - or Ni(0) -catalyzed coupling of ArZnX and a second coupling partner (e.g., aryl halide or triflate, acid chloride). The operational complexity of the Negishi reaction and the generation of substantial zinc waste are two factors that may have contributed to the limited use of this coupling for the large-scale synthesis of pharmaceuticals. Progress on the Negishi reaction has been previously reviewed.^{104,108}

Ku and co-workers at Abbott incorporated the Negishi coupling of arylzinc **194** and aryl bromide **195** into the scalable synthesis of **197**, a nonsteroidal ligand for the glucocorticoid receptor.¹⁰⁹ As shown in Scheme 44, arylzinc **194** was prepared

Scheme 44



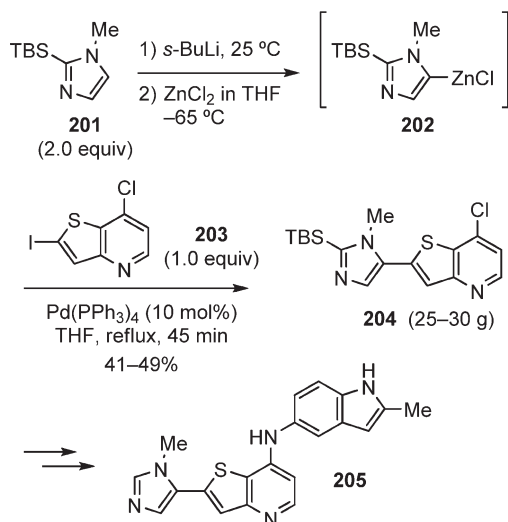
Scheme 45



by lithiation of 1,3-dimethoxybenzene (**193**) followed by the slow addition of solid ZnCl_2 (exothermic) in portions to maintain an internal temperature below 5°C . The solution was warmed to rt and recooled to 0°C , and the resulting ArZnCl was treated with bromide **195** and $\text{PdCl}_2(\text{PPh}_3)_2$. The mixture was allowed to warm to rt, and an exotherm developed at 20°C that increased the temperature to 45°C . Conveniently, the coupling product **196** precipitated upon formation and was isolated easily by filtration after reaction completion.

Pérez-Balado and co-workers at Johnson & Johnson developed the Negishi coupling of pyridylzinc **198** and iodopyrimidine **199** for the synthesis of **200** (Scheme 45), an intermediate to a selective PDE-V inhibitor (not shown).¹¹⁰ Metallic zinc was unable to convert 2-bromopyridine (**51**) to the requisite ArZnX ; alternatively, metal–halogen exchange of **51** with HexLi generated a 2-pyridyllithium that was converted to **198** upon treatment with ZnCl_2 in THF. Hexyllithium was used as an alternative to BuLi, as the hexane from HexLi hydrolysis remains in the reaction mixture whereas gaseous butane from BuLi hydrolysis poses safety and environmental concerns.¹¹¹ Pérez-Balado also reported several advantages to using ZnCl_2 instead of ZnBr_2 , such as the greater solubility of ZnCl_2 in THF (with a lesser exotherm of dissolution) and the greater reactivity of ArZnCl **198** than the corresponding ArZnBr for coupling with iodide **199**. The Negishi reaction of **198** and **199** was conducted at room temperature in the presence of 2 mol% $\text{Pd(PPh}_3)_4$, and using <2 equiv of ArZnCl diminished the yield of product **200**. The reaction workup incorporated the trisodium salt of EDTA, thiol-modified silica gel, and activated charcoal to reduce metals

Scheme 46

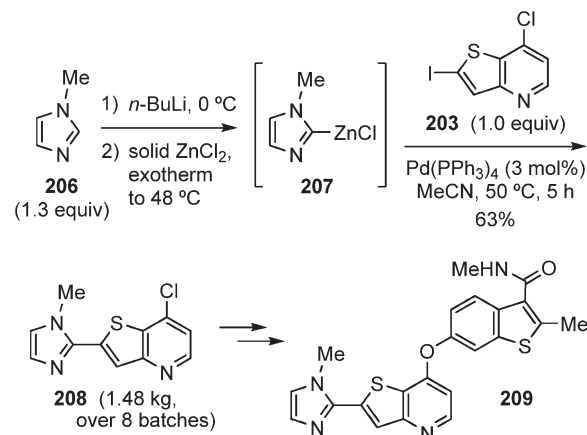


in the isolated product to 10–20 ppm Pd and 25–50 ppm Zn. On a laboratory scale (50 g of **199**), biaryl **200** was isolated in 65–70% yield; however, the yield fell to 40–48% on scale-up in the mini-plant (29 mol). This lower yield was attributed to the clumping of precipitate after ZnCl_2 addition, which was not observed on smaller scale. To compensate for this clumping, the temperature of ZnCl_2 addition on larger scale was increased from -55°C (laboratory scale) to -45°C ; however, this warming led to greater impurities and lower yields of Negishi product. Even with lower yields, six batches of this Negishi coupling were run in the mini-plant to synthesize 16 kg of **200**. The metal-scavenging workup was less effective at purging zinc on a larger scale (200–500 ppm), but residual Zn was purged downstream.

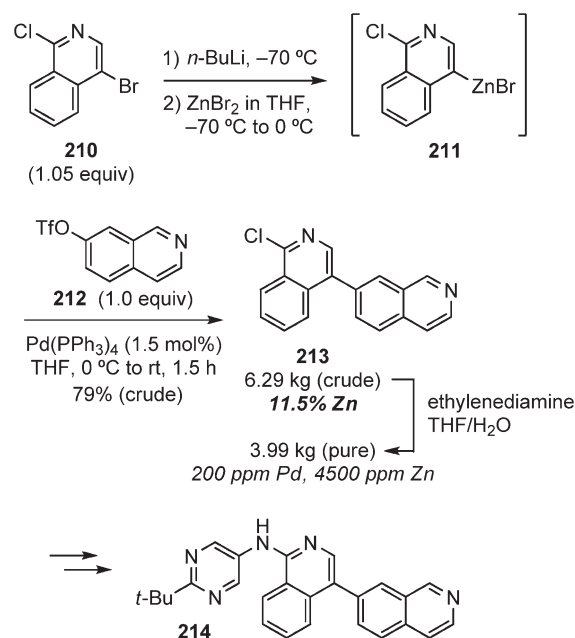
Ragan and co-workers at Pfizer explored the Negishi coupling of imidazolylzinc **202** and iodothienopyridine **203** en route to **205**, a VEGFR kinase inhibitor with promising antitumor activity (Scheme 46).¹¹² This reaction was pursued as a less toxic alternative to a previously successful Stille coupling involving a tributylstannylimidazole (**252**, Scheme 58). The Negishi coupling of **202** and **203** provided **204** on a laboratory scale (~ 50 g); however, reactions on a larger scale proved unreliable and would unpredictably fail. The researchers attributed reaction variability to the purity of iodide **203** but were unable to identify an analytical method to predict coupling success. In addition, alternative attempts to reverse the role of coupling partners were unsuccessful on a smaller scale (i.e., the reaction of a thienopyridinylzinc reagent and a bromo- or chloroimidazole).

Several years later, Scott and co-workers at Pfizer explored a similar Negishi coupling for the synthesis of another VEGFR inhibitor **209** (Scheme 47).¹¹³ The coupling of imidazolylzinc **207** and aryl iodide **203** had poor reproducibility that was attributed to the limited solubility of ArZnCl in THF (the requisite solvent for imidazole lithiation and ArZnCl formation). Solvent screens identified acetonitrile as a better solvent than THF for the dissolution and coupling of imidazolylzinc **207**; however, MeCN was incompatible with ArZnCl formation via $n\text{-BuLi}$ and had to be added afterward. Thus, to minimize THF dilution of the final mixture, ZnCl_2 was added as a solid, causing a rapid temperature spike from 0 to 48°C that was controllable on a 5-L laboratory scale. Iodide **203** was subsequently added to the ArZnCl as a solution in MeCN for Negishi coupling with

Scheme 47



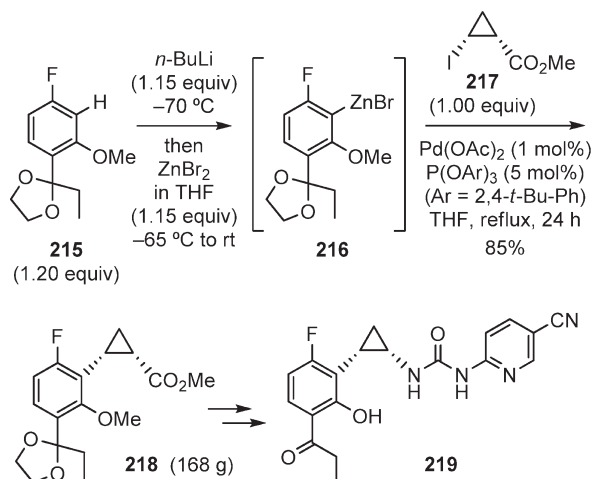
Scheme 48



$\text{Pd(PPh}_3)_4$ at 50°C . Negishi product **208** was precipitated along with inorganic salts by adding water to the reaction mixture, and these salts were purged by dissolving the crude drug intermediate in hot DMSO and filtering the solution through Celite. Unfortunately, this protocol could not reduce Pd levels in recrystallized material below 5000 ppm. The overall procedure was performed over eight batches to convert 2.85 kg of iodide to 1.48 kg of **208**.

Bänziger and co-workers at Novartis employed a Negishi coupling as the key step in their synthesis of B-Raf kinase inhibitor **214** (Scheme 48).¹¹⁴ Arylzinc **211** was readily available from the metal–halogen exchange of bromoisquinoline **210** and $n\text{-BuLi}$ followed by the addition of ZnBr_2 in THF. This bromo–lithium exchange occurred rapidly at -70°C ; however, a small amount of bromide **210** remained due to the competitive side reaction of $n\text{-BuLi}$ and $n\text{-BuBr}$ to form octane. The reaction of arylzinc **211** and triflate **212** varied with the quality of $\text{Pd(PPh}_3)_4$, and fresh batches of catalyst were crucial for reasonable conversion. On scale-up, this coupling provided >6 kg of crude Negishi product **213**; however, the product was isolated

Scheme 49



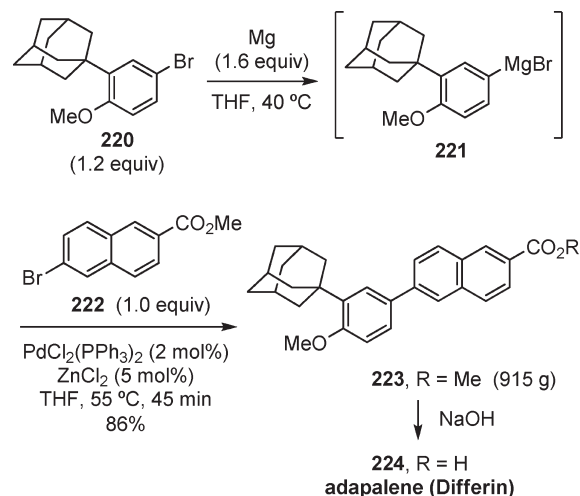
with complex-bound zinc (7–14 wt% Zn) that interfered with subsequent chemistry. After considerable optimization, the residual metals were purged to acceptable limits (200 ppm Pd, 4500 ppm Zn) by mixing **213** as a slurry with ethylenediamine in aqueous THF.

Shang and co-workers at Chiron Corporation incorporated the stereospecific Negishi coupling of aryl zinc **216** and iodocyclopropane **217** into their synthesis of **219**, a non-nucleoside reverse transcriptase inhibitor with selective binding for HIV-1 isolates (Scheme 49).¹¹⁵ The arylzinc was prepared by treating anisole **215** with $n\text{-BuLi}$ at $-70\text{ }^{\circ}\text{C}$, followed by addition of ZnBr_2 in THF solution and subsequent warming to rt. The $n\text{-BuLi}/\text{ZnBr}_2$ (1.15 equiv) were undercharged relative to anisole (1.20 equiv), presumably to avoid the reaction of excess butyllithium (or butylzinc) with iodocyclopropane **217** in the ensuing coupling. The resulting solution of ArZnBr was treated with **217**, $\text{Pd}(\text{OAc})_2$, and tris(2,4-di-*t*-butylphenyl)phosphite and heated at reflux to afford the desired coupling product **218** in excellent yield (85%). Importantly, this Negishi coupling proceeded without epimerization at either stereogenic center of the cyclopropane, offering an upgrade over a previous, less convergent synthesis that cyclopropanated a late-stage olefin with poor diastereoselectivity.

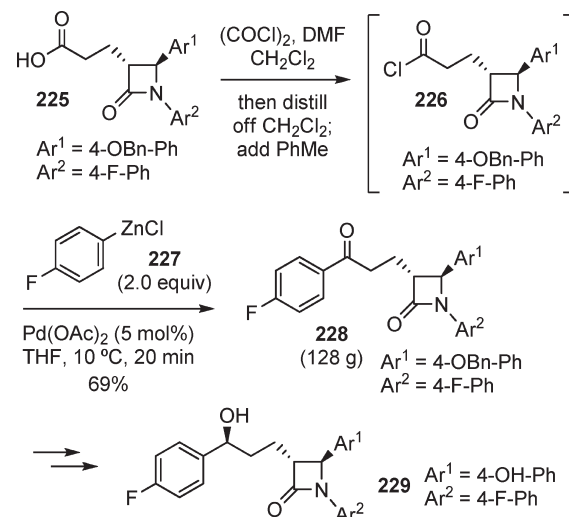
Liu and Xiang at Hunan University in China assembled adapalene (**224**, trade name Differin), a synthetic retinoid for the topical treatment of acne, psoriasis, and photoaging, via the ZnCl_2 -mediated coupling of Grignard reagent **221** and aryl bromide **222** (Scheme 50).¹¹⁶ Transmetalating the entire batch of **221** with ZnCl_2 before introducing the aryl bromide led to a thick suspension of arylzinc and magnesium salts that was difficult to mix without substantial dilution. Instead, the gradual conversion of ArMgBr to ArZnX was effected by the slow addition of Grignard reagent to a mixture of ZnCl_2 (5 mol%), $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mol%), and aryl bromide. This protocol provided Negishi product **223** in excellent 86% yield, and incorporating EDTA disodium salt washes into the reaction workup lowered the total residual Pd/Zn/Mg from 300 ppm to <20 ppm.

Praveen and co-workers at Dr. Reddy's Laboratories incorporated the Negishi coupling of acid chloride **226** and arylzinc **227** into an improved synthesis of ezetimibe (**229**), an acyl-CoA cholesterol acyltransferase inhibitor (Scheme 51).¹¹⁷ Acid

Scheme 50



Scheme 51

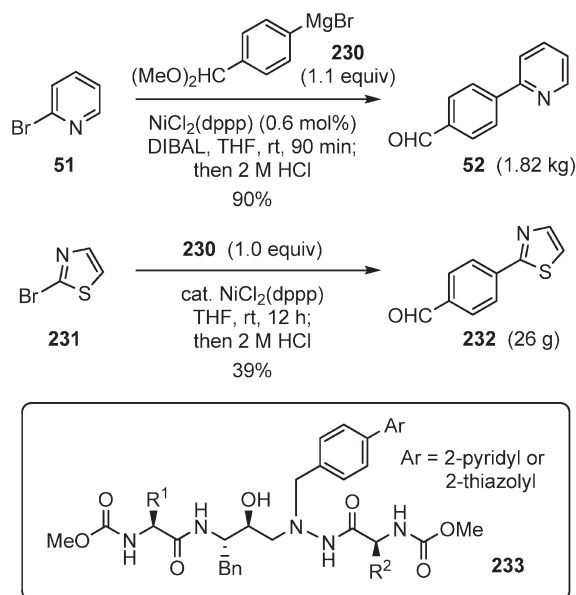


chloride **226**, prepared from carboxylic acid **225**, is reportedly unstable and difficult to handle in large-scale preparations, and so it was carried directly into the Negishi coupling without isolation. The arylzinc **227**, prepared by treating 1-bromo-4-fluorobenzene with magnesium turnings followed by ZnCl_2 , was added to a mixture of chloride **226** and $\text{Pd}(\text{OAc})_2$ (5 mol%), and the resulting coupling was complete within 20 min at $10\text{ }^{\circ}\text{C}$. Aqueous workup and a series of solvent distillations and decantings provided the neat aryl ketone **228** with sufficient quality that column chromatography was not necessary.

2.3. Kumada–Corriu Coupling

The Ni- or Pd-catalyzed coupling of organomagnesium reagents,¹¹⁸ known as the Kumada–Corriu reaction,^{4c–e,119} has found several applications in industry; however, because of the high reactivity of Grignard reagents relative to other organometallic species, the scope of this transformation for the large-scale synthesis of pharmaceuticals has been limited to the preparation of simple substrates. In addition to the more commonly used Ni and Pd, other metals such as Fe,¹²⁰ Co,¹²¹ and Mn¹²² can also promote Kumada couplings. Some

Scheme 52



applications of the Kumada–Corriu reaction have been reviewed.^{118a,123}

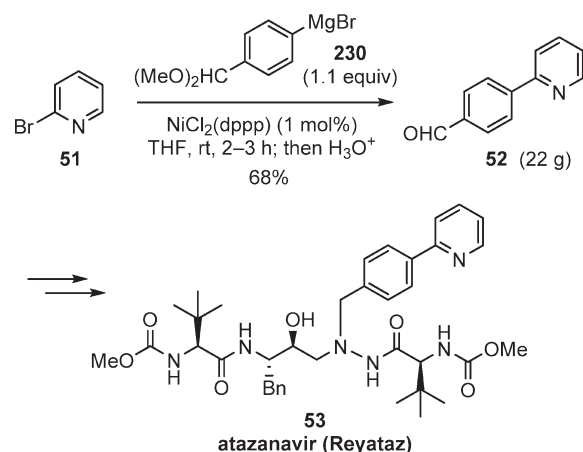
Bold and co-workers at Ciba–Geigy reported Kumada couplings to prepare biaryl aldehydes **52** and **232** for the synthesis of aza-dipeptide HIV-1 protease inhibitors of type **233** (Scheme 52).¹²⁴ The scale-up of biaryl **52** involves the coupling of 2-bromopyridine (**51**) and Grignard reagent **230**, the latter freshly prepared from 4-bromobenzaldehyde dimethyl acetal using 1.1 equiv Mg relative to bromide and catalytic I_2 . A THF solution of 2-bromopyridine, 0.6 mol% $\text{NiCl}_2(\text{dppp})$, and DIBAL was treated with ArMgBr **230** over 45 min, maintaining a temperature between 15 and 20 °C. (DIBAL should initiate the catalytic cycle via reduction of Ni(II) to Ni(0), although Bold and co-workers did not comment on this.) After reaction completion, the mixture was poured into a slurry of citric acid (metal chelator), ice, aqueous HCl, and Hyflo Super Cel. The Kumada product was extracted into toluene, treated with NaOH and then charcoal, and filtered through silica gel. Concentration of the filtrate provided 1.82 kg of biaryl aldehyde **52** in 90% yield.

The synthesis of biaryl aldehyde **232** from the Kumada coupling of **230** and bromide **231** (Scheme 52) was performed on a smaller scale under different reaction conditions (no DIBAL to initiate the catalytic cycle via Ni(II) reduction), and the result was a lower yield.

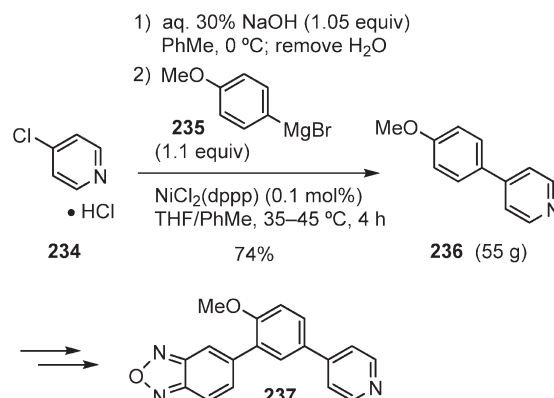
Ten years later, Long and co-workers at the State Key Laboratory of Drug Research in China reported the aforementioned Kumada coupling of 2-bromopyridine (**51**) and arylmagnesium bromide **230** to prepare biaryl **52**, an intermediate in the synthetic route to HIV protease inhibitor atazanavir (**53**, trade name Reyataz; Scheme 53).¹²⁵

Manley and co-workers at Novartis employed the Kumada coupling of 4-chloropyridine (**234**) and arylmagnesium bromide **235** to prepare biaryl **236** en route to **237**, an inhibitor of the phosphodiesterase type 4D isoenzyme and potential asthma treatment (Scheme 54).¹²⁶ The commercial HCl salt of 4-chloropyridine was mixed with aqueous 30% NaOH and toluene, and the toluene layer containing the free base **234** was heated at reflux under reduced pressure using a water trap to remove residual

Scheme 53



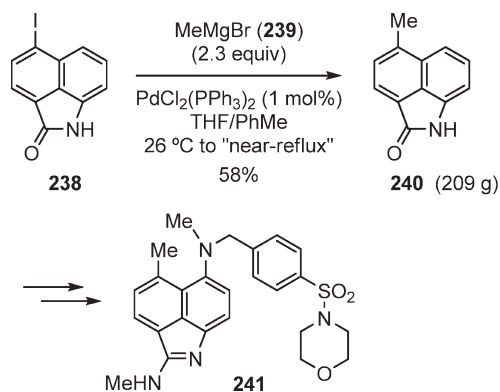
Scheme 54



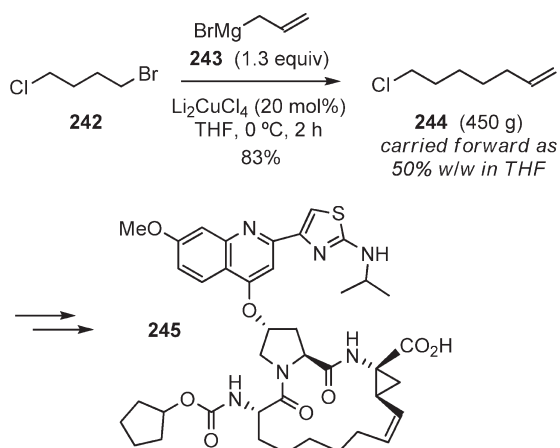
water azeotropically (drying was critical for successful Kumada coupling). Care was taken to avoid the loss of toluene during reflux, which could lead to the autopolymerization of chloropyridine (highly exothermic) and also the loss of the volatile chloropyridine via codistillation. The dried solution was treated sequentially with $\text{NiCl}_2(\text{dppp})$ and a small portion of ArMgBr **235** solution in THF (~ 0.1 equiv); the resulting mixture was held below 30 °C for 15 min to mitigate the exotherm as Ni(II) was reduced to Ni(0). The remaining ArMgBr was added slowly over 1 h while maintaining an internal temperature of 35–45 °C to suppress hazardous rate acceleration from reagent accumulation. After completion, the cooled reaction mixture was quenched with aqueous solutions of citric acid (metal scavenger) and HCl, and the resulting HCl salt of Kumada product **236** was extracted into toluene, treated with aqueous NaOH solution, and concentrated from toluene to provide 55 g of **236** with <20 ppm Ni.

Marzoni and Varney at Agouron Pharmaceuticals applied the methylation of aryl iodide **238** under Kumada conditions for their improved synthesis of **240**, an intermediate to thymidylate synthase inhibitor and potential cancer treatment **241**.¹²⁷ As outlined in Scheme 55, a solution of methylmagnesium bromide (1.4 M in 1:3 THF/toluene) was added in a steady stream to iodide **238** and 1 mol% $\text{PdCl}_2(\text{PPh}_3)_2$ in THF over 90 min. Grignard addition increased the reaction temperature from 26 °C to “near-reflux”, and after reaction completion the mixture

Scheme 55



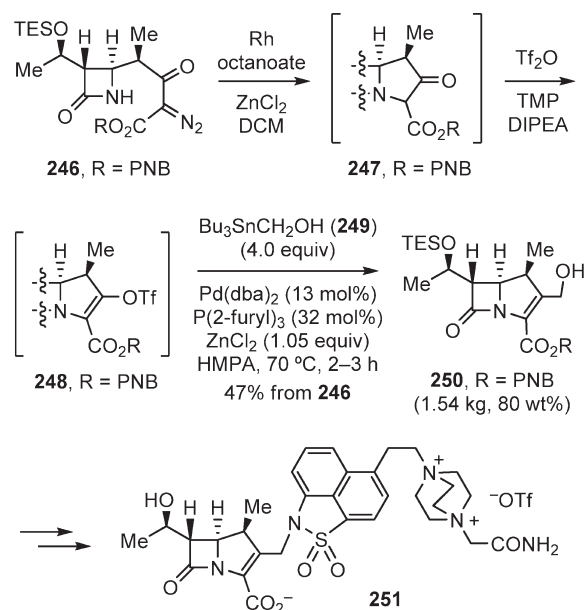
Scheme 56



was cooled below 30 °C and quenched with aqueous NH_4Cl solution. The quenched mixture was passed through a filter to remove precipitate, concentrated to a residue that was suspended in methanol at reflux, and diluted with water. The resulting solids were collected on filter and recrystallized from chlorobenzene to provide 209 g of **240** in 58% yield. These conditions are an upgrade over a previously explored Stille methylation, which required highly toxic tetramethyltin, a high catalyst loading (10 mol% $\text{PdCl}_2(\text{PPh}_3)_2$), and chromatography to remove tin byproducts.

Wang and co-workers at Novartis applied the Cu-catalyzed coupling of 1-bromo-4-chlorobutane (**242**) and allylmagnesium bromide (**243**) to the preparation of 7-chloro-1-octene (**244**), a very early intermediate in the synthesis of protease inhibitor **245** (Scheme 56).¹²⁸ Although commercial solutions of the Li_2CuCl_4 are widely available, Wang prepared the catalyst *in situ* by premixing anhydrous CuCl_2 and 2 equiv of anhydrous LiCl in THF. Following the Johnson procedure,¹²⁹ the solution of preformed Li_2CuCl_4 and bromobutane **242** in THF was cooled at 0 °C and treated with allylmagnesium bromide (1 M in THF) over 30 min. The reaction proceeded to completion at 0 °C within 2 h, and the mixture was quenched with 10% sulfuric acid solution. The volatile Kumada product **244** was extracted into MTBE and isolated as a 50% w/w THF solution (containing 450 g of product by ^1H NMR assay) after careful concentration under vacuum (20 °C, 100 mmHg).

Scheme 57

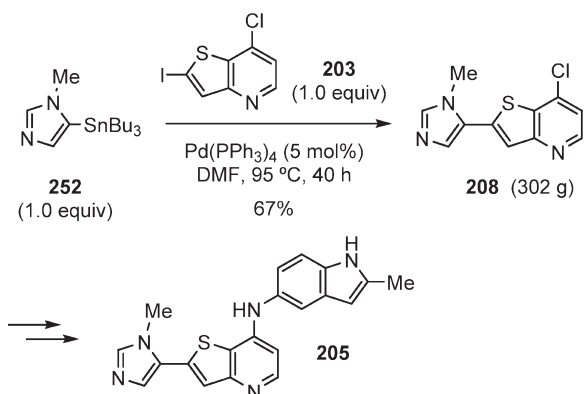


2.4. Stille Coupling

The Stille reaction, first reported in the late 1970s,¹³⁰ has been used sparingly for the large-scale synthesis of pharmaceuticals mostly due to the toxicity of organotin reagents and the difficulty of purging tin byproducts from drug intermediates and API. Despite these issues, many organotin reagents used for Stille coupling are widely available, stable to air and moisture, and compatible with various functional groups. The synthetic¹³¹ and mechanistic¹³² aspects of the Stille reaction have been previously reviewed.

Yasuda and co-workers at Merck employed the Stille coupling of triflate **248** and $\text{Bu}_3\text{SnCH}_2\text{OH}$ (**249**) in their large-scale synthesis of **251**, a compound with potent activity against gram-positive pathogens.¹³³ This hydroxymethylation was based on previous couplings of aryl halides and $\text{Bu}_3\text{SnCH}_2\text{OH}$.¹³⁴ As shown in Scheme 57, triflate **248** was generated in two steps from diazo compound **246** and carried forward into the Stille coupling without isolation. A solution of triflate and $\text{Bu}_3\text{SnCH}_2\text{OH}$ in HMPA was added over 40–60 min to a heated solution (70 °C) of Pd(dba)_2 , P(2-furyl)_3 , and ZnCl_2 in HMPA under an argon atmosphere. Of the catalysts screened, Pd(dba)_2 was more robust than either $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ or Pd(OAc)_2 , and the Stille reaction did not occur without the added phosphine ligand. Faster reaction rates and higher yields of **250** were obtained with tri(2-furyl)phosphine than with other triarylphosphine ligands such as PPh_3 and P(2-thienyl)_3 , and bidentate ligands (BINAP, dppf, dppe, dppp) only provided trace amounts of **250**. Highly toxic HMPA was essential for this coupling; yields were much lower in other solvents (DMPU, DMF, THF, NMP, DMSO), although reactions in 10:1 DMPU/HMPA provided the same yields as those in neat HMPA. Under these conditions, the triflate was consumed within 2 h at 70 °C, and only a small amount of butylated side product was observed from the transfer of a butyl group from $\text{Bu}_3\text{SnCH}_2\text{OH}$. Reaction workup partitioned the mixture between MTBE and water and concentrated the organic layer to a crude residue. Silica gel chromatography provided Stille product **250** with 80 wt% purity, from which a pure sample of **250** was prepared by recrystallization from hexane.

Scheme 58



Ragan and co-workers at Pfizer incorporated the Stille coupling of imidazolylstannane **252** and iodothiopyridine **203** into the synthesis of VEGFR kinase inhibitor **205**, a compound with promising antitumor activity (Scheme 58).¹¹² An exhaustive survey of coupling reactions revealed this Stille approach as the only robust and scalable method for coupling the imidazole and thienopyridine rings (an alternative Negishi approach would later be developed; Schemes 46 and 47). The Stille coupling of equimolar amounts of stannane **252** and iodide **203** was catalyzed by 5 mol% $\text{Pd}(\text{PPh}_3)_4$ in DMF at 95 °C, proved to be nondiscriminating with respect to catalyst source, and proceeded to completion within 40 h. Workup partitioned the mixture between aqueous 1 M HCl and EtOAc, removed the precipitate via filtration, and subjected the filtrate to a series of aqueous washes and organic back-extractions. Ultimately, the organic layers were concentrated to provide Stille product **208** as a solid that was reslurried in MTBE and collected by filtration.

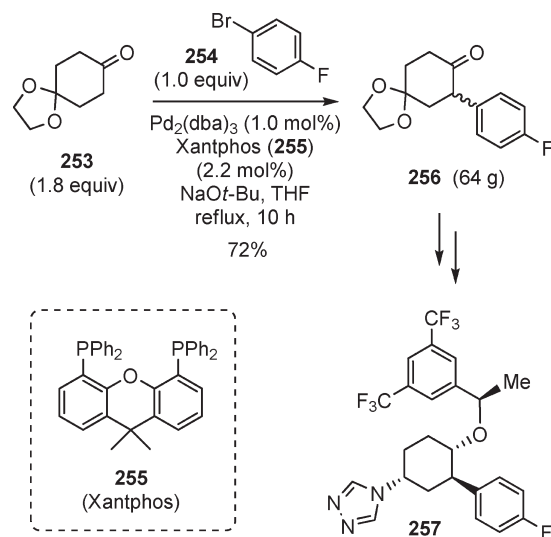
2.5. Enolate Arylation

The transition metal-catalyzed α -arylation of carbonyl groups has received considerable attention over the past three decades.¹³⁵ Early reports on the Ni- or Pd-catalyzed arylation of K,¹³⁶ Li,¹³⁶ Zn,¹³⁷ and Sn¹³⁸ enolates gave rise to more general methods in recent years.¹³⁹ Palladium is currently the transition metal catalyst of choice, and the scope of this transformation has been expanded to encompass the enolates of amides, esters, nitriles, cyano esters, β -keto esters, and malonates. The alkenylation of enolate-type nucleophiles has also been reported.¹⁴⁰

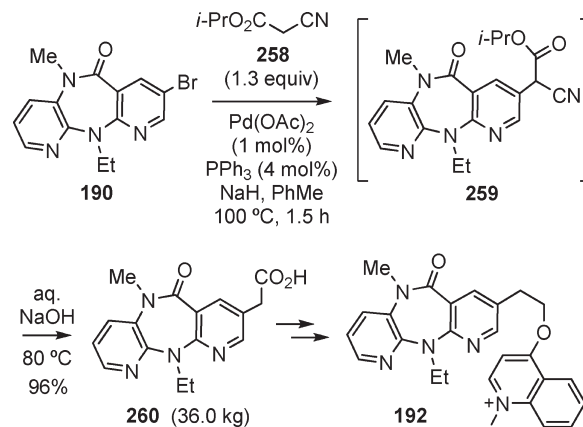
Dirat and co-workers at Merck Sharp & Dohme utilized the α -arylation of cyclohexanone **253** with 1-bromo-4-fluorobenzene (**254**) to prepare intermediates to novel NK₁ antagonists such as **257** (Scheme 59).¹⁴¹ A mixture of cyclohexanone, $\text{Pd}_2(\text{dba})_3$, Xantphos (**255**), and NaOt-Bu in THF was degassed by bubbling nitrogen through the mixture for 20 min. The degassed mixture was then heated to reflux, and bromide **254** was added. After reaction completion, the mixture was cooled to room temperature and partitioned between ethyl acetate and water for aqueous workup, and racemic **256** was isolated via silica gel chromatography in 72% yield.

Busacca and co-workers at Boehringer Ingelheim employed a Pd-catalyzed enolate arylation for their synthesis of **192**, an analogue of HIV non-nucleoside reverse transcriptase inhibitor nevirapine (Scheme 60).¹⁰³ The first step of this one-pot, arylation–decarboxylation sequence coupled aryl bromide **190** and isopropyl cyanoacetate (**258**) to form intermediate **192** using Beletskaya¹⁴² conditions: $\text{Pd}(\text{OAc})_2$, PPh_3 , and

Scheme 59

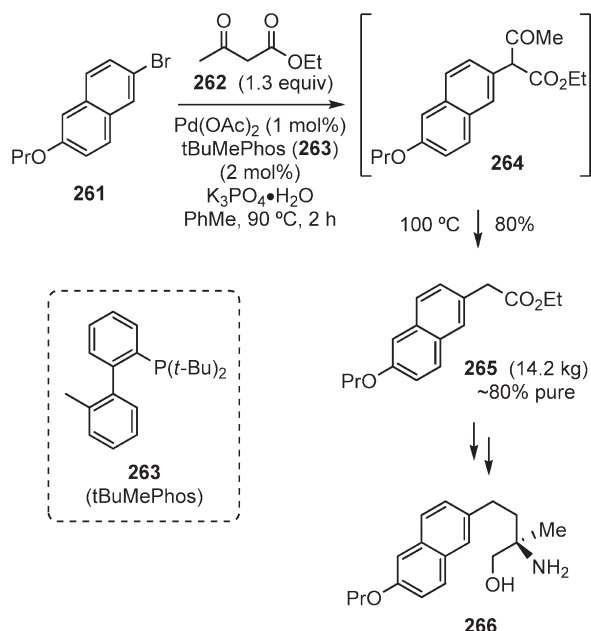


Scheme 60



NaH in heated toluene. Isopropyl cyanoacetate was a surrogate for diethylmalonate in this coupling; the latter successfully participated in arylation but only with Buchwald biphenyl ligands¹⁴³ (potentially expensive) or $\text{P}(t\text{-Bu})_3$ (expensive and pyrophoric). The slow addition of **258** to a mixture of NaH and the other reaction components at 60 °C allowed for control over deprotonation (and accompanying H₂ and heat generation), and then increasing the temperature to 100 °C effected the carbon–carbon bond formation to generate intermediate **259** (degassing prior to heating was necessary to avoid oxidation). After complete arylation, the mixture was cooled to 35 °C and residual NaH was quenched with *i*-PrOH. Quenching with alcohol was essential, as aqueous quench led to insoluble clusters that were difficult to disperse. The subsequent addition of aqueous NaOH solution and heating to 80 °C saponified the isopropyl ester with ensuing decarboxylation and hydrolyzed the nitrile to acid **260**. It was necessary to maintain hydroxide concentrations below 1 M to avoid hydrolysis of the lactam linkage. Reaction workup acidified the solution to pH 3.3 with H₂SO₄, which precipitated the product for isolation via centrifugation. This arylation–decarboxylation process provided 36.0 kg of **260** for an outstanding 96% overall yield.

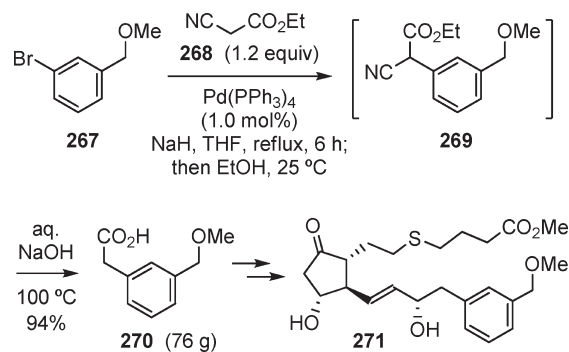
Scheme 61



Prasad and co-workers at Novartis incorporated the arylation of ethyl acetoacetate (**262**) into their scale-up of immunomodulator analogue **266** (Scheme 61).¹⁴⁴ The coupling of bromonaphthalene **261** and **262** via $\text{Pd}(\text{OAc})_2$, *t*BuMePhos (**263**), and K_3PO_4 monohydrate in toluene at 90 °C produced **264** as the immediate product. Deacylation to **265** was then effected by increasing the reaction temperature to 100 °C. This stepwise heating was necessary to suppress the degradation of bromonaphthalene to the desbromo byproduct; prematurely heating the initial coupling at 100 °C led to 15% desbromo-**261** (<2% at 90 °C), which was difficult to purge. The deacylation was promoted by water, and thus K_3PO_4 monohydrate was preferred to anhydrous base. After complete deacylation of **264** to **265**, the latter was isolated as an oil with ca. 80% purity after aqueous workup followed by Celite filtration and concentration of the organic layer.

Ohta and co-workers at Ono Pharmaceutical Group incorporated the arylation of ethyl cyanoacetate (**268**) into their improved synthesis of prostaglandin **271**, a highly selective EP4-receptor agonist and possible treatment for osteoporosis (Scheme 62).¹⁴⁵ Ethyl cyanoacetate was added to a slurry of NaH in THF while maintaining a temperature below 15 °C, and the resulting sodium enolate was treated with a solution of $\text{Pd}(\text{PPh}_3)_4$ and aryl bromide **267** in THF and heated to reflux. After the coupling to generate intermediate **269** proceeded to completion, the reaction mixture was cooled and charged with EtOH to quench residual NaH. The reaction mixture was partially concentrated, charged with aqueous NaOH solution (2 M), and heated at 100 °C (with solvent removal) to complete ester saponification, decarboxylation, and nitrile hydrolysis within 4 h. By comparison, the malononitrile analogue of **269**—from exploring malononitrile as an alternative to ethyl cyanoacetate—required three days for hydrolysis and decarboxylation under similar conditions. The resulting sodium salt of **270** in water was cooled and diluted with 6 M aqueous HCl until pH 2–3. Acid **270** was extracted into EtOAc and isolated as a yellow oil via solvent concentration without further purification. This arylation–decarboxylation proceeded in 94% overall yield to furnish 76 g of drug intermediate.

Scheme 62



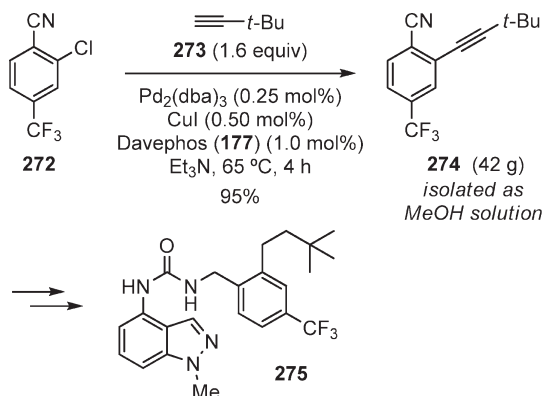
2.6. Sonogashira Coupling

The Cu(I)-mediated coupling of terminal alkynes and aryl halides (via stoichiometric copper acetylides) was first reported in 1963 by Castro and Stephens.¹⁴⁶ In 1975, Sonogashira reported the mild coupling of acetylene gas and aryl halides using a combination of substoichiometric Cu and Pd cocatalysts;¹⁴⁷ the same year, Cassar^{148a} and Dieck and Heck^{148b} independently reported similar Pd-catalyzed transformations in the absence of copper under harsher conditions. Since then, the copper and palladium cocatalyzed Sonogashira reaction, also known as the Sonogashira–Hagihara reaction, has become arguably the most useful method for preparing conjugated arenynes and conjugated enynes through the coupling of terminal alkynes and sp^2 -hybridized carbons (e.g., aryl, heteroaryl, and alkenyl halides).¹⁴⁹ The resulting products are important compounds for the synthesis of natural products, agrochemicals, molecular materials, and pharmaceuticals. Advantages of the Sonogashira reaction include its technical simplicity, efficiency, functional group compatibility, and high yields. Although a combination of Cu/Pd is the typical catalyst system, this coupling can also be promoted by other metal/ligand complexes;¹⁵⁰ however, traces of Cu or Pd in alternative metal sources may contribute to reactivity.

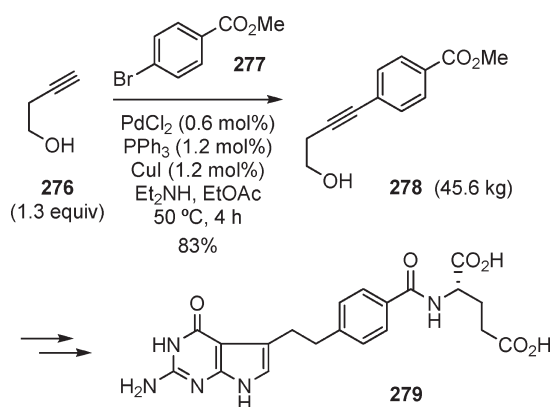
Applications of the Sonogashira reaction have been recently reviewed.¹⁵¹ Typically, electron-rich acetylenes couple under milder conditions than electron-poor acetylenes, and a common impurity from Sonogashira reactions is the diyne from homocoupling of the alkyne. Homocoupling arises via double transmetalation of the alkyne to $\text{Pd}(\text{II})$ followed by reductive elimination of the $\text{Pd}(\text{II})$ –(bis)alkyne species. This side reaction can often be limited by minimizing $\text{Pd}(\text{II})$ via degassing reaction mixtures to remove oxygen and by employing high concentrations of a secondary or tertiary amine base to reduce $\text{Pd}(\text{II})$ to $\text{Pd}(0)$.

Yu and co-workers at Abbott Laboratories commenced a synthetic route to TRPV1 receptor antagonist **275** with the Sonogashira coupling of aryl chloride **272** and *tert*-butylacetylene (Scheme 63).¹⁵² Typically, aryl chlorides exhibit poor reactivity in Sonogashira reactions; however, chloride **272** is highly activated by its electron-withdrawing trifluoromethyl and nitrile groups, and its coupling proceeded well with very low catalyst loading (0.25 mol% Pd; 0.50 mol% Cu) using the hindered and electron-rich Davephos ligand⁹⁹ (structure in Scheme 40) and neat Et_3N as solvent. (Again, the large excess of amine should work to suppress homocoupling by reducing $\text{Pd}(\text{II})$ to $\text{Pd}(0)$, and slower reaction rates were observed when using THF as cosolvent.) The reaction mixture was degassed and heated to

Scheme 63



Scheme 64

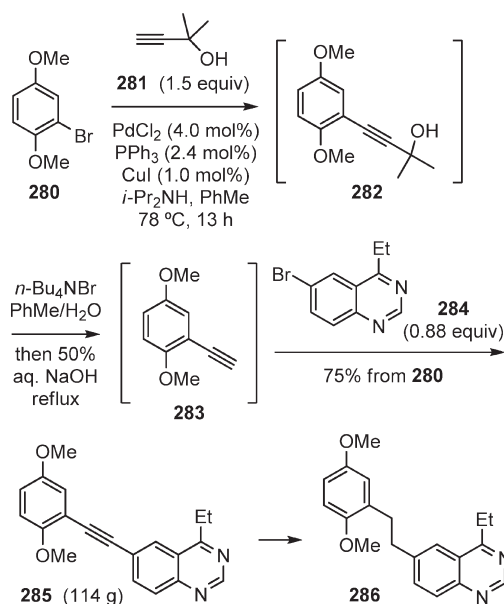


65 °C, and *tert*-butylacetylene was added slowly over 2 h to minimize alkyne homocoupling. The resulting solution was heated for another 2 h before workup. These conditions provided Sonogashira product **274** in 95% yield (as measured by assay). The coupling product was not isolated but rather telescoped as a solution in methanol into the subsequent acetylene hydrogenation.

Barnett and co-workers at Eli Lilly began their synthesis of antifolate **279**, an antitumor agent, with the large-scale Sonogashira coupling of 3-butyn-1-ol (**276**) and bromide **277** (Scheme 64).¹⁵³ This straightforward reaction with low catalyst loadings (0.6 mol% Pd, 1.2 mol% Cu) in EtOAc proceeded to completion within 4 h at 50 °C. Filtration of the reaction mixture removed solid metals and ammonium salts, and the filtrate was treated with Deloxan THP resin to scavenge residual Pd. Crystallization of the coupling product from EtOAc/heptane provided 45.6 kg of Sonogashira product **278**. Subsequent alkyne reduction formed the aliphatic carbon tether connecting the aromatic rings of **279**.

Prasad and co-workers at Novartis developed an elegant process for the one-pot coupling of aryl bromide **280** and heteroaryl bromide **284** via stepwise Sonogashira reactions with an acetylene linker (masked as 2-methyl-3-butyn-2-ol, an inexpensive ethyne surrogate) for the synthesis of antimetabolic agent **286**.¹⁵⁴ A thorough evaluation of several catalysts, ligands, and bases led to the conditions shown in Scheme 65 for the coupling of aryl bromide **280** and protected acetylene **281**. After forming the initial Sonogashira product **282**, the reaction mixture was treated with a solution of heteroaryl bromide **284** in toluene

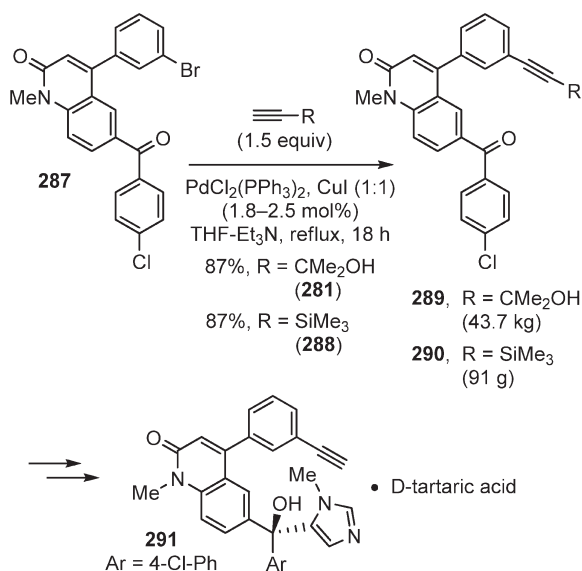
Scheme 65



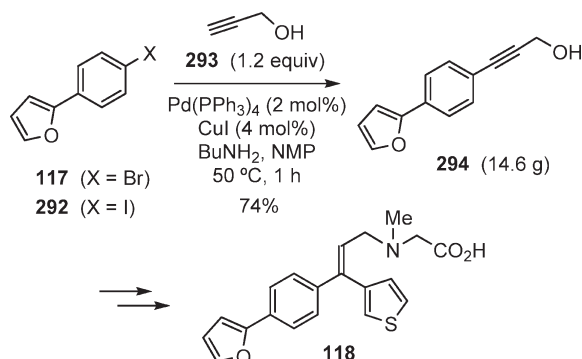
and water, and subsequent addition of 50% aqueous NaOH unmasked terminal alkyne **283** (with the formation of acetone) in the presence of phase-transfer catalyst *n*-Bu₄NBr. The liberated alkyne and bromide **284** then underwent a coupling reaction to form the double Sonogashira adduct **285**. The efficiency of hydroxide ion transport between the aqueous and organic phases affected the rate of the second coupling, and reactions in the plant with baffles and higher tip speeds had better mixing and improved rates compared to laboratory-scale runs. In addition, all reactant solutions required degassing to avoid catalyst deactivation. Upon workup, the phases were split and the organic layer was washed with 30% aqueous hydrogen peroxide solution to convert phosphine ligand to the corresponding oxide. The resulting heavy metals were scavenged with *N*-acetylcysteine, which retained Pd/Cu in the mother liquor solution during the crystallization of **285**. As a result, **285** was isolated in excellent 75% yield (based on **280**) with only 7 ppm Pd and <1 ppm Cu.

Couturier and co-workers at Pfizer developed the Sonogashira coupling of bromide **287** and protected acetylenes for the production of intermediates to quinolinone salt **291**, a farnesyl transferase inhibitor for the treatment of cancer (Scheme 66).¹⁵⁵ The coupling of **287** and 2-methyl-3-butyn-2-ol (**281**) was catalyzed by 2.5 mol% Pd/Cu in THF/Et₃N (2:1) at reflux, and the high concentration of amine presumably maintained a reduced Pd catalyst (when not active in the catalytic cycle) to avoid alkyne homocoupling. Darco treatment of the reaction mixture followed by solvent exchange and crystallization furnished ~44 kg of product **289** (87% yield). Unfortunately, the dimethyl(hydroxy)methyl protecting group of **289** proved incompatible with downstream chemistry, and its removal (traditionally requiring highly alkaline conditions) could not be accomplished without substantial byproduct formation. As a result, a second iteration of this process was developed in which bromide **287** was coupled with trimethylsilylacetylene (**288**) in 87% yield to afford 91 g of silylacetylene **290**. The silyl protecting group was compatible with downstream reactions and later removed without complications.

Scheme 66



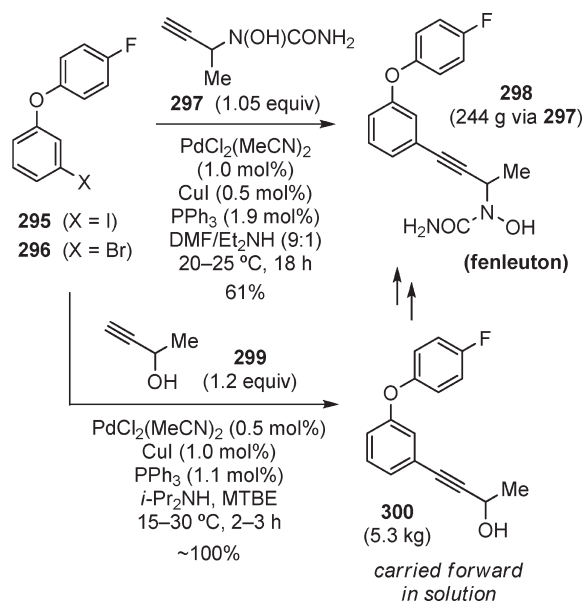
Scheme 67



Houpis and co-workers at Johnson & Johnson prepared intermediate **294** via Sonogashira reaction en route to drug candidate **118** (Scheme 67).⁷⁵ The coupling of aryl bromide **117** and propargyl alcohol (**293**) was complicated by the potential for acetylene dimerization at the elevated temperatures typically required for aryl bromide participation in Sonogashira reactions. Alkyne dimerization was suppressed by degassing to purge O₂ and by limiting the acetylene concentration via slow addition of propargyl alcohol. After an extensive screen of catalysts and reaction conditions, the optimized procedure added propargyl alcohol to a degassed mixture of bromide **117**, Pd(PPh₃)₄, CuI, and butylamine in NMP at 50 °C. The coupling mixture was not heated above 50 °C to avoid a previously observed and uncontrolled exotherm that developed at 70 °C, spiked the temperature to 140 °C, and resulted in dark polymeric material. After reaction completion, most of the Cu was scavenged via aqueous NH₃ washes. Treatment with SiliaBond and activated carbon purged residual Pd and Cu, and the coupling product **294** was crystallized from toluene/heptane with 120–150 ppm Pd and <20 ppm Cu.

The Sonogashira reaction of iodide **292** and propargyl alcohol (**293**) also provided **294** in high yield; however, **292** was not commercially available at the time of this study, and its use as a coupling partner in this reaction was abandoned.

Scheme 68

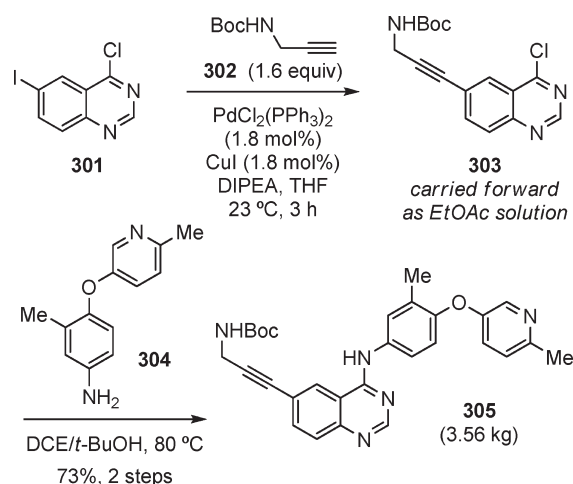


Thomas and co-workers at Abbott Laboratories incorporated Sonogashira couplings into separate processes for the scale-up of fenleuton (**298**), a 5-lipoxygenase inhibitor developed as the racemate (Scheme 68).¹⁵⁶ Their most convergent process coupled iodide **295** and alkyne **297** in the final, API-forming step.¹⁵⁷ The reaction was carried out using low loadings of Pd (1.0 mol%) and Cu (0.5 mol%) with PPh₃ additive (1.9 mol%) in a mixture of DMF and diethylamine at room temperature. Upon complete conversion, the API **298** was precipitated from solution via water dilution and purified by way of a protracted sequence of alternating recrystallizations (three) and carbon treatments (two) to provide 244 g of fenleuton with <20 ppm Pd/Cu. The high costs associated with this arduous workup (necessary to purge Pd/Cu) prompted this group to develop an alternative process that did not use heavy metals in the final chemical step. Their second-generation synthesis coupled iodide **295** and 3-butyn-2-ol (**299**) earlier in the route to fenleuton (Scheme 68). 3-Butyn-2-ol was used as an aqueous 55% solution (a cheaper alternative to the neat reagent), and coupling product **300** was generated in quantitative yield (5.3 kg). The solution of **300** was treated with aqueous ammonia (to sequester metals), washed with acid and base, dried with magnesium sulfate, and carried forward without product isolation.

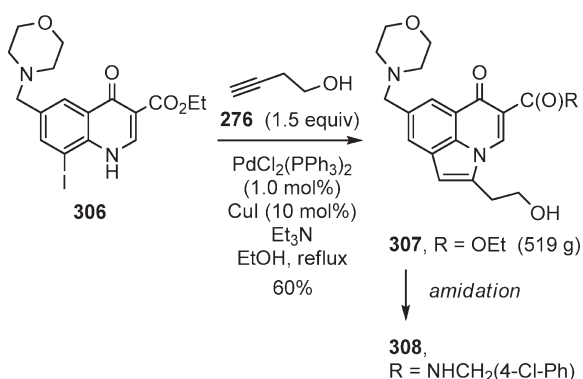
Ripin and co-workers at Pfizer used a Sonogashira reaction in their initial multikilogram synthesis of an oncology candidate, for which **305** is a key intermediate (Scheme 69).¹⁵⁸ Conditions for the coupling of aryl iodide **301** and alkyne **302** (1.6 equiv; enough acetylene to compete with homocoupling) were adopted from the original Discovery route with minor modifications. Heat generation from this exothermic coupling on plant scale was controlled by lowering the Pd/Cu levels. After reaction completion and solvent swapping, a solution of coupling product **303** in EtOAc was treated with Darco to purge heavy metals. Without isolation, **303** was taken into a 1:1 mixture of DCE and *t*-BuOH and treated with 1 equiv of aniline **304** (based on the amount of Sonogashira product calculated from an HPLC potency assay). The resulting S_NAr product **305** was isolated via filtration in 73% yield (3.56 kg) over two steps.

Dorow and co-workers at Pfizer incorporated a tandem Sonogashira coupling-cyclization into their preparation of

Scheme 69



Scheme 70

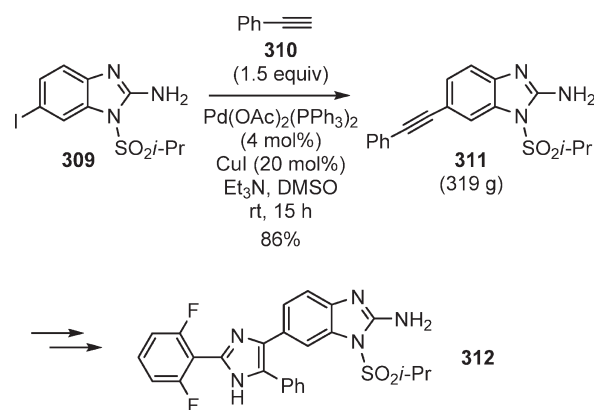


pyrrolquinolone **308**, a compound with promising activity against herpes virus DNA polymerases (Scheme 70).¹⁵⁹ The coupling of aryl iodide **306** and 3-butyn-1-ol (**276**) presumably generates an initial arenyn (not detected) that cyclizes rapidly to pyrrole **307** under reaction conditions. To compensate for alkyne homocoupling, 1.5 equiv of 3-butyn-1-ol were required for the complete conversion of **306** to **307**. Several metal scavengers were evaluated for Pd/Cu removal; the best results were realized by dissolving crude product in aqueous HCl and stirring over Deloxan THP. Crystallization from MeCN/MTBE provided pyrrole **307** with only 20 ppm Pd and 2 ppm Cu.

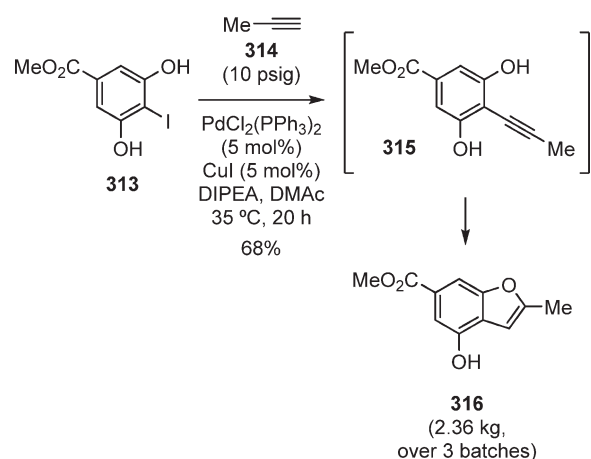
Magnus and co-workers at Eli Lilly incorporated the coupling of iodobenzimidazole **309** and phenylacetylene (**310**) into their scaleup of **312**, a p38 MAP kinase inhibitor with anti-inflammation potential (Scheme 71).¹⁶⁰ This Sonogashira reaction of **309** and **310** in DMSO required high loadings of catalyst (4 mol% Pd, 20 mol% Cu). These high catalyst loadings might be necessary to overcome possible catalyst inhibition from the free amine in the substrate, and using less Pd catalyst adversely affected the rate of coupling. After iodide **309** was consumed, the catalyst was precipitated by water dilution of the reaction mixture and removed via filtration. Dilution of the filtrate with additional water then precipitated coupling product **311** in 86% yield along with diyne from the homocoupling of phenylacetylene. This diyne byproduct did not interfere with subsequent chemistry and was purged downstream.

Berliner and co-workers at Pfizer developed the Sonogashira reaction of propyne gas and iodoresorcinol **313** for the synthesis

Scheme 71



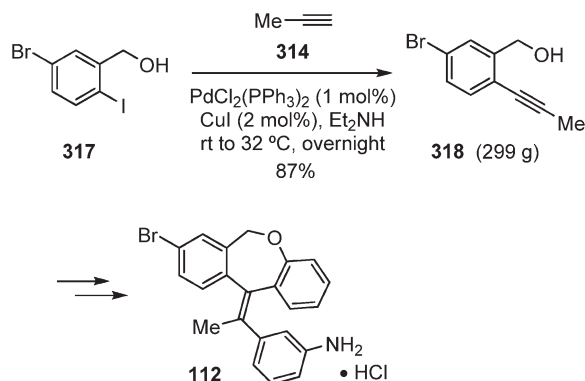
Scheme 72



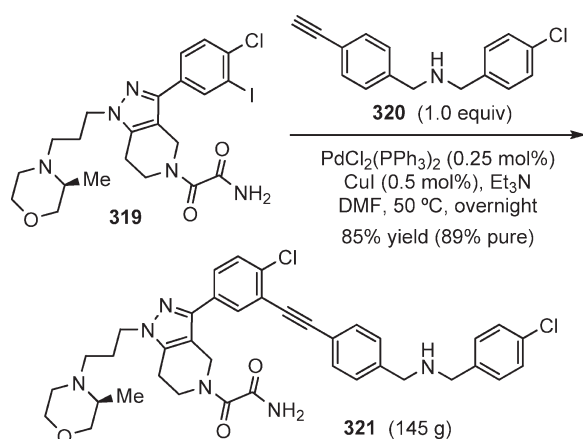
of 4-hydroxy-2-methylbenzofuran **316**, a core intermediate to several compounds of pharmaceutical interest (Scheme 72).¹⁶¹ The coupling of iodoresorcinol **313** and propyne presumably affords alkyne intermediate **315** (not detected), which cyclizes to benzofuran under reaction conditions. This transformation was optimized with respect to pressure, temperature, base, and solvent in standard hydrogenation screening equipment. Calculations by Berliner and co-workers suggested DMAc as the best solvent for propyne solubility (~25 wt% at 10 psig, 35 °C), and these calculations were in agreement with observations that couplings in DMAc provided higher yields of benzofuran with less byproduct formation. Scale-up was conducted in a 30-L Hastelloy pressure reactor under 10 psig of propyne. Reaction workup started with the venting of propyne from the vessel followed by sparging with nitrogen gas. Water dilution prompted the off-gassing of dissolved propyne from solution, and subsequent treatment with saturated aqueous ammonium chloride solution precipitated the transition metals and alkyne oligomers as dark brown tars that were removed via 1% EtOAc/heptane washes. Finally, benzofuran **316** was extracted into EtOAc and crystallized from MeOH/H₂O with <50 ppm Pd. This process was carried out three times on 1.67-kg scale to provide 2.36 kg of 2-methylbenzofuran for a combined 68% yield.

Another Sonogashira coupling with propyne was incorporated into the scale-up of **112**, a key intermediate in the synthesis of a selective hormone receptor modulator, by Richey and Yu at Eli Lilly (Scheme 73).⁷³ In a standard 12-L, three-necked, round-

Scheme 73



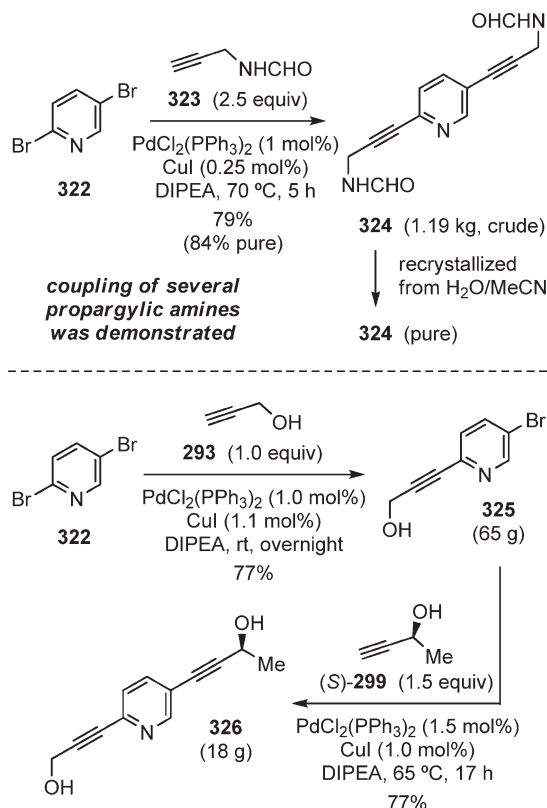
Scheme 74



bottomed flask, a stream of propyne gas was bubbled through a solution of aryl iodide **317**, $\text{PdCl}_2(\text{PPh}_3)_2$, and CuI in diethylamine for 45 min,¹⁶² and the resulting mixture was stirred overnight under a standard nitrogen inlet without special precautions to avoid propyne evaporation. The reaction mixture was then filtered through Celite and concentrated to a dark brown solid. Purification of **318** via silica gel chromatography provided the Sonogashira product as a pale yellow solid. The Sonogashira reaction of **317** appears chemoselective for the iodide, as Richey and Yu did not mention byproducts via coupling at the bromide (which is presumably suppressed in part by maintaining low reaction temperatures).

Deng and co-workers at Johnson & Johnson coupled aryl iodide **319** and alkyne **320** to complete their synthesis of **321**, a cysteine protease inhibitor of cathepsin S and potential treatment for various immunological disorders (Scheme 74).¹⁶³ The Sonogashira conditions used for scale-up were optimized considerably from a previous procedure. The catalyst loading was reduced substantially from 10 mol% each Pd/Cu to 0.25 mol% Pd and 0.5 mol% Cu , the solvent was switched from THF to DMF, and the temperature was increased from room temperature to 50 °C. The reaction mixture required degassing to avoid catalyst decomposition. After complete conversion, arenyne **321** was precipitated by water dilution, extracted into EtOAc, and isolated via solvent concentration as an amorphous solid in 85% yield (89% purity by HPLC). Purification on silica gel provided **321** with >98% purity but only 60% recovery, as the drug substance slowly decomposed during chromatography.

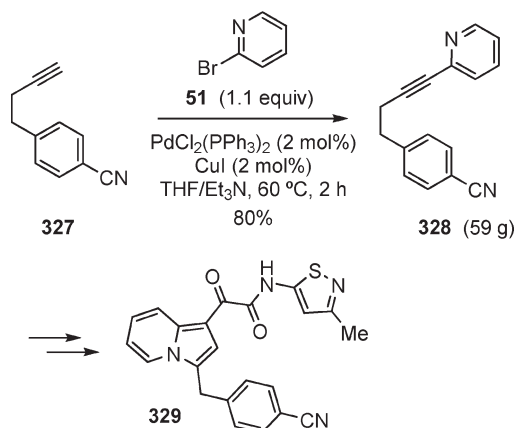
Scheme 75



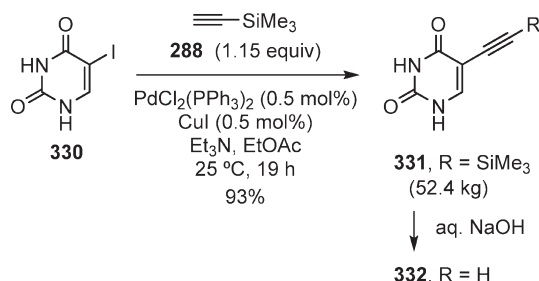
Hartner and co-workers at Merck developed a series of Sonogashira reactions in which various alkynes are coupled with 2,5-dibromopyridine (**322**) at both bromo positions for the preparation of key intermediates to $\alpha_v\beta_3$ antagonists, potential treatments for osteoporosis.¹⁶⁴ As outlined in Scheme 75, the coupling of dibromide **322** and protected propargylic amines such as **323** at 70 °C occurs at both the 2- and 5-bromo positions to provide bisacetylene **324**. The double adduct had low solubility in Hünig's base (solvent) and was isolated via direct filtration of the reaction mixture. Recrystallization of crude **324** from aqueous MeCN provided pure product. A stepwise approach to this double Sonogashira reaction was also reported for differentiation between the acetylenes coupled at the 2- and 5-positions of the pyridine. To this end, Scheme 75 shows the sequential coupling of dibromide **322** and propargylic alcohols **293** and (*S*)-**299**. At room temperature, the first coupling of **322** and propargyl alcohol (**293**) was specific for the 2-Br position to provide **325** with 98:2 mono/bis selectivity. Monoacetylene **325** was isolated via crystallization and subjected to a second coupling at the 5-bromopyridine with (*S*)-**299**. Compared to the first coupling at the 2-Br position, reaction at the 5-Br position (albeit with a bulkier alkyne) required higher temperature (65 °C) and slightly higher Pd loading (1.5 mol%). The resulting solution of bisacetylene **326** was filtered through neutral alumina and a sample of **326** was crystallized from *i*-PrOAc/toluene.

Sun and co-workers at Synta Pharmaceuticals incorporated the Sonogashira coupling of alkyne **327** and 2-bromopyridine (**51**) into an early synthetic route to **329**, a microtubule inhibitor with antitumor activity (Scheme 76).¹⁶⁵ The coupling proceeded smoothly in 1:1 THF/ Et_3N (another example of excess amine improving catalysis) at 60 °C with only a slight excess of aryl bromide (1.1 equiv) and 2 mol% of Pd and Cu catalysts. The

Scheme 76



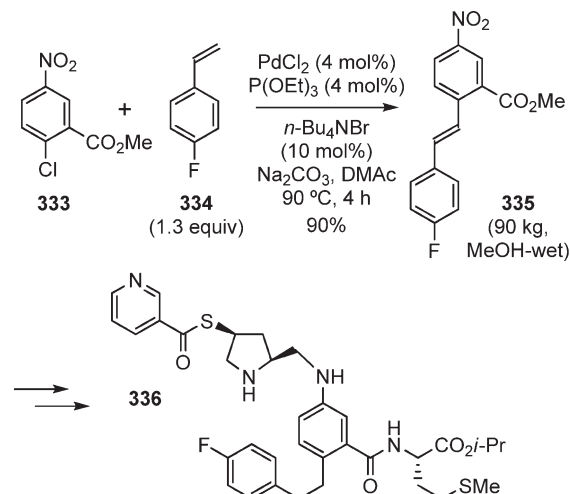
Scheme 77



reaction workup partitioned the mixture between water and EtOAc , and the organic phase was dried and concentrated to furnish the crude coupling product **328** as a brown solid. Crude **328** was triturated with heptane to obtain 59 g of arenyne as an off-white solid. This Sonogashira route was later abandoned in favor of alternative chemistries that avoided transition metals to circumvent regulatory requirements for Pd/Cu levels in drug substances.

Cooke and co-workers at GlaxoSmithKline optimized the Sonogashira coupling of 5-iodouracil (**330**) and trimethylsilylacetylene (**288**) to prepare intermediate **331** for the >60 kg synthesis of eniluracil (**332**), an enzyme inactivator that binds to dihydropyrimidine dehydrogenase to block the metabolism of anticancer drug 5-fluorouracil.¹⁶⁶ The conditions shown in Scheme 77 were optimized from an initial plant process by replacing PdCl_2 (insoluble in EtOAc) and PPh_3 with preformed $\text{PdCl}_2(\text{PPh}_3)_2$ and lowering the catalyst loadings considerably (1.5 to 0.5 mol% Pd; 10 to 0.5 mol% Cu). In addition, the reaction mixture was deoxygenated via three vacuum–nitrogen purge cycles (before alkyne addition) to avoid catalyst decomposition (and presumably homocoupling of the alkyne). These improvements led to a more robust and reproducible procedure that effected 95% conversion after 6 h. Coupling product **331** had very limited solubility in EtOAc and was isolated via direct filtration of the reaction mixture with 550 ppm Pd and 120 ppm Cu. Crude **331** was reslurried in water to remove triethylammonium salts and treated with 40–60 wt% charcoal in THF/MeOH at reflux to purge heavy metals, thus lowering residual Pd/Cu in purified **331** to 1.6 ppm Pd and <0.7 ppm Cu. Subsequent desilylation in aqueous NaOH afforded eniluracil (**332**).

Scheme 78



2.7. Heck Reaction

In the late 1960s, Heck discovered that the transmetalation of organomercury compounds provided arylpalladium salts that could be employed as substrates for several types of olefinic substitution reactions.² A few years later, Heck and Nolley^{2h} and Mizoroki et al.^{3a} independently found that organic halides could be coupled with olefins in the presence of catalytic Pd and base. This versatile transformation, known as the Heck reaction (or Mizoroki–Heck reaction), has become widely used for the synthesis of pharmaceuticals¹⁶⁷ and natural products,¹⁶⁸ as well as for other industrial applications.¹⁶⁹

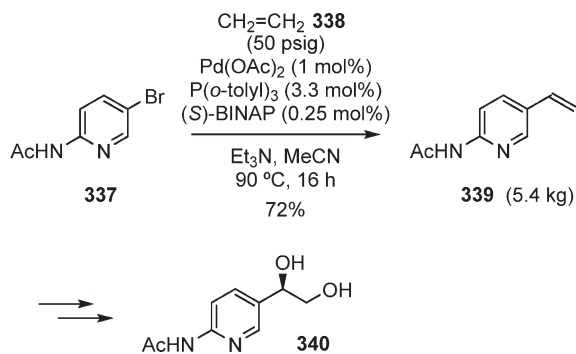
The Heck reaction has been reviewed extensively.¹⁷⁰ The mechanistic aspects^{19b,171} of this coupling have been well-documented, as have asymmetric¹⁷² and intramolecular¹⁷³ variations of this transformation. Originally, only aryl or alkenyl iodides and bromides were suitable coupling partners for the Heck reaction; however, recent advances have expanded the field to include triflates, carbonyl and sulfonyl chlorides, diazonium salts, iodonium salts, and chlorides as substrates.^{174–176}

Aryl bromides and iodides are the most common substrates in large-scale applications of the Heck reaction for the synthesis of pharmaceuticals, but examples with aryl chlorides can also be found. In addition, there are a few instances of intramolecular Heck reactions for the assembly of cyclic products.

2.7.1. Intermolecular Heck Reaction. Robinson and co-workers at AstraZeneca in the U.K. described the pilot plant synthesis of **336**, a novel, orally active antiproliferative agent for the treatment of breast cancer and other tumors (Scheme 78).¹⁷⁷ Intermediate **335** was prepared from the Heck reaction of methyl 2-chloro-5-nitrobenzoate (**333**) and 4-fluorostyrene (**334**). Typically, aryl chlorides have poor reactivity in the Heck reaction; however, **333** is strongly activated by the nitro and ester groups, and its coupling was effected using equimolar PdCl_2 and $\text{P}(\text{OEt})_3$ (4 mol% each) and $n\text{-Bu}_4\text{NBr}$ (10 mol%) in DMAc at 90 °C. Workup diluted the reaction mixture with toluene and filtered off insoluble materials. The concentrated filtrate was diluted with MeOH and cooled to precipitate **335** in 90% yield. This Heck product was carried into the next step as a MeOH-wet solid.

Raggon and Snyder at Pfizer reported the Heck coupling of bromopyridine **337** and ethylene gas (**338**) to prepare vinylpyridine **339**, a precursor to drug intermediate **340** (Scheme 79).¹⁷⁸

Scheme 79

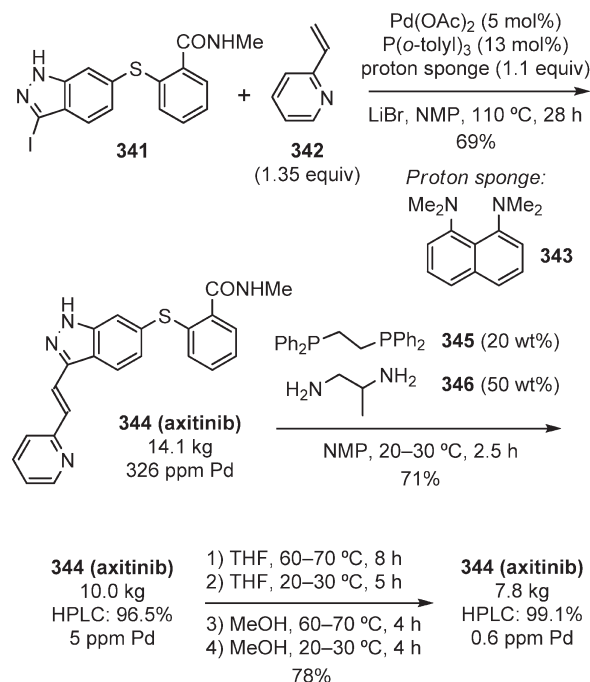


Initial runs employing $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tolyl})_3$ as the catalyst system with Et_3N in MeCN at 90 °C provided the Heck product **339** in the 37–66% range. The reaction tended to stall with the formation of Pd black on the reactor walls, and additional charges of Pd catalyst and ligand were necessary to bring the reaction to completion. Because BINAP had been previously employed in asymmetric Heck reactions,^{172b,179} the researchers explored this ligand for their vinylpyridine synthesis. When 0.5 mol% of (*S*)-BINAP¹⁸⁰ was added to $\text{Pd}(\text{OAc})_2$ (1 mol%), $\text{P}(\text{o-tolyl})_3$ (3.3 mol%), and Et_3N in MeCN under 50 psig of ethylene, the reaction was complete in 16 h (versus 3 days without (*S*)-BINAP) and provided **339** in 58% yield. Interestingly, the reaction was sluggish with (*S*)-BINAP in the absence of $\text{P}(\text{o-tolyl})_3$. After additional optimization, the final protocol heated a mixture of bromopyridine **337**, 1 mol% $\text{Pd}(\text{OAc})_2$, 3.3 mol% $\text{P}(\text{o-tolyl})_3$, and 0.25 mol% (*S*)-BINAP in degassed DMF at 90 °C under 50 psig of ethylene gas. Upon reaction workup, the mixture was filtered through Celite and concentrated. Heck product **339** was obtained in 72% yield after crystallization from water and reslurries in water and hexanes. As expected, racemic BINAP performed equally well and was considerably less costly.

Flahive and co-workers at Pfizer have described the process development for the preparation of **344** (axitinib), an inhibitor of vascular endothelial growth factor for the treatment of cancer (Scheme 80).¹² A very detailed account on efforts to efficiently remove residual Pd from the API was presented in this publication. The synthesis of **344** for phase II studies was completed with a Heck reaction of iodide **341** and 2-vinylpyridine (**342**). This coupling was effected using $\text{Pd}(\text{OAc})_2$ (5 mol%), $\text{P}(\text{o-tolyl})_3$ (13 mol%), LiBr, and proton sponge as base in NMP at 110 °C for 28 h. Polar solvents such as NMP and DMAc were required because of the low solubility of Heck product **344**; however, cysteine on silica was not a suitable metal scavenger in these solvents due to cysteine leaching from the solid support. Flahive and co-workers were able to purge Pd from **344** considerably by reslurrying the Heck product in various solvents, although neither 4:1 THF/MeOH, 4:1 MEK/ H_2O , nor 9:1 THF/ H_2O were able to lower Pd below the required goal of <20 ppm. Salt formation (e.g., AcOH, TsOH) and crystallization had no appreciable effect either.

Because of the low solubility of **344** in aqueous media, organic solvent-soluble Pd scavengers were explored as an alternative approach to purging metal from the API. The solvent mixture NMP/MeOH was selected for this screen, as **344** is very soluble in NMP and crystallized with MeOH addition. Of all the metal scavengers tested (EDTA, *N*-acetyl-cysteine, thiosalicylic acid, 1,2-ethylenediamine, 1,2-diaminopropane, diethylenetriamine,

Scheme 80

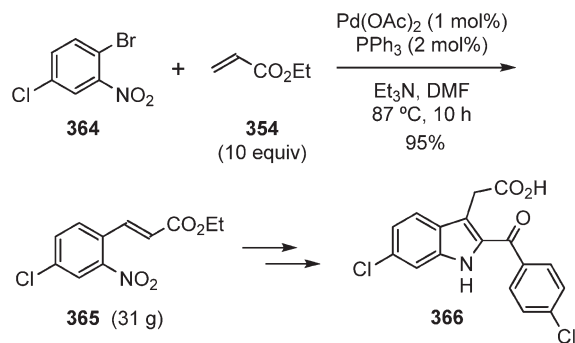


triethylenetetramine, tris(2-aminoethyl)amine), the diamine series provided the best results and 1,2-diaminopropane was the leading candidate based on efficiency and cost. Because the final Pd content varied between batches of **344**, even when the same scavenger was employed (perhaps due to variations in the Pd oxidation state), a combination of scavengers was tested.¹⁸¹ Thus, some modest additive effects were observed for 1,2-ethylenediamine and 1,2-bis(diphenylphosphino)ethane and silica-supported reagents Si-TAAcOH (supported EDTA) and Si-Thiol (supported ethanethiol from Silicycle Inc.). A combination of 1,2-diaminopropane/1,2-bis(diphenylphosphino)ethane was finally chosen for the pilot plant campaign, as these scavengers consistently provided **344** with <20 ppm Pd. The final protocol stirred the API in 5 volumes of NMP over 20 wt% of 1,2-bis(diphenylphosphino)ethane (**345**) and 50 wt% of 1,2-diaminopropane (**346**). MeOH was added (40 volumes) to crystallize the API, and after granulating for 18 h, the solids were filtered and isolated with only 5 ppm of residual Pd. Subsequent slurries in THF (10 volumes) and MeOH (10 volumes) increased the chemical purity to >99% and further reduced the Pd level to only 0.6 ppm.

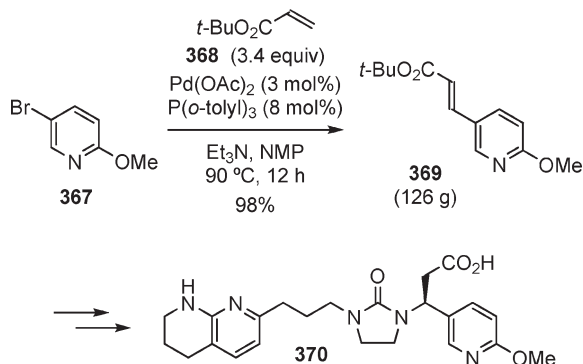
Bold and co-workers at Ciba-Geigy AG in Switzerland used a Heck reaction to assemble **232** as an intermediate to potential HIV-1 protease inhibitors of type **349** (Scheme 81).¹²⁴ In a transformation that might be confused for C–H activation, the Heck coupling of 4-bromobenzaldehyde (**347**) and thiazole (**348**) was catalyzed by $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) and KOAc in DMAc at 150 °C in a sealed tube.¹⁸² After filtration and aqueous workup, the crude residue was purified by chromatography to afford coupling product **232** in 61% yield.

Gauthier and co-workers at Merck effected the Heck reaction of imidazotriazine **350** and aryl bromide **351** to complete their synthesis of orally active $\alpha_{2/3}$ -selective GABA_A agonist **49**, a drug candidate for the treatment of anxiety, convulsions, and cognitive disorders (Scheme 82).⁴⁸ Because of its low cost and robustness, the $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ catalyst system was chosen for the coupling

Scheme 85



Scheme 86

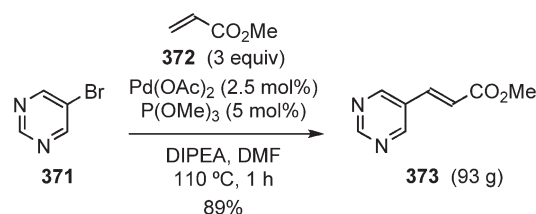


revealed that ligand S-Phos²⁶ provided the Heck product **361** in 69% yield after chromatography, and subsequent treatment with NaOEt/EtOH cyclized the Heck product to naphthyridinone **362**. During process development, the researchers found that a combination of P(*t*-Bu)₃ and aromatic solvents promoted the one-pot formation of **362** from **359** and **360** under Heck conditions, as shown in Scheme 84. Optimized conditions for this tandem coupling–cyclization employed Pd(OAc)₂ (2 mol%), P(*t*-Bu)₃·HBF₄ (4 mol%), (*c*-Hex)₂NMe as base,^{175a} and cumene as solvent. Applying these conditions to chloropyridine **359** and *n*-butyl acrylate at 150 °C for 4–5 h provided the cyclized product **362** in 76% yield. Voight and co-workers proposed that a palladium hydride species facilitated the requisite isomerization of *trans*-**361** to *cis*-**361** prior to cyclization.

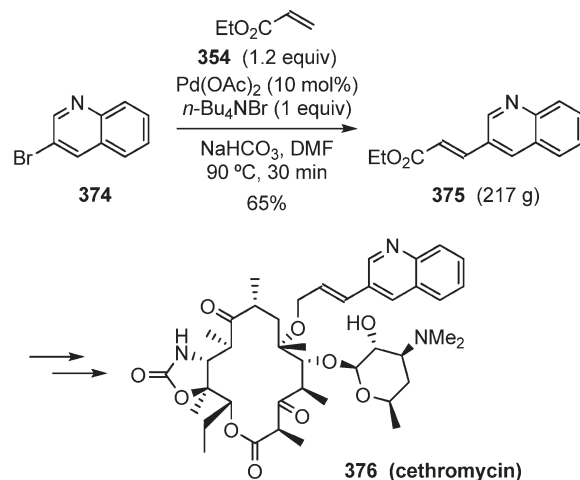
Caron and co-workers at Pfizer have reported the preparation of chloroindole **366**, a selective cyclooxygenase 2 (COX-2) inhibitor with potential applications to treat pain and anti-inflammatory-related disorders (Scheme 85).¹⁸⁸ The Heck coupling of aryl bromide **364** and a large excess of ethyl acrylate (**354**) installed the carbon side chain of indole precursor **365**. The reaction was effected with a Pd(OAc)₂/PPh₃ catalyst system and Et₃N in DMF at 87 °C for 10 h. Aqueous workup and crystallization from hexanes provided cinnamate **365** in 95% yield.

Yasuda and co-workers at Merck incorporated a Heck reaction into their synthesis of α_vβ₃ integrin antagonist **370**, a potential treatment for osteoporosis (Scheme 86).¹⁸⁹ 5-Bromo-2-methoxypyridine (**367**), obtained via bromination of 2-methoxypyridine,¹⁹⁰ and *tert*-butyl acrylate (**368**) were coupled via Pd(OAc)₂ and P(*o*-tolyl)₃ to provide intermediate **369** in near-quantitative yield after silica gel chromatography. The *tert*-butyl ester was chosen as a coupling partner to avoid

Scheme 87



Scheme 88

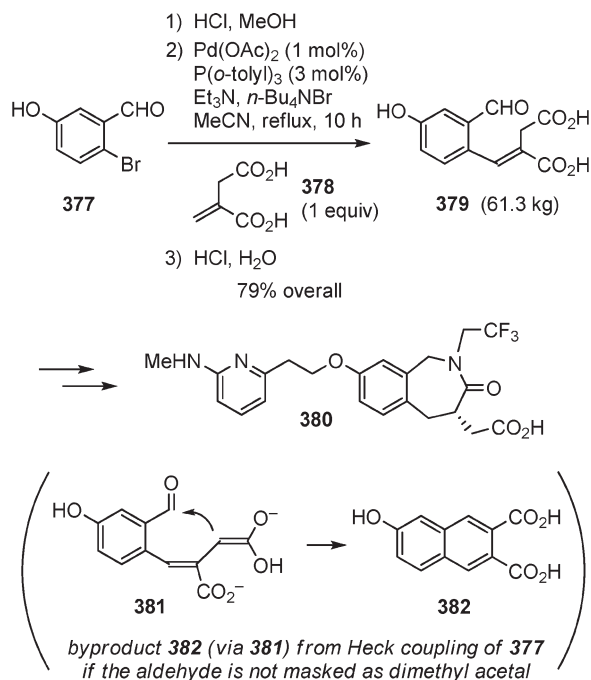


addition to the carbonyl, and the exothermic reaction was controlled by the slow addition of olefin to the reaction mixture at 90 °C. During the workup, a toluene solution of crude **369** was treated with aqueous NaOCl to oxidize the phosphine ligand, thus preventing catalyst poisoning in a subsequent catalytic hydrogenation.

Kwok and Virgilio at SynDesign developed a Heck coupling for the synthesis of methyl (heteroaryl)acrylates such as **373** as pharmaceutical intermediates (Scheme 87).¹⁹¹ Applying standard Heck conditions to heteroaromatic halides¹⁹² such as 5-bromopyrimidine (**371**) and methyl acrylate (**372**) often leads to poor yields of coupling product. On the basis of reports in which electron-rich and bulky phosphine^{175a,193} and phosphite ligands¹⁹⁴ produce highly active catalyst systems, Kwok and Virgilio explored several phosphorus-based ligands for the synthesis of **373**. A ligand screen identified P(OMe)₃ as optimal for this coupling, and its pairing with Pd(OAc)₂ effected the reaction of 5-bromopyrimidine (**371**) and methyl acrylate as shown in Scheme 87. The desired Heck product was crystallized from hexane/EtOAc in 89% yield. These conditions were applied to seven other heteroaromatic halides to afford yields in the 17–99% range.

Research groups at Abbott and Theravance collaborated on the synthesis of **376** (cethromycin), an antibiotic with superior potency against macrolide-resistant respiratory tract pathogens (Scheme 88).¹⁹⁵ The quinoline moiety on the API was assembled from the Heck reaction of 3-bromoquinoline (**374**) and ethyl acrylate (**354**) via 10 mol% Pd(OAc)₂, 1 equiv of *n*-Bu₄NBr, and NaHCO₃ in DMF at 90 °C for 30 min. The DMF solvent presumably serves as a ligand under these phosphine-free conditions, and the phase-transfer catalyst should also lend some stability

Scheme 89



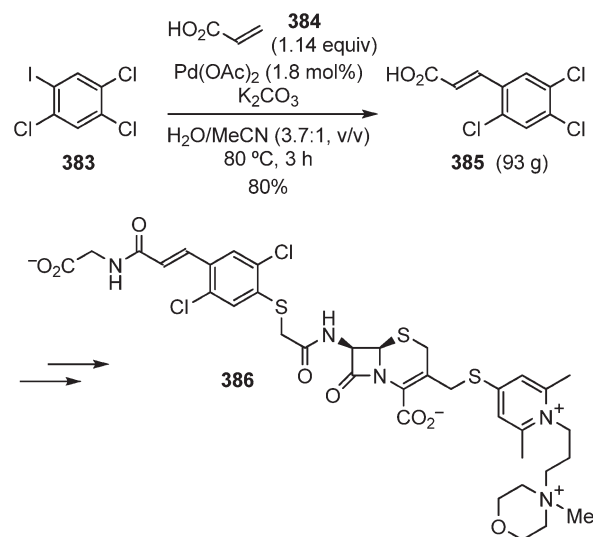
to the metal catalyst. After an aqueous workup, the desired quino-line-3-propenoic ester 375 was obtained in 65% yield.

Wallace and co-workers at GlaxoSmithKline have published the preparation of 2,4,9-trisubstituted-2-benzazepine-3-one 380, a potent second-generation $\alpha_v\beta_3$ receptor antagonist for the treatment of osteoporosis (Scheme 89).¹⁹⁶ Prior to the Heck coupling of aryl bromide 377 and itaconic acid (378), it was necessary to protect the aldehyde of 377 as the dimethyl acetal; otherwise, an intramolecular aldol reaction leading to naphthalene dicarboxylic acid 382 occurred under Heck reaction conditions. Once the acetal formation was complete (as monitored by ReactIR or ¹H NMR), the reaction mixture was treated with a MeCN solution of itaconic acid (378), Pd(OAc)₂/P(*o*-tolyl)₃, Et₃N, and *n*-Bu₄NBr (10 mol%) and heated at reflux for 10 h. This coupling of itaconic acid, a geminal disubstituted olefin, is expected to be less facile than typical Heck couplings of monosubstituted olefins. After reaction completion, acetal cleavage with aqueous HCl provided diacid 379. This product was extracted into aqueous KOH, washed with MTBE to remove organic-soluble impurities, reacidified, and crystallized from MTBE/MeCN to provide the desired drug intermediate as the exclusive (*E*)-isomer in 79% overall yield from 377.

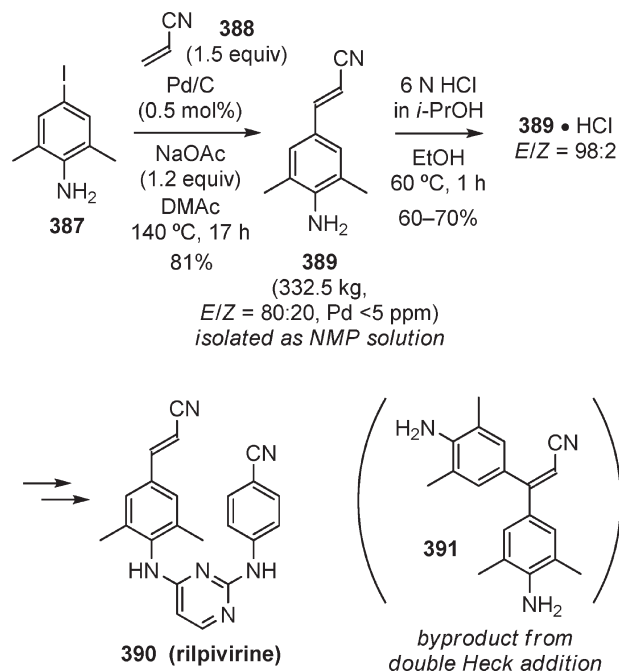
Researchers at Bristol–Myers Squibb have described the synthesis of double zwitterion 386, an antimethicillin resistant *Staphylococcus aureus* cephalosporin (Scheme 90).¹⁹⁷ To prepare intermediate 385, the Heck coupling of 2,4,5-trichloro-1-iodobenzene (383) and acrylic acid (384) was effected using Pd(OAc)₂ and K₂CO₃ in a H₂O/MeCN mixture at 80 °C for 3 h. After adjusting the pH to 9 with NaOH on workup and extracting the aqueous layer with EtOAc to remove organic impurities, acidification to pH 4 with 12 N HCl and further water dilution precipitated the cinnamic acid 385 in 80% yield.

Researchers at Johnson & Johnson in Belgium have described the industrial-scale preparation of intermediate 389 en route to rilpivirine (390), a potent non-nucleoside reversed transcriptase inhibitor developed as part of their HIV program (Scheme 91).¹⁹⁸ A very thorough study on the optimization of

Scheme 90



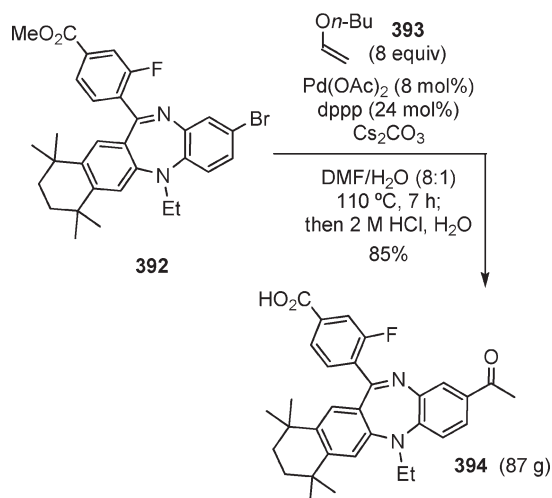
Scheme 91



the Heck reaction leading to 389 was undertaken to develop a robust process that could become part of the commercial route to 390.

Both 4-iodo-2,6-dimethylaniline (387) and its 4-bromo analogue were evaluated as coupling partners for acrylonitrile (388). When 4-bromo-2,6-dimethylaniline was employed (not shown), either Pd₂(dba)₃/P(*t*-Bu)₃ or Pd(OAc)₂/P(*o*-tolyl)₃ gave >90% conversion, and the addition of *n*-Bu₄NCl (1 equiv)¹⁹⁹ led to complete conversion. Because homogeneous catalysts provided high levels of residual Pd (6600 ppm for 389), Pd/C as a heterogeneous source of catalyst (10% Pd/C, wet)^{34,200} was tried in combination with phosphine ligands (P(*o*-tolyl)₃, P(*t*-Bu)₃·HBF₄) and similar conversions were obtained. The pilot plant conditions on 150-kg scale employed Pd/C (2.5 mol%), P(*o*-tolyl)₃ (5 mol%), *n*-Bu₄NCl (1 equiv), and NaOAc in DMAc

Scheme 92



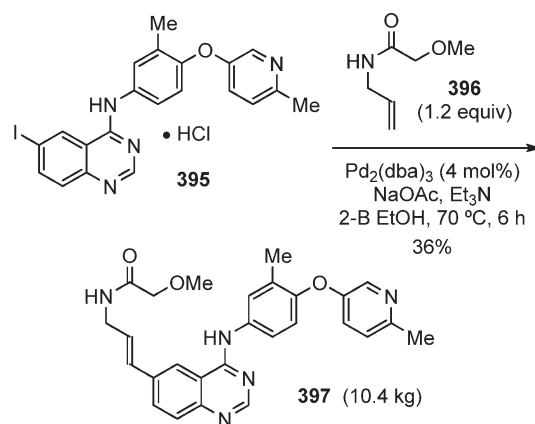
at 140 °C. Under these conditions, the Pd content in the Heck product **389** oscillated from 96 to 1196 ppm, and for the latter, a batch rework was required via formation of the free base and treatment with Si-Thiol. This high Pd level was attributed to poor washing of the cake after isolation through centrifugation.

When iodide **387** was tested as an alternative to the bromo analogue, the reaction proceeded well with 10% Pd/C (wet) without the need for phosphine ligands or ammonium salts, and byproducts desiodo-**387** and **391** from dehalogenation and double Heck addition, respectively, were each formed below 1%. As little as 0.1 mol% catalyst was enough to reach completion, but 0.5 mol% was used in the plant to ensure robustness. Because the reaction with iodide **387** showed a significant exotherm, the heat evolution was managed through the controlled addition of a DMAc solution of iodide and acrylonitrile to a suspension of Pd/C and NaOAc in DMAc at 140 °C. Upon reaction completion, the reaction mixture was passed through Dicalite to remove catalyst and purge Pd in the filtrate to 500 ppm. After aqueous workup, an activated charcoal treatment further reduced the residual Pd content to 20 ppm.

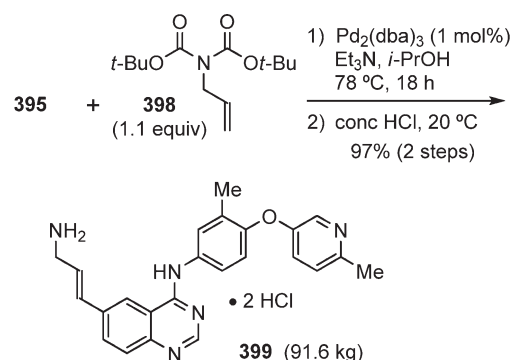
Although both bromo and iodoanilines performed equally well in the Heck coupling, iodoaniline **387** was finally chosen for the commercial process based on overall cost. Although the iodide was more expensive than the corresponding bromide at the time this work was performed, the iodide required a lower Pd catalyst loading and coupled well in the absence of phosphine ligand or ammonium salt. (The researchers mentioned that the number of suppliers for iodide **387** considerably increased in a short period of time and its cost had dropped substantially since their initial order.) Also, the lower catalyst loadings with **387** provided Heck product with lower and more reproducible levels of residual Pd. Thus, the Heck reaction of the iodoaniline and acrylonitrile was demonstrated on 250-kg scale to provide nitrile **389** in 81% yield with <5 ppm of residual Pd as a 80:20 mixture of *E/Z* isomers, in agreement with literature reports. This mixture was treated with 6 N HCl in *i*-PrOH/EtOH to afford the (*E*)-isomer (**389**·HCl; 98:2 *E/Z*) in 60–70% yield. This upgrade in the ratio of olefin isomers was attributed to the selective destruction of the (*Z*)-isomer via Michael addition of the solvent, which was aided in part by the higher solubility of the (*Z*)-olefin in *i*-PrOH/EtOH.

Jiang and co-workers at Novartis prepared diazepinylbenzoic acid **394**, a retinoid X receptor antagonist for the treatment of

Scheme 93



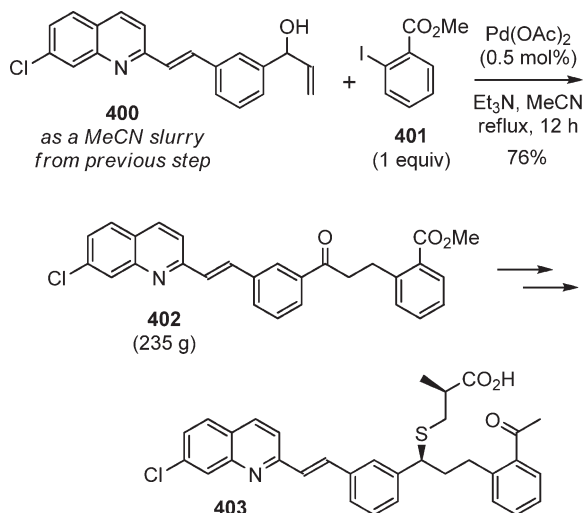
Scheme 94



diabetes and other metabolic diseases (Scheme 92).²⁰¹ The last step of the synthesis was installation of the methyl ketone via Heck coupling of aryl bromide **392** and vinyl butyl ether (**393**).²⁰² This acetylation was effected with Pd(OAc)₂ (8 mol%), dppp (24 mol%), and Cs₂CO₃ in aqueous DMF at 110 °C, and these conditions were also designed to saponify the methyl ester. The regioselectivity of Heck reaction with enol ethers is influenced by catalyst system, additives, and solvent,²⁰³ and this coupling of electron-rich olefin **393** is an example of electronics governing regiochemistry over sterics, as the aryl group becomes bonded to the more-hindered but electron-deficient olefin position. Bromide **392** was fully consumed after 1 h, and complete ester hydrolysis required another 6 h. After hydrolysis of the coupled enol ether product with 2 N HCl, the crude methyl ketone **394** was isolated in 85% yield and >98% purity. The Pd level (1411 ppm) in the crude material could be reduced by treating an EtOH suspension of **394** with a solution of *N*-acetylcysteine in 3 N NaOH at 40 °C for 1 h. After seeding and filtration, **394** was recovered in 85% yield with only 8 ppm of residual Pd.

Ripin and co-workers at Pfizer explored a Heck coupling strategy to complete their synthesis of **397**, a selective ErbB2 angiogenesis inhibitor for the treatment of breast, ovarian, and other types of cancer.¹⁵⁸ Two Heck reactions were developed to install the olefinic side chain on the quinazoline ring (Schemes 93–94). In the first approach (Scheme 93), the coupling of aryl iodide **395** and allylamine methoxyacetamide (**396**) using Pd₂(dba)₃, NaOAc, and Et₃N in 2-B EtOH²⁰⁴ at 70 °C provided API **397** in 36% yield after chromatography and

Scheme 95



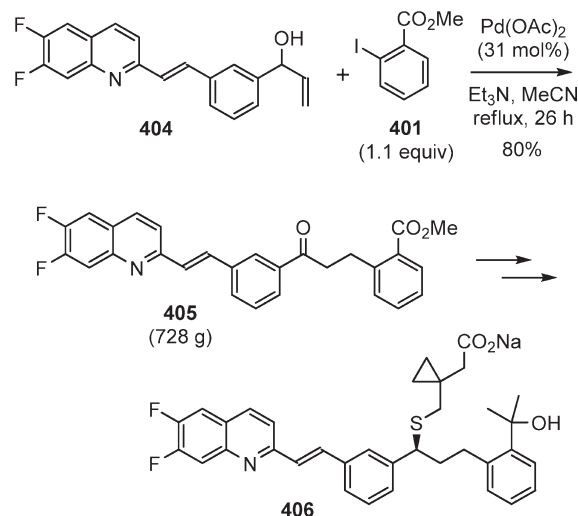
crystallization from acetone. The coupling produced a complex mixture with a major impurity that was tentatively characterized as the 1,1-disubstituted regioisomer from coupling at the internal olefinic position (not shown). After considerable process development, it was found that the use of Et_3N as solvent or cosolvent promoted the formation of **397** over this 1,1-disubstituted regioisomer. In addition, $\text{Pd}_2(\text{dba})_3$ without any phosphine ligand gave better results than $\text{Pd}(\text{OAc})_2$ with PPh_3 or $\text{P}(o\text{-tolyl})_3$. Attempts to recrystallize the API from MeCN to avoid chromatography only provided **397** in 10% yield.

In the same publication,¹⁵⁸ Ripin and co-workers searched for a better coupling partner for iodide **395** (e.g., acrolein acetal, acrylamide, acrylonitrile, allylamine imide) and identified bis-Boc allylimide (**398**) as superior in terms of regioselectivity and yield (Scheme 94). A 94:6 regioselectivity favoring **399** over the 1,1-disubstituted coupling product (not shown) was obtained from the Heck reaction of **395** and **398**. After reaction completion, the mixture was treated with Darco at 50 °C for 3 h and filtered through Celite. The filtrates were then treated with concentrated HCl to cleave the Boc groups and liberate allylamine **399** as the bis-HCl salt in 97% yield.

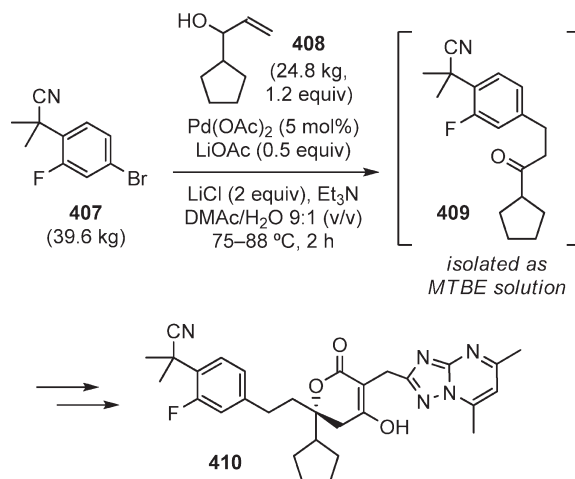
An early example of the Heck reaction on a large scale has been reported by King and co-workers at Merck during the synthesis of LTD₄ antagonist **403**, a candidate for the treatment of asthma (Scheme 95).²⁰⁵ This Heck coupling of allylic alcohol **400** is a clever strategy for introducing the ketone, as the coupling intermediate undergoes β -hydride elimination to afford the thermodynamically favored ketone (via the enol). Allylic alcohol **400** was prepared from the addition of vinylmagnesium bromide to the aldehyde precursor and used in the Heck coupling as a slurry in MeCN. The coupling of **400** and iodide **401** was effected by 0.5 mol% of $\text{Pd}(\text{OAc})_2$ and Et_3N in MeCN at reflux for 12 h. After a hot filtration through Solka-Floc and cooling, the desired ketone **402** precipitated from solution. Thorough washes of the filtered product with MeCN and H_2O purged residual NH_4I salts and provided **402** in 76% yield (from the aldehyde precursor to **400**).

Sidler and co-workers at Merck incorporated a similar Heck coupling of an allylic alcohol into their synthetic route to **406**, another LTD₄ antagonist candidate for the treatment of asthma (Scheme 96).²⁰⁶ The coupling of allylic alcohol **404** and aryl iodide **401** was accomplished with high catalyst loading (31

Scheme 96



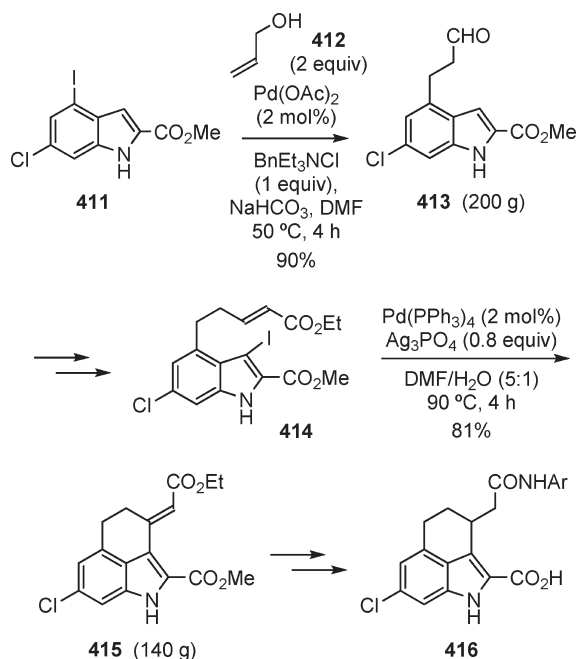
Scheme 97



mol%) and Et_3N in MeCN at reflux. Concentrated mixtures (1.5–2.0 M) proceeded to completion in ~ 24 h, whereas more dilute experiments (0.3 M) doubled the reaction time. The hot reaction mixture was filtered through Solka-Floc to remove Pd, and Heck product **405** crystallized from the filtrate on cooling for 80% yield. The researchers did not comment on the need for such high catalyst loading.

Scott and co-workers at Pfizer have described the kilogram-scale preparation of **410**, a hepatitis C viral polymerase inhibitor.²⁰⁷ Early intermediate **409** was synthesized from the Heck reaction of aryl bromide **407** and allylic alcohol **408** (Scheme 97).²⁰⁸ The reaction was performed with chloride ligands (via LiCl additive), which stabilized the catalyst, and ligating bases such as Et_3N , DIPEA or (*c*-Hex)₂NMe, which allowed for lower catalyst loadings. The optimized conditions that were applied on a large scale employed $\text{Pd}(\text{OAc})_2$ (5 mol%), LiCl (2 equiv), LiOAc (0.5 equiv), and Et_3N in a DMAc/ H_2O (9:1 v/v) mixture at 75–88 °C. During safety studies in an RC1 reactor, it was found that this transformation was exothermic with a maximum adiabatic temperature rise of 84 °C. In the plant, this exotherm was easily controlled by adding the Et_3N in three portions (10%, 20%, and 70% of the total amount), which

Scheme 98



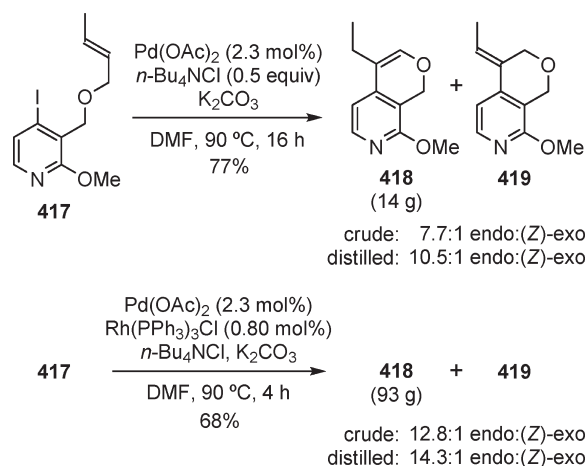
produced a maximum internal temperature of 88 °C. The consumption of Et₃N during reaction progression decreased the reaction rate, and so LiOAc was added as a nonamine cobase that contributed to catalyst stabilization and allowed for complete conversion with a single catalyst charge. After an efficient workup of the Heck reaction mixture involving Darco treatment, the product **409** (an oil) was carried forward as a solution in MTBE.

Nagata and co-workers at Sumitomo Pharmaceuticals Co. in Japan have described the preparation of several indoles of type **416** as a new class of potent NMDA–glycine antagonists for the treatment of stroke and neurodegenerative disorders such as Alzheimer's and Huntington's diseases.²⁰⁹ The tricyclic system in this type of molecule was assembled via two Heck coupling reactions (Scheme 98).

The Heck reaction of iodoindole **411** and allyl alcohol (**412**) was effected by Pd(OAc)₂, BnEt₃NCl, and NaHCO₃ in DMF at 50 °C for 4 h to afford aldehyde **413** in 90% yield. Whereas the literature conditions²¹⁰ employ *n*-Bu₄NCl as phase-transfer catalyst, Nagata and co-workers used BnEt₃NCl as a less expensive and readily available alternative. After a charcoal treatment and filtration, the Heck product **413** precipitated from solution upon the addition of water.

The second Heck reaction was an intramolecular process on later intermediate **414** to assemble the tricyclic core. The standard conditions (Pd(OAc)₂, PPh₃, Et₃N) gave a slow conversion of **414** to **415** and produced the desiodo-**414** as a substantial byproduct. After extensive optimization, the researchers discovered that the addition of Ag salts such as Ag₃PO₄ improved the yield. Water was also found to be beneficial, because its presence increased the rate of cyclization and overall conversion. Phase-transfer catalysts such as *n*-Bu₄NHSO₄ were able to replace Et₃N to afford the desired product but were not necessary when Pd(PPh₃)₄ and water were present. The final conditions on a large scale called for Pd(PPh₃)₄ and Ag₃PO₄ in DMF/H₂O (5:1 v/v) at 90 °C for 4 h. After a charcoal treatment, an aqueous workup, a second charcoal treatment, and trituration

Scheme 99



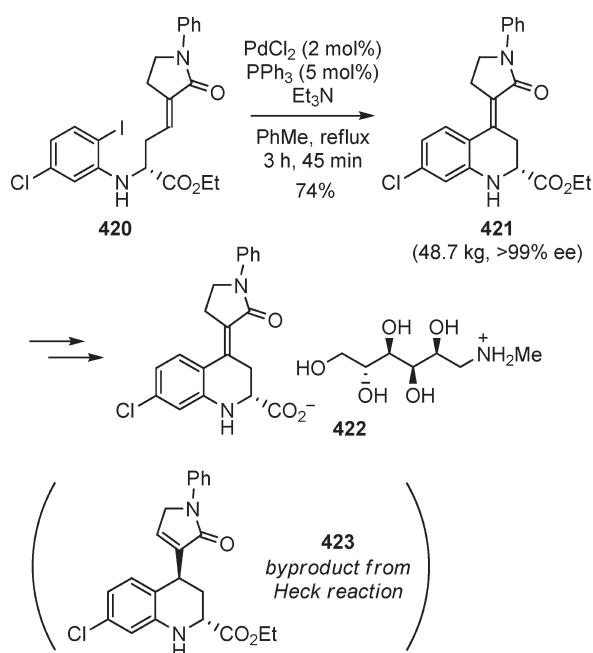
in toluene, the intramolecular Heck product **415** was isolated in 81% yield.

2.7.2. Intramolecular Heck Reaction. Bankston and co-workers at GlaxoWellcome have developed a new catalyst system to carry out an intramolecular Heck reaction on a number of crotyl ethers.²¹¹ When the original conditions developed by Jeffery were applied to **417** (*n*-Bu₄NCl, K₂CO₃, and Pd(OAc)₂ in DMF at 90 °C),^{210,212} a mixture of *endo*-**418** and (Z)-*exo*-**419** products was obtained in 3:1 to 8:1 ratio after 16–20 h (Scheme 99). The ratio for desired *endo*-**418** improved slightly after distillation. Because compound **418** is a key intermediate in the synthesis of a topoisomerase inhibitor,²¹³ the researchers investigated the use of Wilkinson's catalyst,²¹⁴ iron pentacarbonyl,²¹⁵ and Collman's reagent²¹⁶ as a catalyst for the isomerization of *exo*-**419** to *endo* product. The best results were obtained when Wilkinson's catalyst was employed in combination with K₂CO₃ in *n*-PrOH, presumably due to the formation of dipotassium tetracarbonylferrate, a similar species to disodium tetracarbonylferrate (Collman's reagent). During the search for a more efficient and reproducible method, this group tested several cocatalysts in conjunction with Pd(OAc)₂, such as CuI and Wilkinson's catalyst.²¹⁷ The combination of Rh(I) and Pd increased the reaction rate considerably, favored the formation of the *endo* product, and gave more reproducible results. No improvements were observed when using Pd(OAc)₂/PPh₃ in the absence of Rh, which seemed to indicate that Rh plays a critical role in the *endo*/*exo* selectivity. After further experimentation, it was proposed that the initial complexation between Rh and the crotyl ether promotes faster cyclization and better selectivity via subsequent isomerization of *exo* to *endo* product.

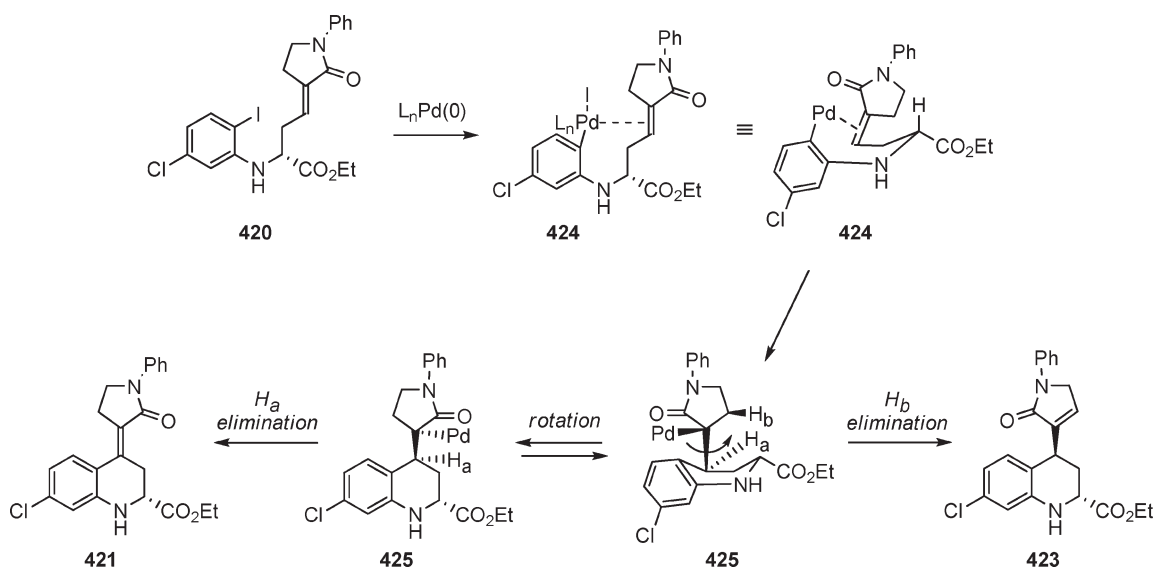
Researchers at GlaxoSmithKline have reported the preparation of chiral tetrahydroquinoline carboxylic acid *N*-methyl-D-glucamine salt **422**, a glycine antagonist for the treatment of nicotine craving (Scheme 100).²¹⁸ An intramolecular Heck reaction was carried out on iodo alkene **420** to assemble the tetrahydroquinoline core of intermediate **421**. Process optimization screened many Pd catalysts, ligands (e.g., phosphines, palladacycles, carbenes), bases, and solvents. Choice conditions treated iodo alkene **420** with PdCl₂ (2 mol%), PPh₃ (5 mol%), and Et₃N in toluene at reflux. Because the contribution of the Pd catalyst and PPh₃ to the overall cost was low, no further work was implemented to reduce their loadings. Under these conditions, no epimerization was observed and the ratio of desired Heck

product **421** to major impurities **423** and desiodo-**420** was 88:7:5. Because this ratio was constant throughout the course of the reaction, the researchers assumed that no equilibration of products occurred and suggested the mechanism shown in Scheme 101 in which the rotation of intermediate **425** led to the desired Heck product **421** via H_a elimination or byproduct **423** via H_b elimination. Once the reaction was complete, the mixture was treated with 2,4,6-trimercaptotriazine (6 mol%)¹³ in toluene at reflux to reduce the Pd content in isolated **421** from 2000 to <15 ppm. After filtration and aqueous workup, **421** was crystallized from the addition of isooctane and isolated in 74% yield. This process was scaled to prepare 245 kg of intermediate **421** (>99% ee) containing only 0.16–0.21% of endo isomer **423** (and no desiodo-**420**).

Scheme 100



Scheme 101



The bromo analogue of **420** was also tested as a substrate for an intramolecular Heck reaction. A solvent and base screen revealed that, with PPh_3 as ligand, the best conditions were K_2CO_3 in dioxane, which led to a 86:9:5 ratio of **421**/**423**/desiodo-**420**.

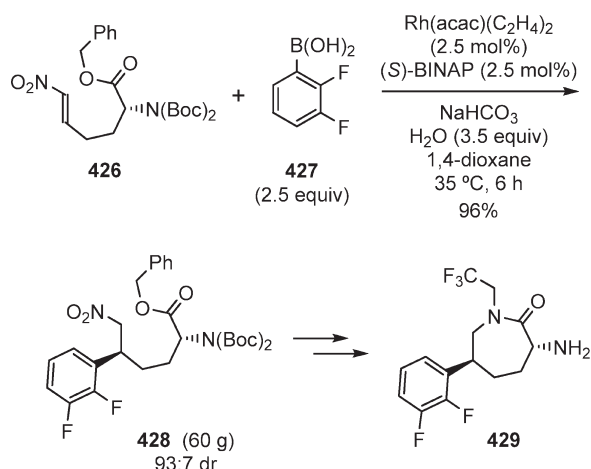
2.8. Hayashi–Miyaura Coupling

In 1997, Miyaura and co-workers described the 1,4-addition of alkenyl and arylboronic acids to α,β -unsaturated ketones catalyzed by $Rh(acac)(CO)_2$ and $dppb$.²¹⁹ A year later, the first asymmetric variant was reported by Hayashi, Miyaura, and co-workers using $Rh(acac)(C_2H_4)_2$ and BINAP as chiral ligand in 10:1 dioxane/water at 100 °C.²²⁰ In recent years, the Rh-catalyzed, 1,4-additions of organoboron reagents to activated olefins have been extensively reviewed.^{221,222} Advantages of this method compared to other 1,4-additions include (a) the greater oxygen- and moisture-stability of organoboron reagents compared to other organometallic reagents; (b) the absence of 1,2-addition byproducts; (c) the fact that both alkenyl and arylboronic acids are competent coupling partners; (d) the fact that chiral ligands can be used to achieve asymmetric additions;²²² (e) the fact that, in addition to enones, olefins activated by esters, amides, phosphonates, and nitro groups can perform as substrates. Despite these advantages, the relative novelty of the Hayashi–Miyaura reaction has limited its application on a large scale to date.

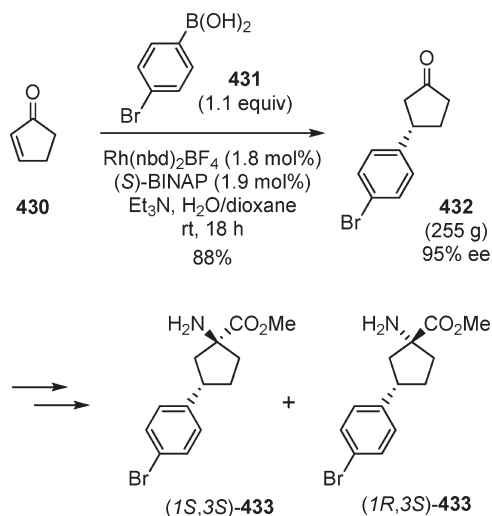
Researchers at Merck have described the preparation of azepan-2-one **429** en route to telcagepant, a calcitonin gene-related peptide receptor antagonist for the treatment of migraine (Scheme 102).²²³ Initially, the aryl group was introduced via Suzuki reaction of 2,3-difluorophenylboronic acid (**427**) and an alkenyl bromide (not shown), and the seven-membered ring was formed via ring-closing metathesis. However, this route presented several drawbacks, such as the need for a high Grubbs second-generation catalyst loading (30%) and the low diastereoselectivity of the subsequent alkene reduction via hydrogenation. As a result, a new approach outlined in Scheme 102 introduced the difluoroaryl moiety via the unprecedented Rh-catalyzed asymmetric 1,4-addition of 2,3-difluorophenylboronic acid (**427**) to nitro olefin **426** via $Rh(acac)(C_2H_4)_2$ (2.5 mol%) and (S)-BINAP as chiral ligand.²²⁴ The high reaction

temperature typically used for Hayashi–Miyaura coupling (100 °C) caused decomposition of the boronic acid to 1,2-difluorobenzene. Less decomposition was observed at lower temperature (45 °C), but additional metal, ligand, and boronic

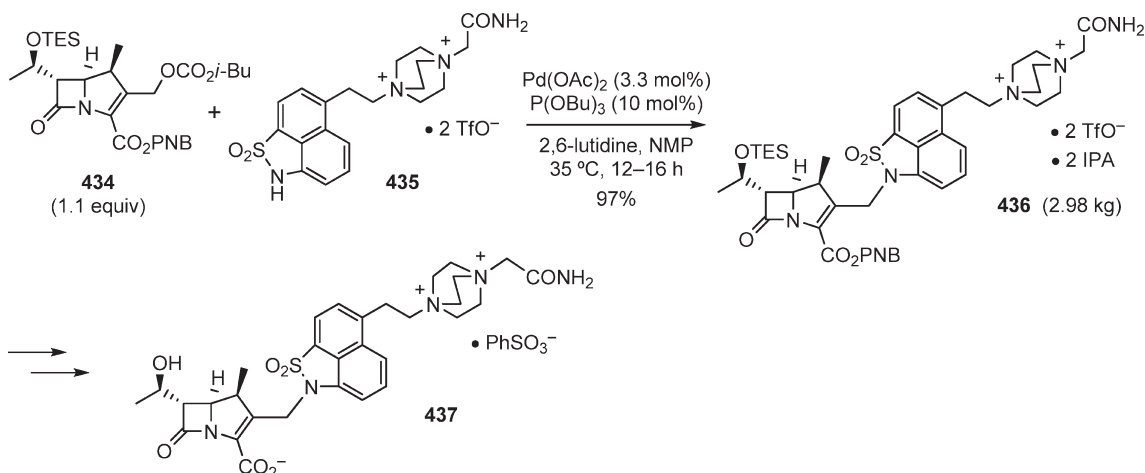
Scheme 102



Scheme 103



Scheme 104



acid were required to fully consume the olefin. In agreement with previous work showing that inorganic bases increase the rate of Rh-catalyzed additions,²²⁵ Merck researchers found that NaHCO_3 allowed the process to reach completion within 6–12 h at 35 °C with only 2.5 mol% catalyst and ligand and 2.5 equiv of boronic acid. The desired adduct **428** was obtained in 96% yield and 93:7 diastereomeric ratio after chromatography in a process that was eventually performed on 2-kg scale.

Wallace and co-workers at Abbott have prepared the (1S,3S) and (1R,3S) isomers of **433** as key intermediates in the synthesis of sphingosine-1-phosphate-1 (S1P1) receptor agonists for immunomodulation (Scheme 103).²²⁶ The bromophenyl moiety of these diastereomers was installed via the asymmetric 1,4-addition of 4-bromophenylboronic acid (**431**) to cyclopentenone (**430**) in the presence of bis(norbornadiene)rhodium(I) tetrafluoroborate and (S)-BINAP in degassed water/dioxane at rt. After aqueous workup and chromatography, 255 g of cyclopentanone **432** were isolated in 95% ee for an 88% yield.

2.9. Tsuji–Trost Allylation

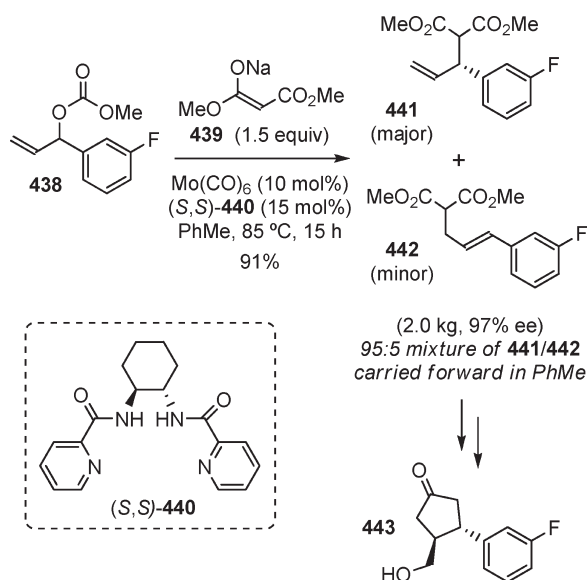
The Tsuji–Trost reaction, discovered by Tsuji¹ and subsequently developed by Trost, was the first example of a Pd-mediated, carbon–carbon bond formation.²²⁷ Originally, this transformation was stoichiometric in Pd, but it was later developed to be substoichiometric in metal.²²⁸ Unlike allylic compounds of other metals such as Mg, the π -allylpalladium species from the Tsuji–Trost reaction is electrophilic in nature. Asymmetric versions of this transformation have been reported,²²⁹ as well as couplings catalyzed by Ir²³⁰ and Fe²³¹ as alternatives to Pd.

Merck researchers described the preparation of **437**, a potent anti-Methicillin-resistant *Staphylococcus aureus* β -methylcarbapenem containing a releasable side chain (Scheme 104).²³² The synthetic strategy prepared advanced intermediate **436** from carbonate **434** and sultam **435**. The usual conditions for the activation of allylic carbonates to the corresponding π -allylpalladium species employ $\text{Pd}(\text{OAc})_2$ and PPh_3 , which reduce the Pd(II) to Pd(0) and avoid the precipitation of Pd black. Unfortunately, exposing sultam **435** to 3 mol% $\text{Pd}(\text{OAc})_2$ and 9 mol% PPh_3 in a toluene/aqueous Rochelle's salt mixture at 80 °C for 2 h led to the Hofmann elimination of its quaternary DABCO moiety. After alternatives to PPh_3 were investigated, the Tsuji–Trost reaction of carbonate **434** and sultam **435** was carried out using $\text{P}(\text{OBu})_3$ and 2,6-lutidine in NMP at 35 °C to

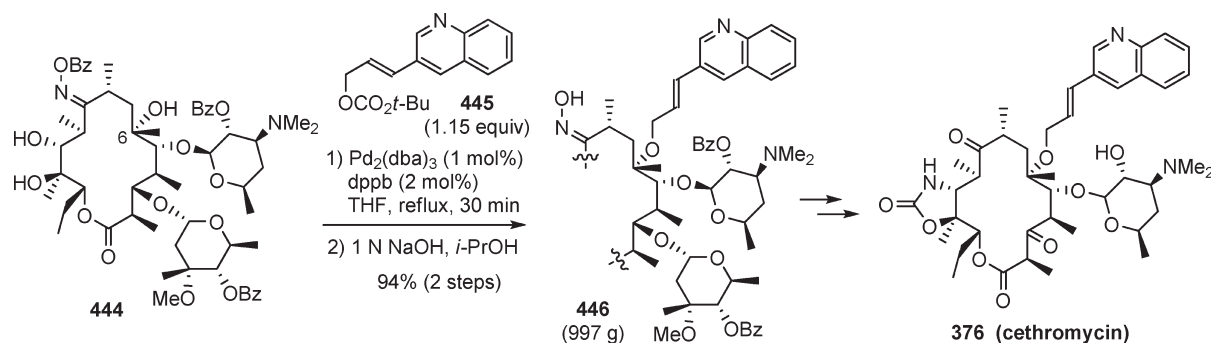
afford coupling product **436** in 97% yield after recrystallization from $\text{H}_2\text{O}/i\text{-PrOH}$. In addition, the recrystallization purged residual Pd to provide **436** with <100 ppm of Pd. Other ligands (PPh_3 , AsPh_3) were tested with $\text{Pd}(\text{OAc})_2$ as catalyst in the 2,6-lutidine/NMP mixture, but very low conversions were observed.

Palucki and co-workers at Merck reported the preparation of cyclopentanone **443**, an advanced intermediate in the synthesis of a drug candidate (Scheme 105).²³³ The introduction of the first chiral center was accomplished via the Tsuji–Trost reaction of carbonate **438** and sodium salt **439**. When the original conditions developed by Trost were tested using $(\text{EtCN})_3\text{Mo}(\text{CO})_3$ and ligand $(S,S)\text{-440}$, excellent yields (75–90%) and stereoselectivities (88–96% ee) were obtained. Since neither the catalyst nor the ligand were commercially available at the time this work was carried out,²³⁴ this group developed a protocol for the large-scale manufacture of $(S,S)\text{-440}$ and, as an alternative to $(\text{EtCN})_3\text{Mo}(\text{CO})_3$, found that air-stable $\text{Mo}(\text{CO})_6$ performed equally well.²³⁵ Optimized reaction conditions preformed the catalyst by heating a mixture of 10 mol% $\text{Mo}(\text{CO})_6$ and 15 mol% $(S,S)\text{-440}$ in toluene at 85–88 °C for 4 h. This catalyst solution was then added to a mixture of carbonate **438** and sodium salt **439** in toluene at 70 °C via cannula. The resulting mixture was heated at 85 °C for an additional 15 h, washed once with water, and passed through silica to remove the ligand and molybdenum residues. The filtrate contained a 95:5 mixture of coupling products **441** (97% ee) and **442** that were

Scheme 105



Scheme 106



carried forward as a solution in toluene. Alternatively, it was possible to isolate **441** via crystallization from toluene in >99% chemical purity and >99% ee, but ~20% of the product was lost to the mother liquor.

Plata and co-workers at Abbott Laboratories have described the Tsuji–Trost reaction for the preparation of intermediate **446** en route to cethromycin (**376**) (Scheme 106).¹⁹⁵ Traditionally, the alkylation of the C-6 hydroxy group in erythromycin A has been carried out through the use of alkyl halides and a strong base,²³⁶ but when these conditions were tested on C-6 alcohol **444**, overalkylation, irreproducible yields, and cleavage of protecting groups were observed. On the other hand, the treatment of alcohol **444** with t -butyl carbonate **445** in the presence of $\text{Pd}_2(\text{dba})_3$ (1 mol%) and dppb (2 mol%) in THF at reflux afforded the desired coupling product in almost quantitative yield. Subsequent treatment with NaOH in $i\text{-PrOH}$ cleaved the benzoyl-protected oxime and provided intermediate **446** in 94% yield for the two steps combined. Plata and co-workers mentioned that the coupling can be carried out with as little as 0.1 mol% $\text{Pd}_2(\text{dba})_3$, but the reaction rate was much slower. No justification was provided for the excellent regioselectivity of the Tsuji–Trost reaction for the C-6 alcohol.

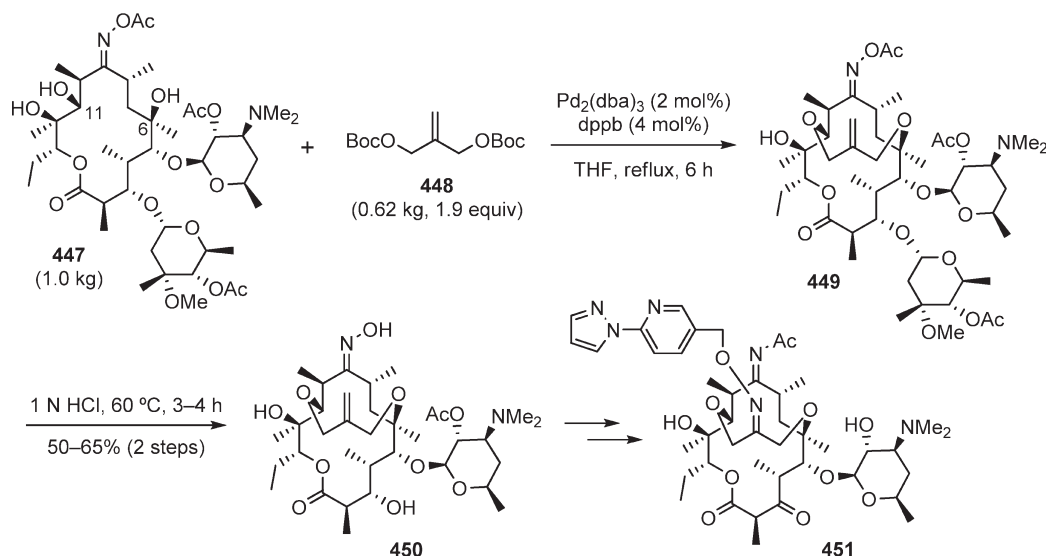
Tang and co-workers at Enanta Pharmaceuticals reported the preparation of **451**, a first-in-class bridged bicyclic macrolide antibiotic candidate for the treatment of community-acquired pneumonia (Scheme 107).²³⁷ Intermediate **449** was prepared by treating diol **447** and allyl dicarbonate **448** with $\text{Pd}_2(\text{dba})_3$ (2 mol%) and dppb (4 mol%) in THF at reflux for 6 h. A regioselective tandem diallylation took place at the 6,11-hydroxyl groups to provide 6,11- O,O -bridged **449**. After reaction completion, the mixture was filtered and concentrated. The residue underwent selective cleavage of the 9-oxime acetate in 1 N HCl at 60 °C to afford monoacetate **450** in 50–65% yield after recrystallization from cold MeCN.

Allyl dicarbonate **448** was manufactured on a kilogram-scale from the reaction of 2-methylene-1,3-propanediol and Boc_2O in a biphasic system of 6 N aqueous NaOH/ CH_2Cl_2 with phase-transfer catalyst $n\text{-Bu}_4\text{NHSO}_4$ at 25 °C for 2–3 h. This material could be used as the crude even though it contained 5% of residual Boc_2O .

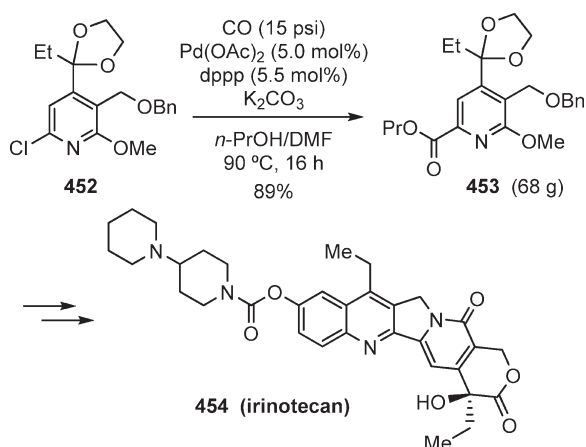
2.10. Carbonylation

Since the first report on the Pd-catalyzed carbonylation of aryl and vinyl halides by Heck more than 30 years ago,²³⁸ carbonylations have seen an impressive expansion in the number of applications for the synthesis of aldehydes, ketones, and carboxylic acid derivatives. The mild reaction conditions and functional group compatibility contribute to its broad

Scheme 107



Scheme 108

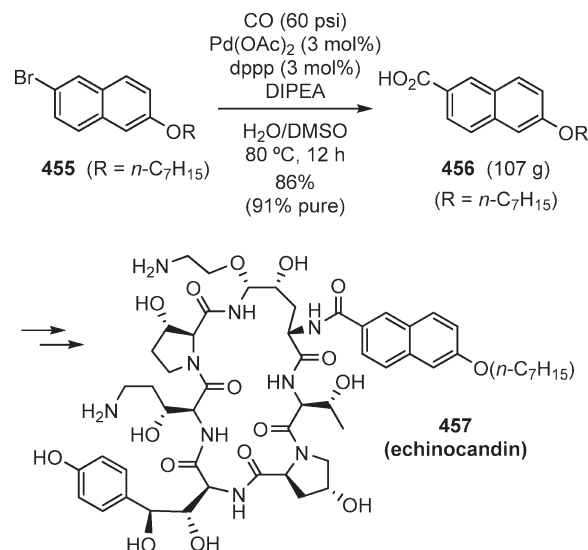


applicability. Industrial carbonylations are very common, and organo halides, sulfonates, and diazonium salts can be employed as substrates. Several reviews on transition metal-catalyzed carbonylations have recently appeared in the literature.²³⁹

Henegar and co-workers at Pharmacia & Upjohn incorporated the carbonylation of 2-chloropyridine 452 into the synthesis of a key intermediate to irinotecan (454), an FDA-approved treatment for refractory colorectal cancer (Scheme 108).²⁴⁰ Prior to the development of this chemistry, Pd-catalyzed carbonylations of 2-chloropyridines had not been reported. The reaction of chloride 452, $\text{Pd}(\text{OAc})_2$, dppp, and K_2CO_3 in *n*-PrOH/DMF at 90 °C proceeded smoothly under an atmosphere of carbon monoxide to install the propyl ester. This carbonylation required low CO pressure for good conversion (15 psi or less) and was performed in standard glassware. The propyl ester was chosen because the corresponding alcohol (*n*-PrOH) had a sufficiently high boiling point to allow for heating at 90 °C under atmospheric pressure. After reaction completion, the ester 453 was extracted into MTBE and purified by silica gel chromatography.

Journet and co-workers at Merck prepared acid 456 via carbonylation of bromonaphthalene 455 for the synthesis of antifungal lipopeptide echinocandin (457).²⁴¹ As illustrated in

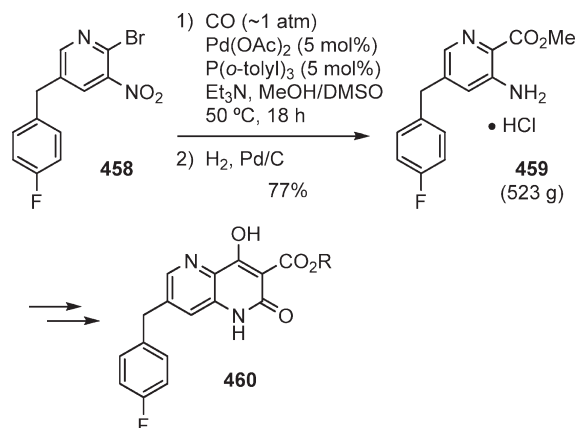
Scheme 109



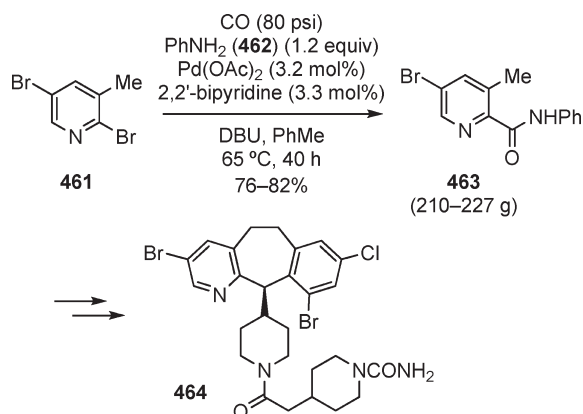
Scheme 109, a mixture of bromide 455, $\text{Pd}(\text{OAc})_2$, dppp, and DIPEA in aqueous DMSO was heated in an autoclave at 80 °C under 60 psi of carbon monoxide. Conversion to acid 456 was monitored by CO uptake, and after reaction completion the mixture was extracted into EtOAc and filtered through a pad of Solka-Floc. The filtrate was concentrated to provide acid 456 in 86% yield (91% pure) as a pale-yellow solid containing 5% desbromo-455. The crude acid was carried forward without additional purification.

Boros and co-workers at GlaxoSmithKline developed the alkoxycarbonylation of bromopyridine 458 for the synthesis of 7-benzyl-naphthyridinones (of type 460) that behave as HIV-1 integrase inhibitors (Scheme 110).²⁴² In a standard 20-L jacketed glass laboratory reactor, bromide 458 was converted to methyl ester 459 by heating in MeOH/DMSO at 50 °C under an atmosphere of carbon monoxide in the presence of $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tolyl})_3$, and Et_3N . The carbonylation product was carried directly into the subsequent hydrogenation, and the resulting

Scheme 110



Scheme 111

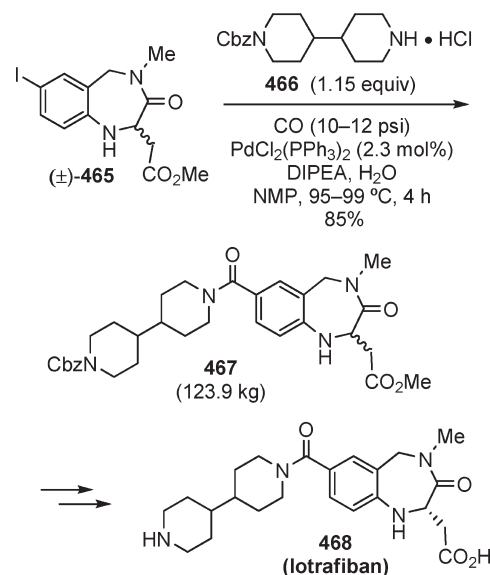


amine from nitro reduction was isolated after acid wash and filtration as the HCl salt **459** in 77% yield from bromide **458**.

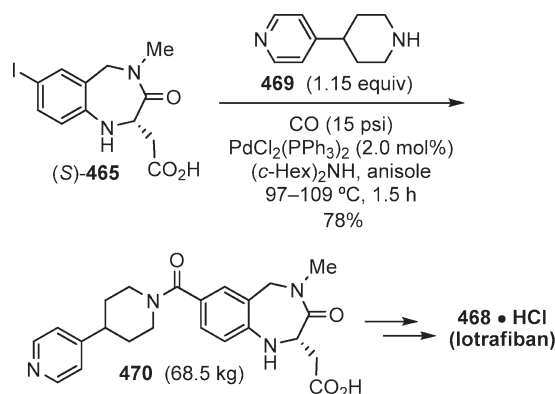
For the synthesis of potential oncologic treatment **464**, Wu and co-workers at Schering–Plough demonstrated 2,2'-bipyridine as a novel ligand for the regioselective Pd-catalyzed carbonylation of dibromopyridine **461** (Scheme 111).²⁴³ Initial development studies using $\text{PdCl}_2(\text{PPh}_3)_2$ for the carbonylation of **461** with aliphatic amines led to 95:5 mixtures of the desired monoamide (at the 2-position) and the bisamide byproduct. Reactions with arylamines, however, led to greater amounts of bisamide (20–40%) and lower isolated yields of monoamide (typically <50%). Following the conditions outlined in Scheme 111, switching to 2,2'-bipyridine as a ligand²⁴⁴ for Pd-catalyzed carbonylation with aniline furnished amide **463** with 98:2 mono-/bisamide selectivity. The reaction was conducted in an autoclave, and after completion the mixture was filtered through Celite and concentrated to dryness. The crude residue was crystallized from *i*-PrOH to provide pure **463** in 76–82% yield.

Hayes and co-workers at SmithKline Beecham reported the aminocarbonylation of aryl iodide **465** in their synthesis of lotrafiban (**468**), a potent glycoprotein IIb/IIIa antagonist that inhibits platelet aggregation (Scheme 112).²⁴⁵ Iodide **465** was heated in NMP under an atmosphere of carbon monoxide in the presence of piperidine **466** to prepare amide **467**. Several screened Pd catalysts worked as well as the chosen $\text{PdCl}_2(\text{PPh}_3)_2$ for this transformation ($\text{Pd}(\text{OAc})_2$, PdCl_2 , PdBBr_2 , PdNa_2Cl_4); phosphorus-based ligands did not seem to play an important role

Scheme 112



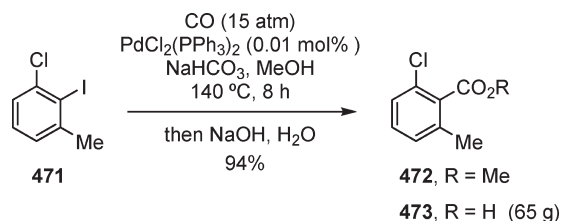
Scheme 113



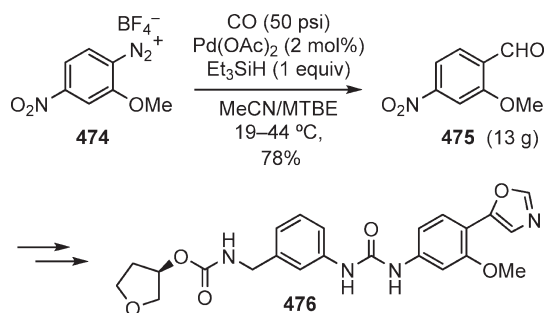
in aminocarbonylation. The reaction proceeded very slowly under anhydrous conditions, and water was a necessary additive for acceptable reaction rate. (There was no mention of competitive hydroxycarbonylation from the reaction of water.) Higher pressures of carbon monoxide increased the rate of iodide consumption, and efficient stirring was required to maintain a sufficient concentration of CO in solution. Reaction workup entailed a Celite filtration followed by a series of solvent exchanges that precipitated amide **467** for isolation via centrifugation. This process afforded 123.9 kg of **467** for an excellent 85% yield.

Four years later, Carey and co-workers at GlaxoSmithKline published a revised aminocarbonylation for a later-generation synthesis of amide **470** en route to lotrafiban (Scheme 113).²⁴⁶ Their modified route used pyridylpiperidine **469** as the coupling partner and maintained the same $\text{PdCl}_2(\text{PPh}_3)_2$ catalyst and 2.0 mol% loading from the previous conditions outlined in Scheme 112,²⁴⁵ but increased the carbon monoxide pressure from 10 to 15 psi and switched the solvent from EtOAc to anisole (8 volumes). In addition, secondary amines were found to improve the reaction profile, and the DIPEA from the previous protocol was replaced with dicyclohexylamine. The bulky (*c*-Hex)₂NH did not participate in aminocarbonylation to form

Scheme 114



Scheme 115

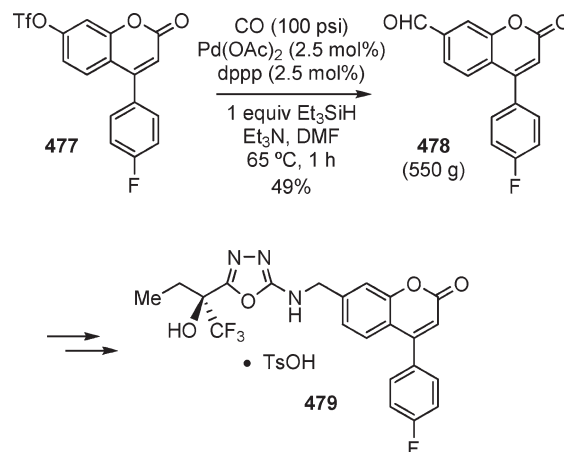


an amide side product, and its hydrogen iodide salt precipitated from solution for easy removal by filtration during workup. These revised conditions afforded 68.5 kg of amide **470** as an intermediate to lotrafiban.

Daniewski and co-workers at Hoffmann–La Roche reported the preparation of 2-chloro-6-methylbenzoic acid (**473**) via the alkoxycarbonylation of iodobenzene **471** followed by ester hydrolysis (Scheme 114).²⁴⁷ The optimized conditions (developed from extensive screening of catalyst, ligand, and base) included heating iodide **471** in an autoclave in MeOH at 140 °C under 15 atm of carbon monoxide in the presence of PdCl₂(PPh₃)₂ and NaHCO₃. The catalyst loading was particularly low; <30 mg of PdCl₂(PPh₃)₂ were required to convert 100 g of iodide to methyl ester **472**. After reaction completion, dilution with aqueous NaOH solution saponified the ester to provide crude benzoic acid **473** as a pale-yellow solid in 94% overall yield (99.5% pure by GC analysis). Charcoal treatment and recrystallization then provided **473** as a white solid (89% recovery). Attempts to convert iodide **471** to the benzoic acid directly via carbonylation in water led to low yields of **473** (<30%) and 3-chlorotoluene as the major product (50–80%).

Herr and co-workers at Albany Molecular Research employed the formylation of diazonium salt **474** to prepare aldehyde **475**, a key intermediate for the construction of hepatitis C drug candidate **476** (Scheme 115).²⁴⁸ As a modification to the procedure of Kikukawa et al. for the carbonylation of aryldiazonium salts,²⁴⁹ an autoclave was charged with solutions of diazonium salt **474** in MTBE and Pd(OAc)₂ in MeCN and pressurized to 50 psi of carbon monoxide, and Et₃SiH was pumped into the pressurized vessel via the inlet port over 1.5 h (raising the temperature to 44 °C and the pressure to 90 psi). The slow addition of silane controlled the exothermic oxidation/reduction reaction and minimized the side reduction of **474** to 3-nitroanisole. These relatively mild conditions were an upgrade over previous formylations requiring higher CO pressures, temperatures, and catalyst loadings. After reaction completion and aqueous workup, the carbonylation product was purified via silica gel chromatography to afford 13 g of aldehyde **475**.

Scheme 116



Gosselin and co-workers at Merck incorporated the Pd-catalyzed formylation of triflate **477** into the synthesis of 5-lipoxygenase inhibitor **479** for the treatment of inflammatory diseases such as asthma, chronic obstructive pulmonary disease, and atherosclerosis (Scheme 116).²⁵⁰ In a high-pressure vessel, a solution of triflate **477**, Pd(OAc)₂, and dppp in DMF was pressurized with carbon monoxide to 100 psi and heated to 65 °C. A mixture of Et₃SiH (1 equiv) and Et₃N was added gradually over 1 h to minimize the competitive reduction of **477** to destriflyl-**477** (similar to the preceding example by Herr et al.²⁴⁸ in which slow silane addition minimizes dehalogenation). The resulting solution was maintained at 65 °C and 100 psi for another hour to provide aldehyde **478** contaminated with 5% of the corresponding carboxylic acid and 10% of destriflyl-**477**. Upon workup, the cooled and depressurized mixture was washed with heptane to remove silane residues. Aldehyde **478** was extracted into EtOAc, washed with water to remove DMF, treated with Darco at 60 °C, and filtered through Solka-Floc. The filtrate was concentrated to low volume and cooled at 5 °C to precipitate 550 g of carbonylation product **478** (49% yield, 95% pure).

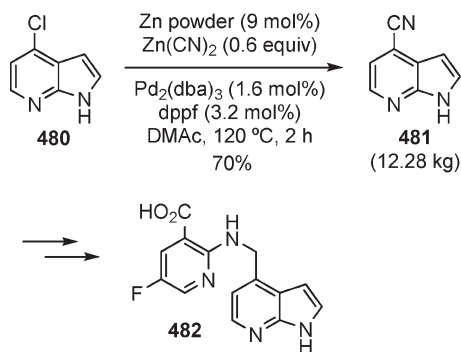
2.11. Cyanation

Nitriles are commonly found in pharmaceuticals, agrochemicals, dyes, and natural products. These versatile moieties can be transformed into a wide array of other functional groups via organic synthesis, which makes cyano compounds important synthetic intermediates. Traditionally, cyano groups have been introduced via the Sandmeyer²⁵¹ or Rosenmund–von Braun²⁵² reactions in protocols requiring stoichiometric amounts of Cu, and the latter reaction requires high temperatures in which densely functionalized substrates might not be compatible. On the other hand, the Pd-catalyzed cyanation of aryl halides,^{253,254} first introduced by Takagi et al. in 1973,²⁵⁵ avoids these limitations and offers an excellent alternative via mild conditions and cheap cyanide sources such as sodium, potassium, or zinc cyanide. Nickel²⁵⁶ and copper²⁵⁷ have also been used as catalysts for transition metal-catalyzed cyanation, but Pd offers better versatility for this transformation.

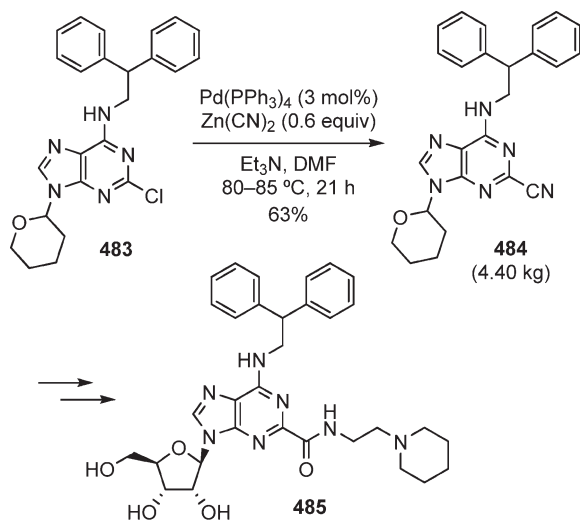
Transition metal-catalyzed cyanations have been previously reviewed.²⁵⁸

The preparation of pharmaceutical intermediate **482** has been published by Wang and co-workers at Amgen (Scheme 117).²⁵⁹ The aminomethyl bridge connecting the heterocycles originated

Scheme 117



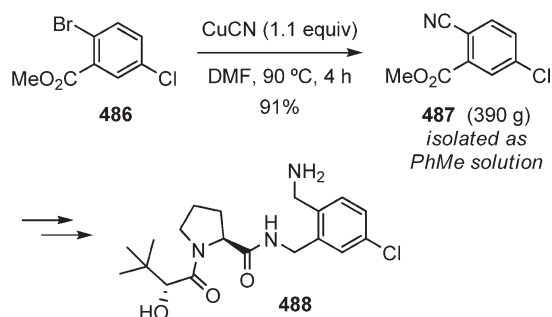
Scheme 118



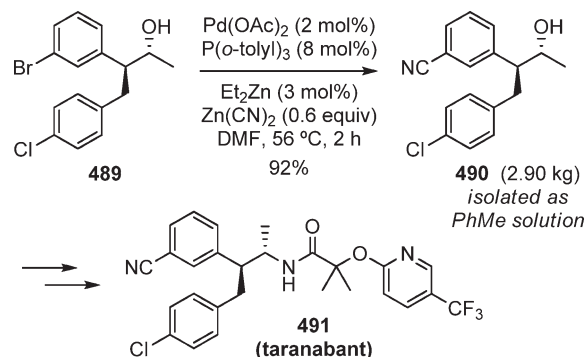
from the reduction of a cyano group that was installed via the Pd-catalyzed reaction of 4-chloroazaindole **480** and $\text{Zn}(\text{CN})_2$. As cyanide binds strongly to Zn as well as Pd, zinc is a common metal for cyanations to avoid catalyst inhibition via cyanide binding solely to Pd. (Furthermore, slow cyanide addition protocols are used frequently to overcome the problem of cyanide inhibition of Pd.) Wang heated **480**, $\text{Zn}(\text{CN})_2$, dppf, and catalytic zinc in DMAc at 120°C for 2 h.²⁶⁰ After reaction completion, the addition of water precipitated the crude cyanoazaindole **481** from solution. After forming the HCl salt with 3 N HCl and filtering off insoluble material, neutralization with aqueous 50% NaOH (to pH 12) furnished nitrile **481** in 70% yield.

Smith and co-workers at Pfizer reported the synthesis of A2a agonist **485** for the treatment of chronic obstructive pulmonary disease (Scheme 118).²⁶¹ The original cyanation procedure used by the medicinal chemistry group treated chloride **483** with methanethiolate, oxidized the corresponding thioether to the sulfone, and displaced the sulfone with cyanide.²⁶² On scale, the researchers opted for a much more direct introduction of the cyano group via Pd-catalyzed cyanation.²⁶³ Thus, when **483** was treated with $\text{Pd}(\text{PPh}_3)_4$ and $\text{Zn}(\text{CN})_2$ in the presence of Et_3N , nitrile **484** was obtained in 63% yield after recrystallization from hot *i*-PrOH. The researchers had to strike a balance between conversion and the formation of THP-deprotected-**483** and THP-deprotected-**484**, which were the two major byproducts

Scheme 119



Scheme 120

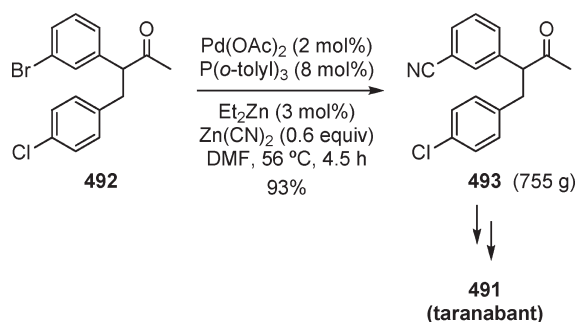


in the reaction mixture along with unreacted starting material. However, it was found that the recrystallization from hot *i*-PrOH and the use of a filter aid sufficiently kept these impurities at satisfactory levels.

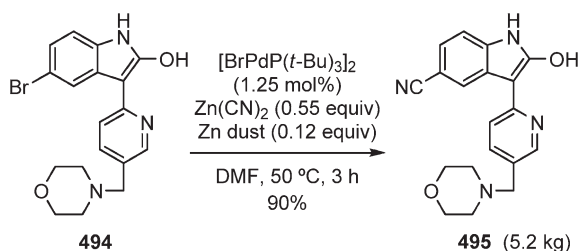
Nelson and co-workers at Merck have described the synthesis of potent thrombin inhibitor **488**, a drug candidate for the treatment of myocardial infarction, unstable angina, stroke, ischemia, restenosis following angioplasty, pulmonary embolism, deep vein thrombosis, and arterial thrombosis (Scheme 119).²⁶⁴ The cyano group that led to the benzylamino functionality in the target molecule was introduced via a Rosenmund–von Braun cyanation reaction²⁵² of aryl bromide **486** and CuCN (1.1 equiv) in DMF at 90°C for 4 h. Less than 0.4% dicyano byproduct was observed from chloride displacement. The Pd-catalyzed cyanation conditions found in the literature²⁶⁵ proved to be irreproducible and gave large amounts of the double cyanation byproduct, as the cyano group of desired monocoupling product **487** activates the chloride for oxidative insertion. Overcyanation was also observed from reactions with the corresponding triflate (in place of bromide). Cyano ester **487** was isolated as a toluene solution and used without further purification in the next nitrile reduction step.

The scaleup of taranabant (**491**), a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity, has been reported by chemists at Merck (Scheme 120).²⁶⁶ The introduction of the nitrile to the molecule was accomplished via Pd-catalyzed cyanation of aryl bromide **489**. The active catalyst, $\text{Pd}[\text{P}(\text{o-tolyl})_3]_4$, was prepared in situ by adding Et_2Zn (3 mol%) to a mixture of $\text{Pd}(\text{OAc})_2$ (2 mol%) and $\text{P}(\text{o-tolyl})_3$ (8 mol%) and heating at 56°C for 1 h. A mixture of aryl bromide **489** and $\text{Zn}(\text{CN})_2$ was then added to the preformed catalyst and the reaction was heated at 56°C for an additional 2 h. After quenching with concentrated NH_4OH to sequester the cyanide ions and filtration through Solka-Floc, nitrile **490** was isolated as

Scheme 121



Scheme 122

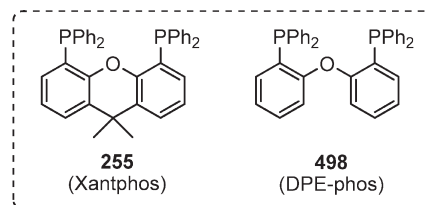
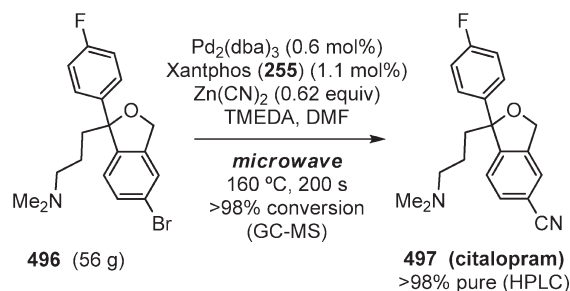


a toluene solution and used in the next step (mesylation) without further purification. The quality of $\text{Zn}(\text{CN})_2$ and the elimination of oxygen by subsurface nitrogen sparging before the catalyst addition were both key to successful cyanation. The combination $\text{Pd}_2(\text{dba})_3/\text{dppf}$ also performed well in this transformation, but the removal of the dppf ligand proved to be difficult and this alternative was not pursued.

An alternative route to taranabant (**491**) has been published by Merck scientists and used near-identical conditions to install the cyano group of the API (Scheme 121).²⁶⁷ As in the case of chiral alcohol **489** (Scheme 120), racemic ketone **492** was treated with $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tolyl})_3$, Et_2Zn , and $\text{Zn}(\text{CN})_2$ to provide nitrile **493** in 93% yield after recrystallization from heptane/toluene.²⁶⁸

Ryberg at AstraZeneca in Sweden has reported the development of a mild, robust, and scalable Pd-catalyzed cyanation for the conversion of aryl bromide **494** to the corresponding nitrile **495** (Scheme 122).²⁶⁹ During the initial process development work, $\text{Pd}_2(\text{dba})_3$, dppf, $\text{Zn}(\text{CN})_2$, and Zn dust in DMF at 120 °C²⁶⁰ worked well on a small scale, but incomplete reactions and low yields were observed on a 50-g scale. A milder method was developed with the goal of producing kilograms of nitrile **495** from the thermally sensitive bromide **494**. A catalyst screen in degassed DMF at 50 °C revealed that $\text{P}(\text{t-Bu})_3$ -based catalysts gave fast and complete reactions. However, when the cyanation reaction was scaled up with the $\text{Pd}(\text{dba})_2/\text{P}(\text{t-Bu})_3$ catalyst system, incomplete reaction was observed again. Reaction stalling was due to catalyst poisoning by cyanide if the charging of ligand to the reaction mixture was delayed. Also, no reaction occurred when there was a delay (as little as 5 min) in heating the reaction mixture after all reagents were mixed. These data, in conjunction with information obtained from experiments investigating the order of reagent addition, resulted in a reliable method for the generation of nitrile **495**. Thus, aryl bromide **494**, $[\text{BrPdP}(\text{t-Bu})_3]_2$ (a commercially available, air-stable catalyst that afforded the cleanest reaction), and Zn dust were heated in degassed DMF to 50 °C. After 5–10 min, $\text{Zn}(\text{CN})_2$ was added and the mixture was stirred at 50 °C for 3 h. The reaction was

Scheme 123

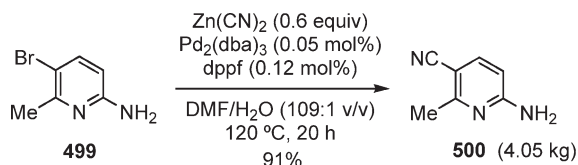


then treated with thiol-functionalized silica (SiliaBond from Silicycle) to lower the residual Pd level below 400 ppm. After filtration and partial concentration of the DMF solution, the addition of aqueous $\text{Na}_4\text{-EDTA}$ precipitated the nitrile **495** from solution while reducing Zn metal below 2000 ppm.

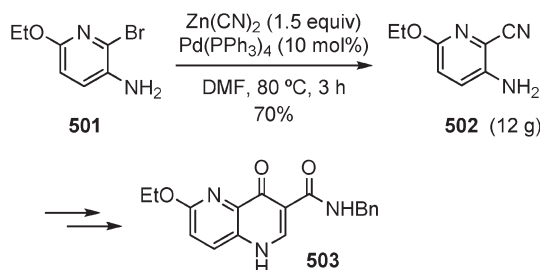
An interesting example of a microwave (MW)-assisted Pd-catalyzed cyanation has been reported by Pitts and co-workers at StylaCats Ltd. in the U.K. and applied to the preparation of citalopram (**497**) (Scheme 123).²⁷⁰ The more traditional Rosenmund–von Braun reaction²⁵² with CuCN required 24 h and provided product in low yield that was difficult to purify. Encouraged by reports on microwave heating to increase the rate of $\text{Pd}(\text{PPh}_3)_4$ -catalyzed cyanations,²⁷¹ Pitts developed microwave conditions for the conversion of aryl bromide **496** to citalopram. DMF was the solvent of choice in combination with $\text{Zn}(\text{CN})_2$, because the solubility of this cyanide source is low in DMF and therefore prevents cyanide inhibition of the Pd catalyst. When the combination $\text{Pd}_2(\text{dba})_3/\text{dppf}$ (1:1, 5 mol%) in DMF at 120 °C was tested on 4-bromoacetophenone as a model study, complete conversion was observed in only 5 min; similar results were obtained with 1 mol% catalyst, whereas the reaction had to be run at 180 °C with only 0.1 mol% catalyst. No cyanation product was generated when these conditions were applied to bromide **496**; thus, further optimization was required.²⁷² Replacing dppf with PPh_3 or $\text{P}(2\text{-furyl})_3$ led to no reaction. Bidentate ligands dppe and dpppe afforded low conversions, whereas bidentate ligands Xantphos (**255**) and DPE-phos (**498**) gave complete reactions. Water was detrimental to the reaction by promoting nitrile hydrolysis and also desbromo-**496** byproduct. In addition, TMEDA led to quantitative yields and high purities, and the final microwave conditions irradiated a mixture of bromide **496**, $\text{Pd}_2(\text{dba})_3$ (0.6 mol%), Xantphos (1.1 mol%), $\text{Zn}(\text{CN})_2$ (0.62 equiv), and TMEDA in DMF at 160 °C for 200 s. Reaction conversion was determined by GC-MS, but no information on the isolated yield was provided.

Maligres and co-workers at Merck have reported a very efficient and robust method for the Pd-catalyzed cyanation of aryl bromides such as **499** (Scheme 124).²⁷³ The first attempts to carry out this transformation used stoichiometric CuCN (1.2 equiv) in DMF or NMP at 150–250 °C to provide cyanopicoline **500** in 60–80% yield after a cumbersome workup. The

Scheme 124



Scheme 125

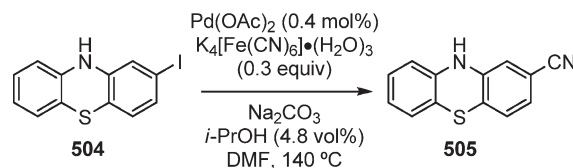


combination of CuCN with $\text{Zn}(\text{CN})_2$, lithium halides, or $n\text{-Bu}_4\text{NBr}$ led to gummy crudes, and $\text{Ni}(\text{CN})_2$ or $\text{Co}(\text{CN})_2$ in NMP gave no reaction. Cyanation proceeded with CuCN in the presence of Zn dust and PPh_3 , but the isolation of product was difficult. The researchers switched to Pd-catalyzed cyanation, and cyanopyridine **500** was obtained in 80–85% yield from $\text{Zn}(\text{CN})_2$ in the presence of 2–4 mol% $\text{Pd}(\text{PPh}_3)_4$ in NMP at 150 °C. This protocol lacked reproducibility at lower Pd catalyst loadings. An extensive screen of phosphine ligands and additives was explored for cyanation, and $\text{Zn}(\text{CN})_2$ (0.6 equiv), $\text{Pd}_2(\text{dba})_3$ (0.05 mol%), and dppf (0.12 mol%) in wet DMF at 120 °C emerged as optimal conditions, giving complete conversion after 20 h. The product **500**, precipitated directly from the reaction mixture by diluting with a solution of NH_3 and NH_4Cl and cooling, was isolated via filtration in 91% yield on a kg-scale. This remarkable process employs extremely low amounts of Pd catalyst and was successfully demonstrated on four more aryl bromides in the same publication.

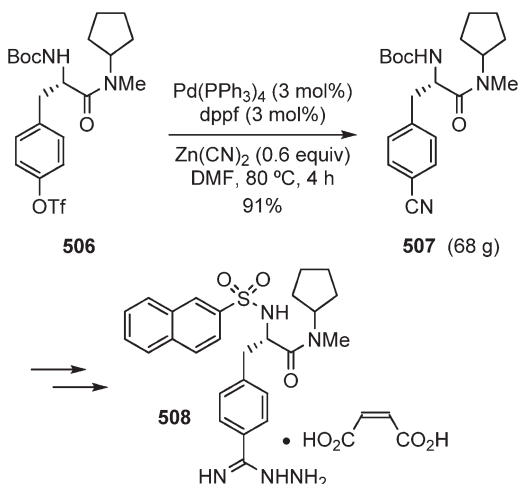
Researchers at Pfizer have described the preparation of **503**, a subtype-selective GABA-A receptor inverse agonist candidate for the treatment of cognition disorders such as Alzheimer's disease (Scheme 125).²⁷⁴ One of the explored routes to the API proceeded through the formation of cyanopyridine **502** via cyanation of electron-rich bromopyridine **501**. This transformation was effected by 1.5 equiv of $\text{Zn}(\text{CN})_2$ and 10 mol% $\text{Pd}(\text{PPh}_3)_4$ in DMF at 80 °C. Cyanopyridine **502** was obtained in 70% yield after recrystallization from 5% EtOAc/hexane.

Wang and co-workers at Henan University of Science and Technology in China developed a robust method for the Pd-catalyzed cyanation of aryl halides in contact with air for the preparation of **505**, a key intermediate in the synthesis of a neuroleptic candidate (Scheme 126).²⁷⁵ Initially, Weissman's ligand-free cyanation conditions²⁷⁶ were applied to aryl iodide **504** for conversion to nitrile **505**, but this approach failed to give satisfactory results, presumably due to small amounts of oxygen in the reaction mixture. The researchers tried to avoid this problem by introducing additives that would protect the Pd catalyst from oxygen poisoning, such as Zn dust or polymethylhydrosiloxane. To this end, they developed an open-air and robust method using *i*-PrOH as an additive to prevent catalyst poisoning by oxygen. The general, large-scale procedure called

Scheme 126



Scheme 127



for combining *i*-PrOH, Na_2CO_3 , $\text{Pd}(\text{OAc})_2$, and the aryl halide in DMF, and after heating the resulting mixture to 140 °C, $\text{K}_4[\text{Fe}(\text{CN})_6]\cdot\text{tri-hydrate}$ was added. The mixture was heated at 140 °C for 0.4–8 h depending on the substrate. After filtration, the product was isolated via fractionation of the filtrate. This article included five examples on 2.5 mol-scale with cyanation yields between 70–92%; however, the specific conversion of iodide **504** to nitrile **505** using these open-air conditions was not discussed.

Shin and co-workers at LG Life Sciences in Korea have reported the synthesis of **508**, a thrombin inhibitor candidate for the treatment of thrombosis (Scheme 127).²⁷⁷ The conversion of triflate **506** to nitrile **507** was first attempted using KCN and Pd catalysis, but incomplete reactions and/or irreproducible results were obtained, presumably due to the catalyst poisoning by cyanide.²⁷⁸ When KCN was replaced with the less-soluble $\text{Zn}(\text{CN})_2$ and the $\text{Pd}(\text{PPh}_3)_4/\text{dppf}$ catalyst system was employed, the desired nitrile **507** was obtained in 91% yield. Interestingly, $\text{Pd}_2(\text{dba})_3$ also performed well in this transformation whereas $\text{Pd}(\text{OAc})_2$ gave no product, and it is likely that the competitive Pd binding of dppf or dba suppressed cyanide inhibition of the metal. DMF proved superior to MeCN, and better results were obtained using dppf than other bidentate ligands such as dppe or dppp. With the goal of reducing costs, the researchers also screened nickel catalysts.^{256,279} The best results with nickel were realized from $\text{NiCl}_2(\text{PPh}_3)_2$ (5 mol%) in either DMF or NMP at 75 °C (85% yield of **507**), whereas other Ni catalysts such as $\text{NiBr}_2(\text{PPh}_3)_2$ and NiBr_2 furnished lower yields of the nitrile. Furthermore, the corresponding mesylate and diethylphosphonate²⁸⁰ variants of triflate **506** were also investigated in combination with Ni catalysts, but only partial conversions (70% and 30%, respectively) were observed from $\text{Zn}(\text{CN})_2/\text{NiCl}_2(\text{PPh}_3)_2$ in MeCN (mesylate) and $\text{KCN}/\text{NiCl}_2(\text{PPh}_3)_2$ in DMF (phosphonate).

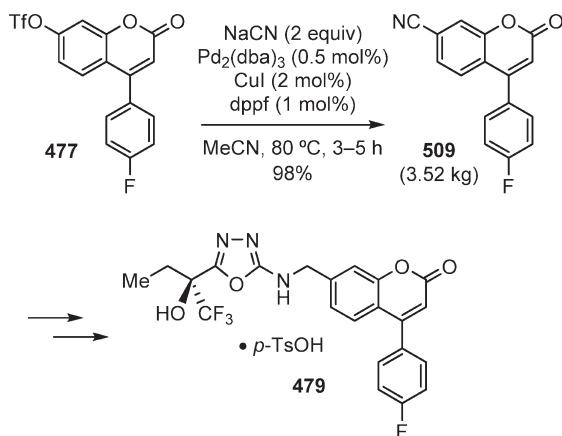
Gosselin and co-workers at Merck described an alternative approach for the preparation of **479**, a selective 5-lipoxygenase inhibitor (Scheme 128).²⁵⁰ The reaction of coumarin triflate **477** with 2 equiv of NaCN and Pd₂(dba)₃/dppf as catalyst in MeCN at 80 °C afforded the corresponding nitrile **509**, and workup with a buffered solution of aqueous NH₄OH/NH₄Cl bound the excess cyanide and precipitated **509** in 98% yield. This transformation could also be effected with Pd(OAc)₂/Et₂Zn/dppf to provide the nitrile in 97% yield.

2.12. Olefin Metathesis

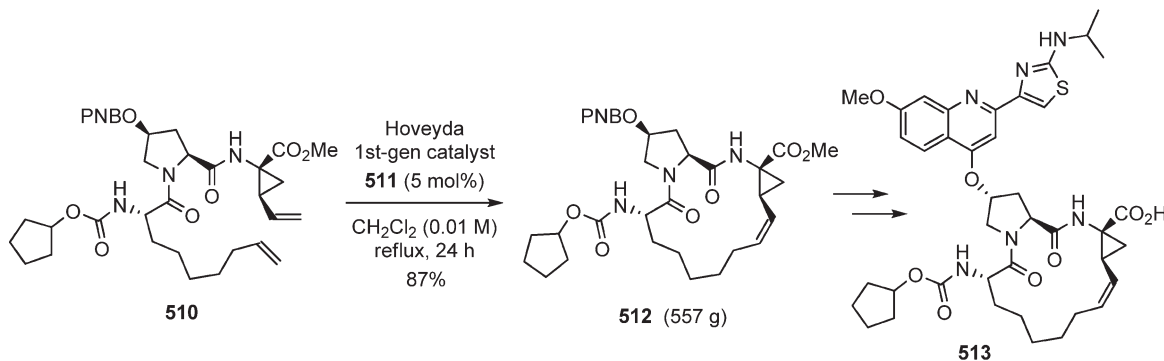
Ring-closing metathesis (RCM) for the preparation of medium and large rings via intramolecular olefin coupling is now a widespread technology in organic synthesis.²⁸¹ Many of the Ru and Mo catalysts that promote this transformation show remarkable functional group tolerance, and this is a major factor contributing to its success. The importance of metathesis in the chemical field was recognized by the Nobel Prize awarded to Yves Chauvin, Richard R. Schrock, and Robert H. Grubbs in 2005.²⁸²

Despite its popularity, RCM was not performed on a large scale in industry until recently for two main reasons: (a) high dilution is required to avoid intermolecular cross metathesis as a competing side reaction, which considerably decreases the throughput, and (b) the cost and limitations in the commercial availability of the catalysts in bulk. However, in 2005 and 2006, the first pilot plant implementations of RCM were reported by Boehringer Ingelheim for the production of hundreds of kilograms of drug intermediate;²⁸³ shortly thereafter, other groups followed with additional examples. With current research efforts

Scheme 128



Scheme 129



searching for more active catalysts and an increase in the use of this technology to lower costs, the implementation of RCM by the pharmaceutical industry is a feasible enterprise.

Numerous reviews have been published on olefin metathesis.²⁸⁴ The green aspects of this technology have been reviewed as well.²⁸⁵

Researchers at Boehringer Ingelheim in the U.S.A. have published a series of articles on the preparation of antiviral drug **513**, a hepatitis C virus NS3 protease inhibitor. The key step for the preparation of the 15-membered macrocycle moiety on the molecule is a ring-closing metathesis reaction carried out on diene **510** (Scheme 129). In a comprehensive report covering the origin of this work,²⁸³ a thorough study of RCM optimization during process development is described. Ru catalysts **511** (first-generation Hoveyda),²⁸⁶ **514** (first-generation Grubbs),²⁸⁷ **515** (second-generation Grubbs),²⁸⁸ and **516** (second-generation Hoveyda)²⁸⁹ were evaluated for RCM of diene **510** (Figure 2). Preliminary experiments provided macrolide **512** exclusively as the *cis*-cycloalkene (more thermodynamically stable than the *trans*-isomer). However, Grubbs's first-generation catalyst caused epimerization of the cyclopropane prior to ring-closing, which was attributed to the presence of liberated PCy₃ from the catalyst in the reaction medium. Further investigations revealed that residual pyrrolidine **517** (precursor to **510**, Figure 3) from the previous step contributed to racemization as well. Alternatively, Hoveyda's first-generation catalyst at 5 mol% loading did not induce epimerization and afforded **512** consistently in >90% yield. The more active, second-generation catalysts of Grubbs and Hoveyda provided greater amounts of cyclic dimers (8–10 mol%), which were difficult to purge without chromatography. Therefore, Hoveyda's first-generation catalyst **511** was chosen for process development.

When Hoveyda catalyst **511** was further investigated for RCM of diene **510**, four issues were identified that would make the cyclization difficult to implement on a large scale: (a) high catalyst loading (5–7 mol%) was needed for reaction completion in CH₂Cl₂ at reflux (although only 2–3 mol% when diene **510** was first passed through a pad of silica), and efforts to recycle the catalyst were unsuccessful; (b) long reaction times were required (24 h in CH₂Cl₂ at reflux); (c) high dilution was required, as the optimal concentration for high yields was 0.01 M and more concentrated mixtures generated oligomers; (d) active catalyst present during workup and concentration promoted ring-opening of **512** and lowered the isolated yield of RCM product. This fourth issue was resolved by using mercaptosuccinic acid as a catalyst inactivator, which could be removed by base and also reduced the amount of residual Ru in the intermediate **512**.

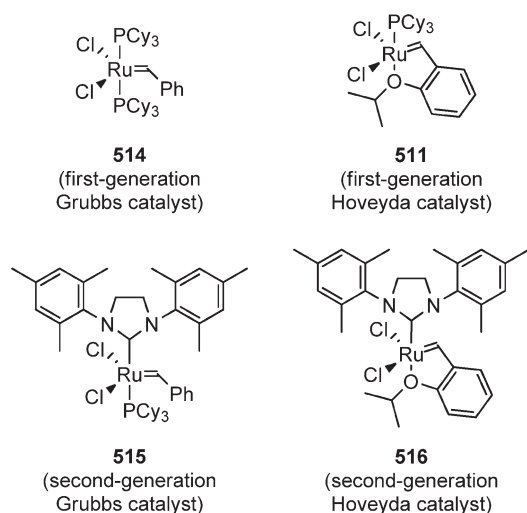


Figure 2

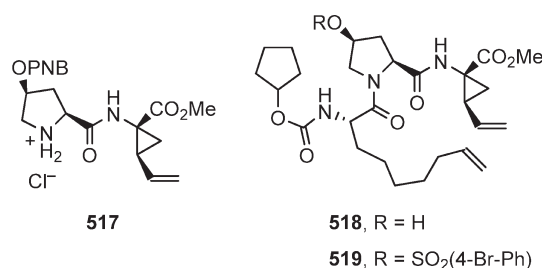


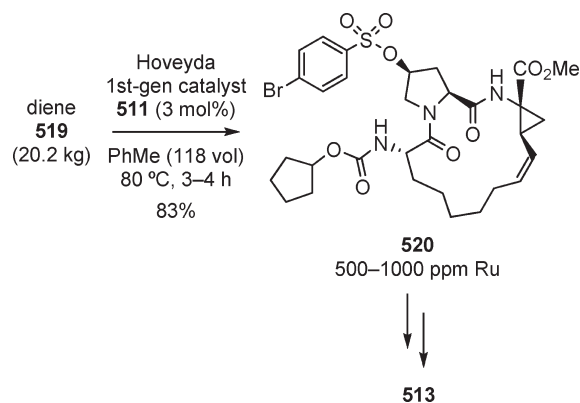
Figure 3

Several techniques were explored for the removal of residual Ru.²⁹⁰ The best results were obtained when the methyl ester precursor to macrolide **513** was treated with charcoal in EtOAc and recrystallized from heptane/EtOAc, which afforded material with only 4 ppm Ru. Other solvents and different charcoal grades gave 5–30 ppm Ru.

Additional dienes **518** and **519** (Figure 3) were also evaluated for RCM with catalyst **511**.²⁸³ The reaction of hydroxy diene **518** led to substantial dimer formation, which could be reduced to 6% when performed in THF. However, purging these dimers was challenging and required chromatography. Alternatively, the RCM of brosyl-containing diene **519** in THF generated somewhat lower amounts of dimers (4–5%), but at the expense of a slower reaction rate compared to **518**.

On the basis of the learnings from these previous studies, the researchers at Boehringer Ingelheim in Germany implemented the first large-scale manufacture of macrolide **513** via RCM on the brosyl-protected **519** (Scheme 130).²⁹¹ Even though RCM reactions are generally performed in CH₂Cl₂, the use of toluene was a major improvement as a more environmentally friendly solvent that also facilitated workup. The optimal reaction temperature was set at 80 °C, as decomposition of the diene and macrocycle were observed above 90 °C. Finally, a compromise between dilution and throughput was found at 118 volumes of toluene. During the reaction, continuous sparging with nitrogen removed oxygen and byproduct ethylene from the solution. Further optimization added Hoveyda's first-generation catalyst **511** (3 mol%) in three portions over 2 h due to its instability at high temperatures over prolonged periods of time. The reaction was complete in 3–4 h, and after an aqueous workup (HCl and

Scheme 130



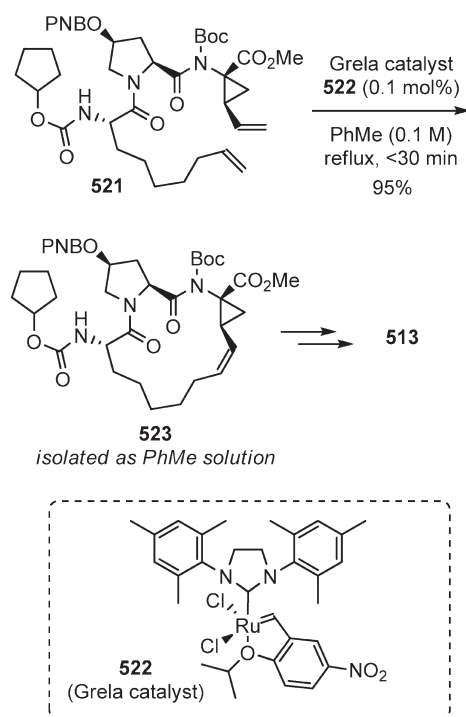
NaHCO₃ washes) and concentration of the toluene solution, macrocycle **520** was isolated from methylcyclohexane as an amorphous solid. This material was contaminated with ~10% dimeric impurities from intermolecular metathesis and 500–1000 ppm of residual Ru. These impurities were purged downstream.

Following this protocol, 400 kg of intermediate **520** was produced in two campaigns in a commercial manufacturing facility. The scale-up was divided among batches to accommodate the high volumes involved. The first batch from manufacturing scale-up behaved differently than laboratory experiments, as a higher catalyst loading was required (5.3 mol%) and 10–15% of a new impurity was formed. The impurity stemmed from epimerization of the cyclopropane and was caused by morpholine present in the technical-grade toluene (<20 ppm) used on scale. Because very large volumes of toluene were employed (2500 L), even such a small amount was equimolecular with respect to the catalyst and altered the catalytic process. This problem was solved in subsequent campaigns by washing the toluene with aqueous HCl followed by azeotropic drying prior to running the reaction.

The last publication in this series by Boehringer Ingelheim on the synthesis of **513** describes a greener, second-generation RCM process for the formation of the macrocycle from diene **521** (Scheme 131).²⁹² RCM catalysts **511** (Hoveyda)²⁸⁶ and **522** (Grela)²⁹³ were evaluated with the goal of reducing solvent usage, catalyst loading, reaction time, and epimerization of the cyclopropane. Second-generation catalysts such as Grela's **522** are more reactive and provide higher TON (turnover number) and TOF (turnover frequency); however, unlike the first-generation catalysts of Grubbs or Hoveyda, Grela's **522** operates under thermodynamic conditions and gives rise to larger quantities of intermolecular metathesis byproducts.

After investigating several substrates for RCM,²⁹⁴ diene **521** was chosen for further development.²⁹² The researchers used the concept of "effective molarity" (EM) as the rate ratio of intramolecular versus intermolecular metathesis ($k_{\text{intra}}/k_{\text{inter}}$), and aimed to increase the EM by a factor of 10 to allow for reactions in standard process equipment and, at the same time, give rise to a greener transformation. Thus, it was found that as little as 0.3–0.4 mol% of Grela's catalyst **522** gave satisfactory results in toluene (0.1 M) at reflux. Under these conditions, the reaction proceeded to completion in <30 min and afforded cyclized product in 95% yield with minimal dimer/oligomer formation. In addition, no epimerization at the cyclopropane was observed. The researchers attributed this lack of epimerization to the Ru catalyst residing at the nonenoic acid

Scheme 131



functionality in its resting state (as determined by ^1H NMR²⁹⁵); as a result, no epimerization is possible even in the presence of basic amines or phosphines. All these improvements resulted in a 27-fold increase in the EM.

Under similar conditions, RCM of the second-generation Boc-protected diene **521** proceeded three times faster than RCM of the first-generation unprotected diene **510**, and on the same diene, Grela's catalyst effected cyclization faster than Hoveyda's **511**. Thus, replacing the diene **510** and catalyst **511** with diene **521** and catalyst **522** shortened the reaction time for RCM from hours (or days) to minutes. The TON was 50–100 times higher for Grela's **522** than Hoveyda's **511**, which allowed for a much lower catalyst loading. Another advantage of this optimized process was that thorough degassing was no longer required, and a simple boil out to remove oxygen before the addition of the catalyst provided satisfactory results. Furthermore, this later-generation RCM avoided epimerization of the cyclopropane without the need for the acidic extraction of residual pyrrolidine **517**, as required by the first-generation process.

A clear benefit of this new technology is the dramatic reduction in solvent usage, as the original method required up to 150000 L of solvent per ton of diene **510** compared to only 7500 L for the reoptimized process with diene **521**. The new process also provided RCM product with lower amounts of residual Ru (usually below 50 ppm without additional metal scavenging). Finally, the E-factor²⁹⁶ (kg of waste per kg of product) was reduced from 370 to 52.

Wang and co-workers at GlaxoSmithKline published several RCM approaches for the preparation of potent cathepsin K inhibitor **526**, a candidate for the treatment of osteoporosis and osteoarthritis. In their first approach,²⁹⁷ the researchers prepared tetrahydroazepine **525** via the RCM of diene **524** using Hoveyda's second-generation catalyst **516**²⁸⁹ in toluene at 80 °C for 2 h (Scheme 132). The influence of possible residual impurities from the preparation of diene **524** on RCM was investigated. The

Scheme 132

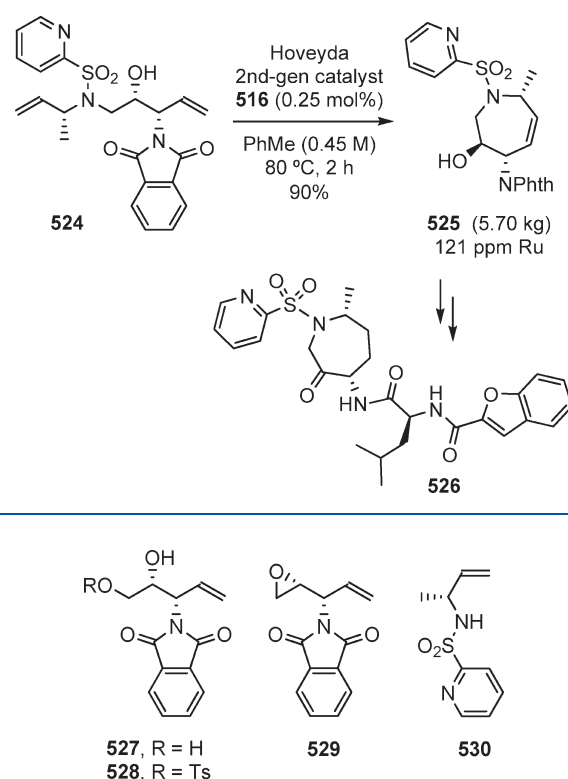


Figure 4

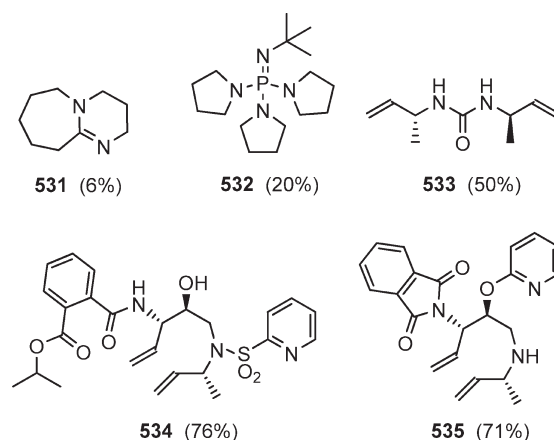
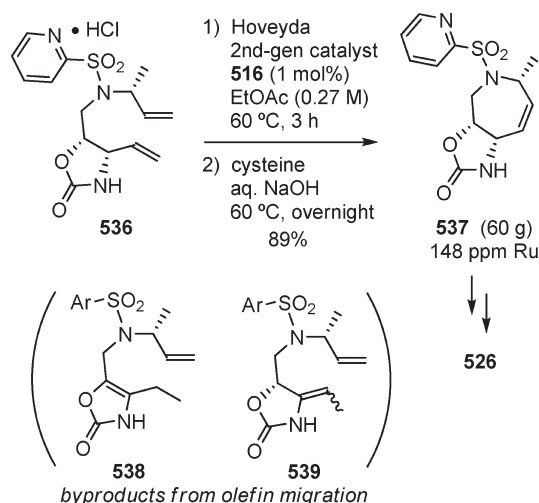


Figure 5

impurities in Figure 4 were found to have no effect on RCM, whereas those in Figure 5 hindered RCM and only allowed the partial conversion shown in parentheses beside each compound number. The largest batch-to-batch variation was influenced mainly by residual **533** and **534** as determined by two projection methods: principal component analysis and projection to latent structure. Once methods were in place for the reproducible production of quality batches of diene **524**, the RCM step was optimized through the use of response surface methodology (RSM).²⁹⁸ Thus, different temperatures (60–90 °C), reaction concentrations (5–10 volumes), and catalyst loadings (0.1–0.3 mol%) were evaluated. The reaction volume had no effect on the transformation, and both high temperature and catalyst loading

Scheme 133

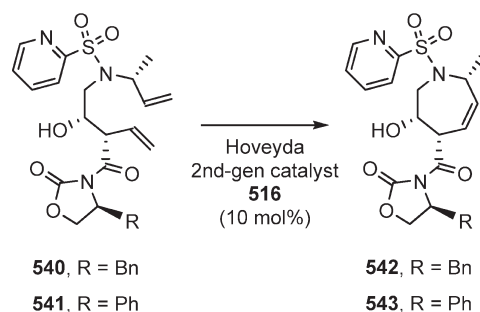


allowed for full conversion. The robustness of the reaction conditions was also tested through the use of a Bayesian reliability approach based on the RSM model data, and it was confirmed that high temperature and catalyst loading afforded a >90% probability of success. As shown in Scheme 132, optimized scale-up conditions heated a solution of diene **524** and 0.25 mol% of Hoveyda's second-generation catalyst in toluene (0.45 M) at 80 °C for 2 h to afford cyclic olefin **525** in 90% yield after crystallization from cold toluene on a kilogram-scale.

After further optimizing this route,²⁹⁹ Wang and co-workers found that very clean diene **524** underwent RCM reaction with as little as 0.1–0.2 mol% of Hoveyda's second-generation catalyst **516** in toluene at reflux, and excellent results were obtained without forming byproducts from double-bond migration. The researchers ascribed this result to the steric bulk of the substituents on the substrate. Once the reaction had reached completion, 80% $\text{P}(\text{CH}_2\text{OH})_4\text{Cl}$ and NaHCO_3 were added and the resulting mixture was stirred at 60 °C for 13 h. After cooling to 40 °C, cyclic olefin **525** (71.8 kg, 96% yield) was crystallized from water and cyclohexane and isolated via filtration with a centrifuge and low Ru content. Alternatively, the second-generation Grubbs catalyst **515** was investigated and effected the RCM of **524** to **525** reproducibly well in small-scale experiments, but inconsistent results and poor conversions were observed on scale-up.

Wang and co-workers at GlaxoSmithKline published a second-generation RCM approach to the tetrahydroazepine of cathepsin K inhibitor **526**.²⁹⁹ This alternative synthetic route generated cyclic intermediate **537** from diene **536** (Scheme 133), which in turn was prepared from the Curtius rearrangement of an acyl azide precursor. Subjecting the free base of **536** to RCM conditions with Hoveyda's second-generation catalyst without first purifying the diene by chromatography led to incomplete reactions and olefin migration byproducts **538** and **539** (20–30% in toluene at reflux). Other solvents and additives (HOAc ,³⁰⁰ styrene, or C_3PO)³⁰¹ did not improve the conversion or eliminate olefin migration. However, when diene **536** was prepared in high purity as the HCl salt, the RCM was more reliable and proceeded in EtOAc at lower temperature (60 °C) while forming only small amounts of olefin migration byproducts (<2%). RCM product **537** was isolated in excellent yield after a basic, aqueous cysteine treatment³⁰² (Ru scavenger) and recrystallization from heptane/EtOAc. The final Ru content in **537** was only 148 ppm.

Scheme 134



Several other approaches for Ru removal were tested. Thus, silica gel or alumina only scavenged <50% of the residual Ru. Alternatively, combinations of $\text{P}(\text{CH}_2\text{OH})_4\text{Cl}$ /base or cysteine/base removed more than 80% Ru. Unfortunately, $\text{P}(\text{CH}_2\text{OH})_4\text{Cl}$ /base generated byproduct HCHO, which reacted with the carbamate nitrogen of **537**, and so cysteine/base was chosen for scale-up. Furthermore, residual phosphorus compounds derived from $\text{P}(\text{CH}_2\text{OH})_4\text{Cl}$ were found to poison the subsequent olefin hydrogenation with 10% Pd/C.

Wang and co-workers at GlaxoSmithKline explored a third-generation RCM approach to the tetrahydroazepine core of cathepsin K inhibitor **526**.²⁹⁹ To this end, several catalysts (**514**, **515**, **516**, and Fürstner's catalyst³⁰³) were screened for the cyclization of oxazolidinone dienes **540** and **541** (Scheme 134); however, only Hoveyda's second-generation catalyst **516** gave complete conversion but required high catalyst loadings (10 mol%). The high catalyst loading led to high Ru content in products **542** and **543**, and metal purging remedies such as $\text{P}(\text{CH}_2\text{OH})_4\text{Cl}/\text{NaOH}$ could not be applied due to substrate decomposition.

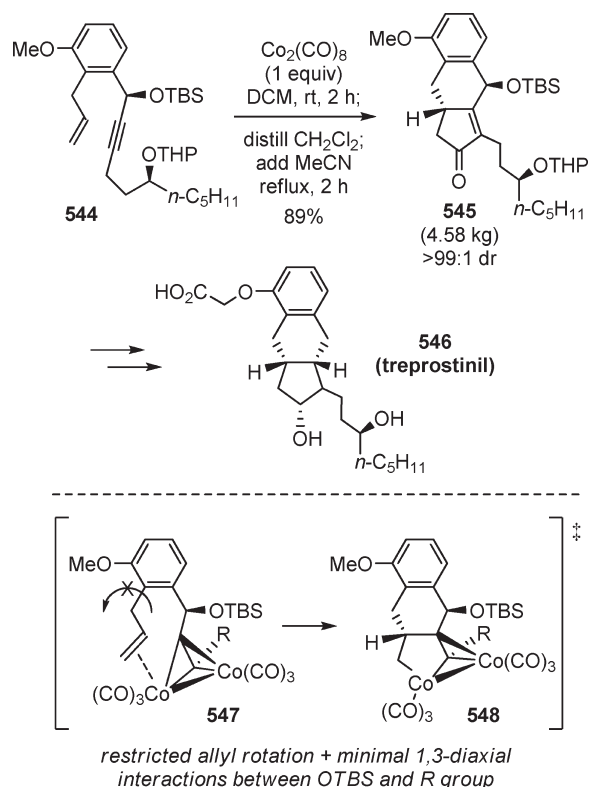
2.13. Pauson–Khand Reaction

Since its seminal publication in 1973,³⁰⁴ the Pauson–Khand reaction has become a powerful tool for the assembly of cyclopentenones from olefins and acetylene–carbonylmetal complexes.³⁰⁵

Moriarty and co-workers incorporated an intramolecular, asymmetric version of this reaction into the novel synthesis of treprostinil (**546**), a benzindene prostacyclin investigated as a treatment for various cardiovascular diseases (Scheme 135).³⁰⁶ A solution of chiral enyne **544** in CH_2Cl_2 was treated with stoichiometric $\text{Co}_2(\text{CO})_8$ and held at room temperature for 2 h, at which point the solvent was removed by vacuum distillation and the residue was redissolved in MeCN and heated at reflux for 2 h. The cooled reaction mixture was purged with air and filtered through Celite, and cyclopentenone **545** was purified via silica gel chromatography to provide 4.58 kg of material as a single diastereomer.

Moriarty attributed the high yield (89%) and diastereoselectivity (>99% dr) of this intramolecular, asymmetric Pauson–Khand reaction to two steric effects. First, the ring tether bearing an *ortho*-methoxy group is believed to restrict rotational conformations of the allyl group and hold the enyne system in the desired orientation via a Thorpe–Ingold-type effect (Scheme 135).³⁰⁷ Also, the configuration of the TBS ether is thought to direct the stereochemical outcome by promoting a transition state that minimizes destabilizing 1,3-diaxial interactions between the silyl ether and the exocyclic side chain of the acetylene (abbreviated as R in the transition state).³⁰⁸

Scheme 135

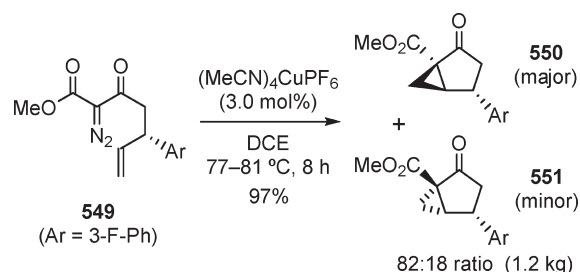


2.14. Cyclopropanation

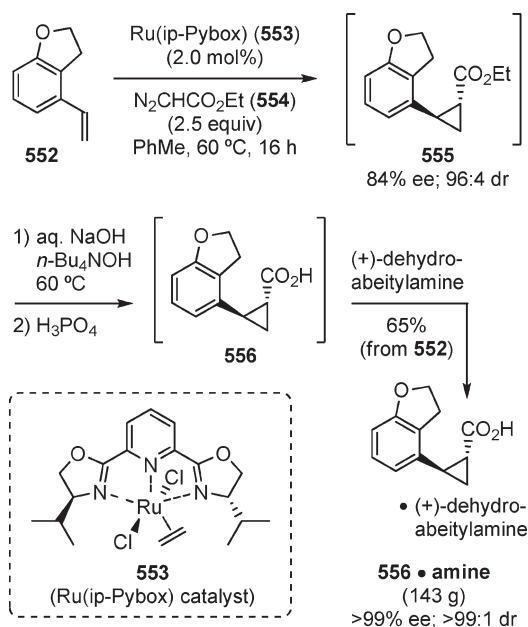
Cyclopropanes are common features of molecules exhibiting antibiotic, antitumor, antibacterial, antifungal, and antiviral activities.³⁰⁹ In 1958, Simmons and Smith were the first to generate cyclopropanes from unactivated olefins using CH_2I_2 in the presence of Zn/Cu (i.e., the Simmons–Smith reaction).³¹⁰ In 1972, Salomon and Kochi reported CuOTf as a catalyst for olefin cyclopropanation via diazo compounds,³¹¹ and subsequent contributions by Davies and Doyle, among others, expanded metal carbenoid cyclopropanations to Ru and Rh catalysts.³¹² These methods have been used for the large-scale manufacture of pharmaceutical compounds. In most cases, the cyclopropane is installed in asymmetric fashion, and some of the methods implemented in the following examples provide products with high stereoselectivity. Enantioselective cyclopropanation reactions have been previously reviewed.³¹³

Palucki and co-workers at Merck developed an intramolecular cyclopropanation for the synthesis of cyclopentanones found in several pharmacologically active compounds.²³³ Scheme 136 shows the optimized conditions for cyclopropanation. Heating diazo compound **549** and 3.0 mol% $(\text{MeCN})_4\text{CuPF}_6$ in 1,2-dichloroethane led to an 82:18 mixture of cyclopropanes **550** and **551**. After quenching the reaction mixture with aqueous saturated NaCl solution, the organic layer was dried over MgSO_4 , filtered through silica gel, and concentrated to provide a mixture of diastereomers **550** and **551**. Greater selectivity was obtained from $(\text{MeCN})_4\text{CuPF}_6$ than from Cu catalysts with stronger coordinating ligands (e.g., CuCl , CuOAc , CuSCN) or Rh catalysts of type Rh_2X_4 ($\text{X} = \text{OAc}$, octanoate, CAP). Interestingly, chiral ligands for Cu or Rh catalysts did not improve the diastereoselectivity for the intramolecular cyclopropanation.

Scheme 136



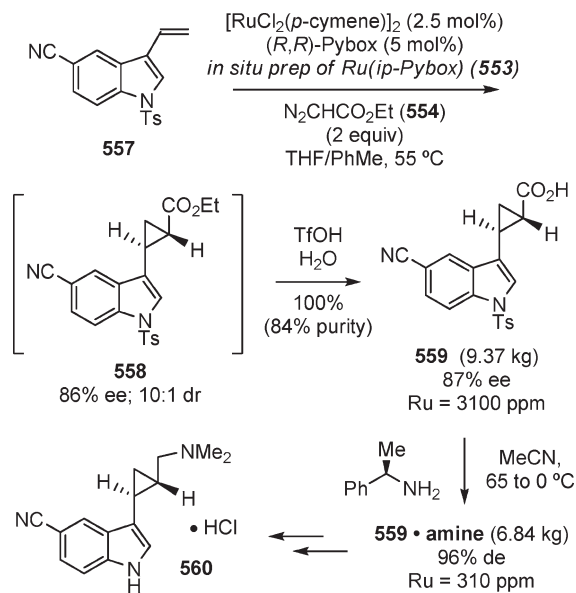
Scheme 137



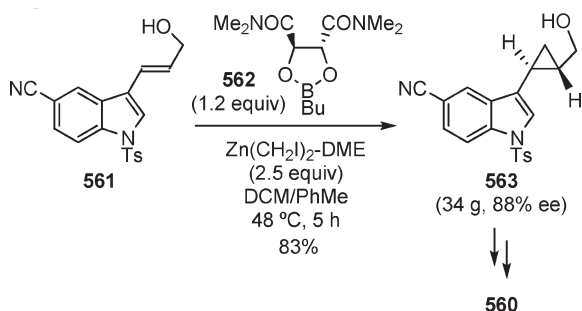
Deshpande and co-workers at Bristol–Myers Squibb developed the asymmetric cyclopropanation of styrene **552** (Scheme 137) for their preparation of melatonin agonists.³¹⁴ Several catalysts were screened for the asymmetric cyclopropanation of **552** via ethyl diazoacetate (**554**), and Nishiyama's $\text{Ru}(\text{ip-Pybox})$ ³¹⁵ system afforded cyclopropane **555** with the best conversion (>97%) and stereoselectivity (84% ee, 96% *trans*-selectivity). The conversion and stereoselectivities were highly sensitive to the stoichiometry and addition rate of ethyl diazoacetate. The optimized process added 2.5 equiv of ethyl diazoacetate (in toluene solution) over 16 h to a mixture of styrene and catalyst in toluene at 60 $^\circ\text{C}$; after complete addition, <2% of **552** remained. The solution of cyclopropyl ester **555** was charged with aqueous NaOH and $n\text{-Bu}_4\text{NOH}$, and the temperature was held at 60 $^\circ\text{C}$ for ester hydrolysis. This saponification proceeded without epimerization, and faster hydrolysis of the *trans*-isomer **555** upgraded the diastereomeric ratio of cyclopropyl acid **556**. Acidic workup and classical resolution with (+)-dehydroabeitylamine crystallized **556** as the amine salt in 65% overall yield with >99% ee and >99% *trans*-selectivity.

Chen and co-workers at Bristol–Myers Squibb developed two asymmetric cyclopropanations for their synthesis of selective serotonin reuptake inhibitor **560**.³¹⁶ The first, outlined in Scheme 138, involves the reaction of vinylindole **557** and ethyl diazoacetate catalyzed by Nishiyama's $\text{Ru}(\text{ip-Pybox})$ **553**.³¹⁵

Scheme 138



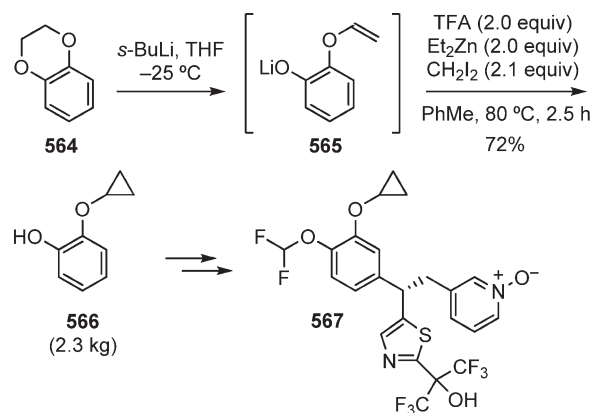
Scheme 139



generated in situ from $[\text{RuCl}_2(p\text{-cymene})]_2$ and Pybox ligand. Slow addition (3 L/h) of ethyl diazoacetate in toluene to the reaction mixture at 55 °C provided cyclopropane ester **558** as the major product with 86% ee and 10:1 *trans*-selectivity. THF was chosen as cosolvent because of its favorable azeotropic properties (vide infra). Cyclopropane ester **558** proved difficult to isolate cleanly and was carried directly into hydrolysis to acid **559**. Basic hydrolysis conditions led to undesired nitrile hydration and detosylation; alternatively, aqueous triflic acid cleaved the ester with minimal nitrile and sulfonamide decomposition after the azeotropic displacement of THF and toluene by water (toluene was a hydrolysis inhibitor). The acidic reaction mixture was heated to remove the EtOH byproduct via continuous distillation and drive hydrolysis to completion, after which the acid **559** was crystallized by water dilution and isolated via filtration. The *trans*-cyclopropane ester **558** was hydrolyzed 3–4 times faster than the *cis*-isomer to increase the diastereomeric ratio of hydrolysis product, and crystallization further increased the diastereomeric ratio from 10:1 to >40:1. Classical resolution of **559** with $(R)\text{-}\alpha\text{-methylbenzylamine}$ further increased the chiral purity to 96% de and reduced Ru levels from 3100 to 310 ppm.

Scheme 139 illustrates an alternative asymmetric cyclopropanation developed at Bristol–Myers Squibb for the synthesis of **560**.³¹⁷ This approach entails the enantioselective Simmons–Smith reaction of allylic alcohol **561**, in which the facial selectivity

Scheme 140



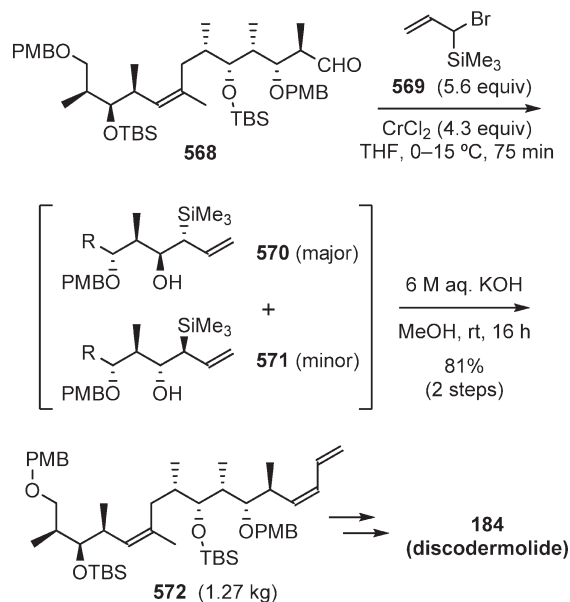
of cyclopropanation is controlled by substrate coordination to dioxaborolane **562** as per the Charetté procedure.³¹⁸ A pre-formed solution of bis(iodomethyl)zinc (from 2:1 $\text{CH}_2\text{I}_2/\text{Et}_2\text{Zn}$) in CH_2Cl_2 and DME was treated with allylic alcohol and dioxaborolane and heated at reflux (48 °C). The resulting cyclopropane **563** was formed with 88% ee. Quenching the reaction mixture with aqueous acid precipitated zinc byproduct that complicated ensuing phase separations; alternatively, quenching with *i*-PrOH and AcOH precipitated zinc acetate for easy removal by filtration. Subsequent NaOH washes of the filtrate removed the butylboronic acid and tartaric amide by-products (from **562**), and after charcoal treatment, **563** was crystallized from heptane dilution without any upgrade in chiral purity.

O'Shea and co-workers at Merck were interested in cyclopropyl-protected catechol **566** as an early intermediate to phosphodiesterase-4 inhibitor **567** (Scheme 140).³¹⁹ Direct installation of the cyclopropyl group via the alkylation of catechol with cyclopropyl bromide failed, and so a one-pot, two-step vinylation–cyclopropanation approach was adopted. The base-induced ring-opening of 1,4-benzodioxane (**564**) with *sec*-BuLi afforded vinylcatechol **565** (incomplete conversion was observed using *n*-BuLi). Subsequent treatment with TFA, Et_2Zn , CH_2I_2 , and toluene at 80 °C provided cyclopropane **566**, and the rate of cyclopropanation was accelerated by the acidic additive (TFA).³²⁰ Aqueous workup and filtration through silica gel provided 2.3 kg of **566**.

2.15. Nozaki–Hiyama–Kishi Reaction

In 1977, Nozaki, Hiyama, and co-workers reported the addition of allylchromium(III) salts to aldehydes and ketones for the synthesis of homoallyl alcohols.³²¹ These organochromium reagents were generated in the presence of the carbonyl electrophiles from allyl halides upon treatment with CrCl_2 . The coupling of less-reactive aryl and alkenyl halides³²² varied with the quality of CrCl_2 ; batches of catalyst contaminated with nickel converted these substrates to the requisite organochromium(III) salts, whereas nickel-free chromium catalysts were less effective. In 1986, Nozaki and co-workers³²³ and Kishi and co-workers³²⁴ independently addressed this inconsistency by deliberately introducing a nickel catalyst to facilitate carbon–chromium bond formation, thus enhancing the reliability of aryl and alkenyl halides (and triflates) for this coupling. Today, this Barbier-type addition of organohalides to carbonyls via the chromium(III) species is called the Nozaki–Hiyama–Kishi reaction.³²⁵

Scheme 141



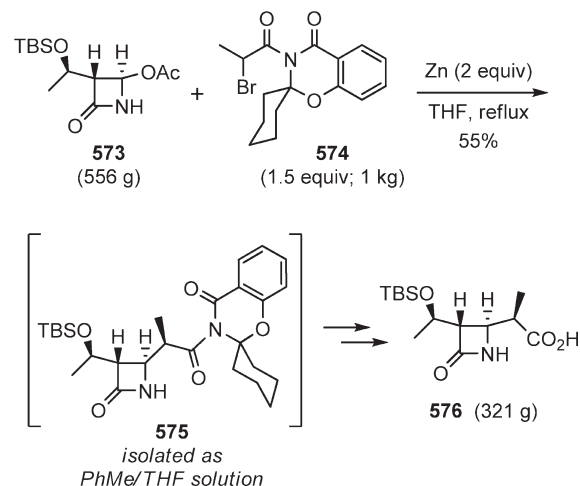
Mickel and co-workers at Novartis, along with Paterson and Florence at the University of Cambridge, incorporated a Nozaki–Hiyama–Kishi reaction (NHK) into the large-scale synthesis of anticancer marine product discodermolide (**184**).¹⁰⁰ They utilized Paterson's one-pot, two-step NHK/Peterson elimination strategy³²⁶ to install the terminal diene (Scheme 141). A suspension of CrCl_2 (4.3 equiv) in THF was treated with aldehyde **568** and allyl bromide **569** (5.6 equiv) to provide a mixture of *anti*-adducts **570** (major) and **571** (minor; actual ratio not disclosed in the report). These combined intermediates were treated with MeOH and 6 M aqueous KOH solution and stirred overnight to effect the Peterson olefination.³²⁷ Both **570** and **571** provided the desired (Z)-olefin, although the diastereomers underwent base-promoted *syn*-elimination at different rates. The KOH used for elimination replaced KH from Paterson's original one-pot NHK/elimination procedure, due to safety concerns with handling hydride base on a large scale.³²⁸ Reaction workup separated and concentrated the organic layer to an oil that was purified via silica gel chromatography to afford 1.27 kg of diene **572** (81% yield over two steps).

2.16. Other Transition Metal-Mediated Couplings for C–C Bond Formation

Examples of Reformatsky and Blaise reactions, Noyori's aldehyde alkylation, Wurtz coupling, and cuprate addition have been included in this section as important transition metal-mediated couplings. Although the stoichiometric Zn or Cu reagents in these transformations do not participate in a catalytic cycle, we believe the utility of these reactions for the synthesis of pharmaceuticals warrants their inclusion in this review. Furthermore, efforts to manage the strong exotherms associated with some of these reactions should capture the attention and interest of process chemists.

2.16.1. Reformatsky Reaction. The Reformatsky reaction, first reported over 120 years ago,³²⁹ is a versatile tool for the addition of metal enolates (typically zinc) to aldehydes and ketones. Progress in the Reformatsky reaction has been reviewed,³³⁰ including catalytic and asymmetric variants.³³¹ A primary concern during implementation on a process scale is the

Scheme 142

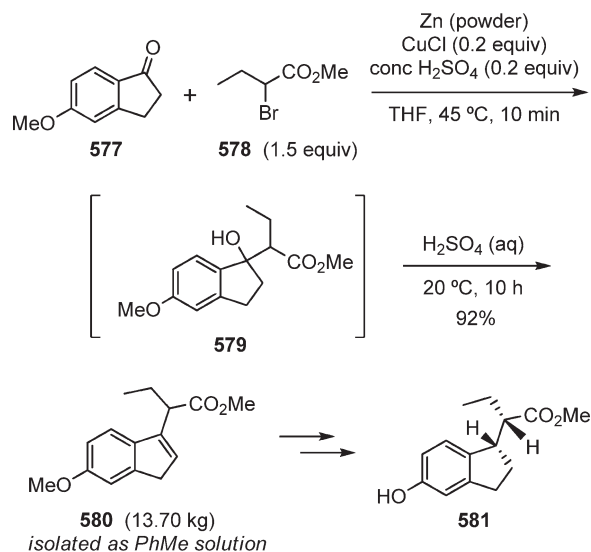


need for careful control of the exotherm associated with zinc enolate formation, because zinc insertion into the α -halo carbonyl precursors is usually preceded by variable induction times that can lead to strong exotherms and runaway reactions. As a result, Zn activation is critical for efficient metal insertion and is generally accomplished in either of two ways: (a) removal of the inactive zinc oxide layer from the surface of Zn metal by chemical or mechanical procedures or (b) preparation of finely distributed metal via reduction of anhydrous zinc halides. The first approach is more common to large-scale applications and accomplished by treating the Zn metal with reagents such as iodine, 1,2-dibromoethane, copper(I) halides, mercuric halides, TMSCl, molecular sieves, or acid washes.^{330e}

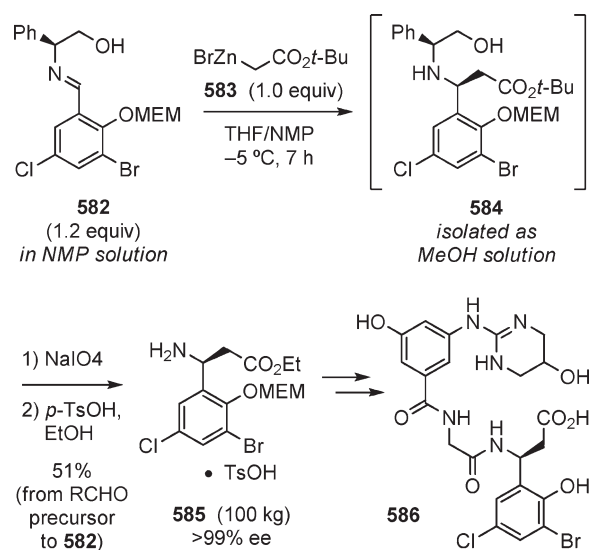
Lu and co-workers at Zhong Shan University in China have incorporated the Reformatsky-type reaction of hemiaminal **573** and bromo amide **574** into the preparation of β -lactam **576**, a key intermediate in the synthesis of 1- β -methyl class of carbapenems (Scheme 142).³³² The main issue during the implementation of the Reformatsky-type reaction of hemiaminal **573** and bromo amide **574** was controlling the large exotherm of coupling. Unfortunately, the slow addition of bromide to a mixture of acetate and Zn in THF at reflux led to long reaction times and low yields from degradation of the acetate. After further process development, these issues were resolved through the simultaneous addition of hemiaminal and bromide to a mixture of Zn and THF at reflux. After reaction completion and aqueous workup, Reformatsky product **575** was carried forward as a toluene/THF solution.

Scherkenbeck and Siegel at Bayer in Germany reported the pilot plant scaleup of the Reformatsky coupling of indanone **577** and methyl 2-bromobutyrate (**578**) en route to indane acetic acid analogue **581**, an intermediate in a drug-discovery program (Scheme 143).³³³ Previously, Zhang and co-workers at Bayer discovered that once even small amounts of Reformatsky product **579** were generated, the coupling consistently progressed to completion despite variable induction periods.³³⁴ Thus, initial pilots were "seeded" with a small-scale batch to promote the coupling for reproducible results; however, this "seeding" procedure was not amenable to scale-up because of the risks associated with charging a vessel containing unquenched contents with new starting materials. Therefore, this group decided to develop a reliable method for Zn activation to overcome these variable induction periods.

Scheme 143

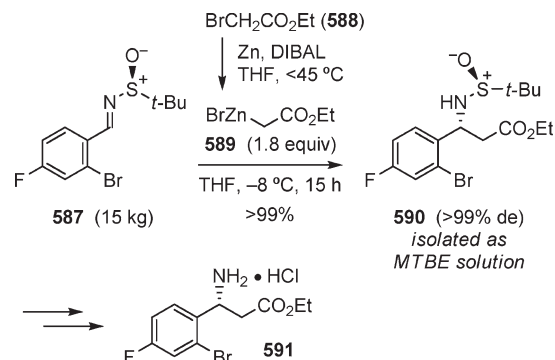


Scheme 144



Zn activation³³⁵ employing I₂, TMSCl, MeMgBr, 1,2-dibromoethane, CuCl, or CuI did not result in an immediate onset for the reaction, and in one instance on a laboratory scale using I₂ as the activator, an exothermic runaway reaction took place. On the other hand, Zn–Cu couple initiated the reaction after only 10% of bromo ester **578** had been added. The in situ preparation of this activated metal was carried out by adding H₂SO₄ to a mixture of Zn and CuCl in THF, which produced an exotherm and hydrogen gas evolution. The Reformatsky reaction was then implemented by adding indanone **577** to the Zn–Cu couple, heating the mixture to reflux, and finally adding bromo ester **578**. The immediate formation of alcohol **579** was then observed. This protocol was scaled up to 350-g batches. Calorimetric data for this reaction suggested a maximum adiabatic temperature rise of 178 °C. To decrease the risk, later campaigns employed more concentrated reactions to increase throughput and managed the exotherm by controlling the addition rate of bromo ester. After the coupling proceeded to completion, the reaction mixture was quenched with aqueous H₂SO₄ to eliminate water and generate

Scheme 145

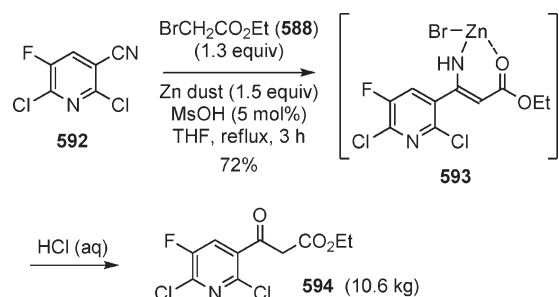


olefin **580**. The sulfuric acid also oxidized excess Zn to ZnSO₄ for easy metal removal by filtration.

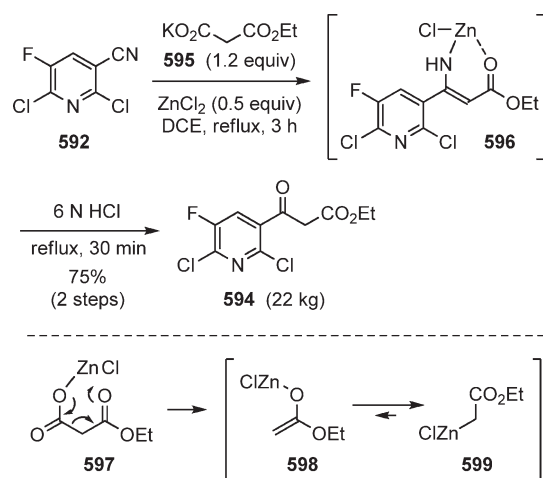
Clark and co-workers at Pfizer have described the pilot plant preparation of β -amino acid ester **585**, a key intermediate in the synthesis of $\alpha_v\beta_3$ integrin antagonist **586** for the treatment of cancer (Scheme 144).³³⁶ On the basis of previous experience with the preparation of chiral β -amino acids through an imino-Reformatsky protocol, this group carried out the asymmetric reaction of chiral imine **582** and Reformatsky reagent **583**. Imine **582** was prepared from the reaction of an aldehyde precursor with (S)-(+)-2-phenylglycinol and isolated as a NMP solution after drying through a column of molecular sieves. Reformatsky reagent **583** was prepared by preactivating Zn with 1,2-dibromoethane in THF at reflux for 1 h and then adding *tert*-butyl bromoacetate in 5 portions at 50 °C to control the exotherm accompanying each addition. Extensive thermokinetic data was collected to develop safe conditions for the preparation of **583**, the most energetic step of the process. The formed Reformatsky reagent was cooled at -15 °C and treated with the solution of imine **582** over 4 h while the internal temperature was held below 5 °C. After an aqueous workup, intermediate **584** was isolated as a MeOH solution and converted to 100 kg of **585** with >99% ee.

Girgis and co-workers at Novartis have published a very detailed study on the Reformatsky coupling of imine **587** and ethyl bromoacetate (**588**) (Scheme 145).³³⁷ This transformation required low temperature for high diastereoselectivity; therefore, any protocol requiring heat for Zn activation had to be implemented separately. Originally, the Zn was activated using 1,2-dibromoethane in THF at reflux, but the yields of the Reformatsky reaction were moderate (50–60%) and several impurities were identified. After further work, DIBAL was identified as the best Zn activator because it performed this task almost instantaneously when a small amount of bromo ester was present (5%). RC1 calorimetric studies revealed that the Zn activation occurred at 40 °C, and at this temperature, a sharp but brief exotherm was detected that could be easily managed in the plant. The final experimental procedure implemented on 800-L scale called for the addition of a 25% DIBAL solution in toluene to a mixture of granular Zn and 5% bromo ester in THF at 32 °C. A small exotherm was observed, and the reaction mixture was heated to 41 °C over 5 min. The rest of the bromo ester was added while the internal temperature was held below 45 °C, and after 1 h, the mixture was cooled to -10 °C. The solution of **589** was then treated with imine **587** while maintaining a temperature below -5 °C. Once the reaction was complete, slow quenching with aqueous NaCl (to control the exotherm) and a solvent

Scheme 146



Scheme 147

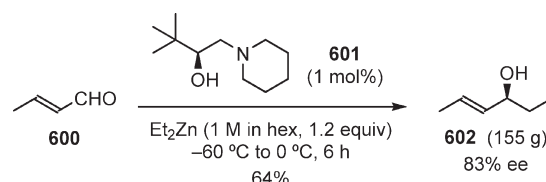


switch to MTBE afforded the desired Reformatsky product **590** in quantitative yield and >99% de.

2.16.2. Blaise Reaction. The Blaise reaction is a variation of the Reformatsky reaction in which the addition of a zinc enolate to a nitrile coupling partner provides an imine intermediate that can be hydrolyzed to the β -keto ester.³³⁸ As with the Reformatsky reaction, the major concern for the Blaise reaction is managing the exotherm and induction times associated with Zn insertion into the α -halo carbonyl precursor. The Blaise reaction has been recently reviewed.³³⁹

Shin and co-workers at LG Life Sciences in Korea reported the kilogram-scale preparation of β -keto ester **594**, an intermediate for the synthesis of quinolone antibiotics possessing a naphthyrindone ring, such as enoxacin, tosufloxacin, trovafloxacin, and gemifloxacin (Scheme 146).³⁴⁰ The Blaise reaction of cyanopyridine **592** and ethyl bromoacetate (**588**) was carried out after activating the Zn dust with MsOH³⁴¹ in THF at reflux for 15 min in the presence of **592**, and then adding the bromo ester dropwise over 2.5 h. An acidic quench hydrolyzed β -aminoacrylate intermediate **593**, and recrystallization from cold H_2O /THF afforded the desired β -keto ester **594** in 72% yield. Zinc activation with MsOH proved simpler than activation with aqueous HCl, although the researchers still reported an unpredictable induction period from this protocol. Any issues regarding an induction period were solved by increasing the amount of MsOH to 5 mol% during Zn activation, which allowed for the coupling to start immediately upon addition of ethyl bromoacetate. This was critical for better control of large-scale reactions.

Scheme 148



LG Life Sciences published a second article on an alternative protocol for the preparation of **594** from a decarboxylative Blaise reaction (Scheme 147).³⁴² The previous method outlined in Scheme 146 was highly exothermic and employed the lachrymator ethyl bromoacetate, which is not optimal for large-scale preparations. On the basis of reports that Cu(I) salts promote the decarboxylation of malonic acid,³⁴³ a new approach employed potassium ethyl malonate in the presence of ZnCl_2 in DCE at reflux with the assumption that zinc ethyl malonate (**597**, derived from **595**) would decarboxylate to **599** for Blaise coupling with nitrile **592**. A screen of Zn salts revealed that ZnCl_2 , ZnBr_2 , and $\text{Zn}(\text{OTf})_2$ provided complete conversion of **592**, whereas ZnI_2 gave only 5% conversion after 15 h and Mg salts (chloride, bromide, iodide) did not provide any Blaise product. Ultimately, ZnCl_2 (0.5 equiv) was chosen in combination with DCE, and lesser stoichiometries of ZnCl_2 reduced the reaction rate considerably.

Most significantly, unlike the aforementioned process using ethyl bromoacetate (Scheme 146), this revised protocol was endothermic and therefore safer to implement in the plant. In addition, the CO_2 evolution could be managed by the controlled addition of reagents.

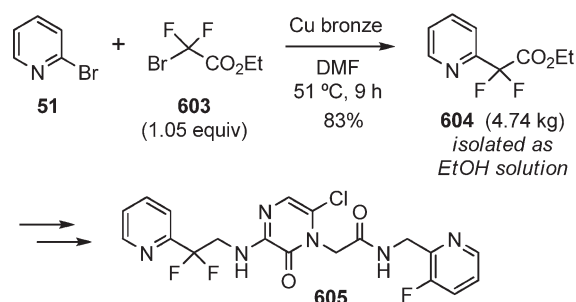
2.16.3. Noyori Aldehyde Alkylation. In 1986, Noyori and co-workers first reported the enantioselective addition of dialkylzincs to aldehydes in the presence of chiral amino alcohols.³⁴⁴ To date, however, the application of this chemistry toward the large-scale synthesis of pharmaceuticals has been very limited.

Moher and co-workers at Eli Lilly described the application of Noyori's amino alcohol (*S*)-**601**³⁴⁵ in the asymmetric ethylation of *trans*-crotonaldehyde (**600**) with Et_2Zn (Scheme 148).³⁴⁶ When the original conditions developed by Noyori were applied to **600** with (*S*)-**601** of 96% ee, Noyori product **602** was obtained in 84% ee and 63% yield after distillation. Efforts to improve the enantioselectivity in different solvents failed.

Interestingly, a previous report using the opposite enantiomer (*R*)-**601** for the reaction of benzaldehyde and Et_2Zn describes nonlinear effects observed from catalyst of low enantiomeric excess.³⁴⁷ On the basis of this information, Moher and co-workers carried out the reaction of *trans*-crotonaldehyde (**600**) and Et_2Zn using (*S*)-**601** of varying chiral purities. Moher and co-workers discovered that (*S*)-**601** of 98% ee provided Noyori product **602** in 86% ee, whereas (*S*)-**601** of only 15% ee afforded Noyori product in 80% ee. As a result of this remarkable asymmetric catalyst amplification, **602** was available with ~80% ee without needing to substantially upgrade the chiral purity of (*S*)-**601** via multiple recrystallizations.

2.16.4. Wurtz Coupling. The traditional Wurtz coupling is the homocoupling of alkyl halides in the presence of sodium metal to give symmetrical products.³⁴⁸ Alternatively, Wurtz-type couplings can be effected using Cu, Zn, Ni, and Mn catalysts. The only example of Wurtz coupling included in this review is a Cu-catalyzed variant that allowed for the preparation of an unsymmetrical intermediate based on previous literature reports.³⁴⁹

Scheme 149



Researchers at Merck have synthesized reversible competitive thrombin inhibitor **605** for the treatment and prevention of deep vein thrombosis and cardiogenic thromboembolism.³⁵⁰ Because 2-bromopyridine (**51**) and ethyl bromodifluoroacetate (**603**) are readily available in large quantities, a Wurtz coupling was explored for the synthesis of intermediate **604** (Scheme 149).³⁵¹ Safety testing determined that there was potential for a runaway reaction in DMSO at 50 °C, and as a consequence, other solvents were evaluated. Only DMF and NMP afforded complete reaction within 24 h, and only DMF gave reproducible yields on scale. In addition, DMF was considered safe for scale-up work, and so it was selected for further development. Thus, the Wurtz coupling of **51** and **603** was performed in DMF at 51 °C for 9 h in the presence of copper bronze.³⁵² After an aqueous workup, ethyl 2,2-difluoro-2-(2-pyridyl)acetate (**604**) was isolated in 83% yield as an EtOH solution.

2.16.5. Cuprate Addition. There are countless examples of cuprate additions to electrophiles (e.g., Michael acceptors) on a laboratory scale; however, large-scale examples for the synthesis of pharmaceuticals are rare.

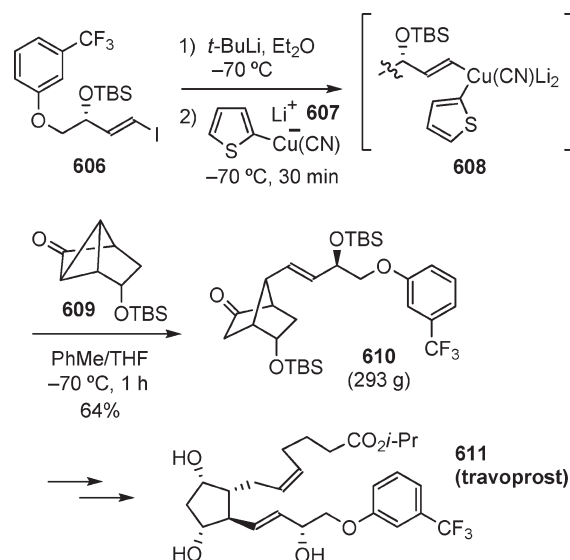
Lennon and co-workers at Chirotech Technology Limited in the U.K. reported the preparation of travoprost (**611**), a potent prostaglandin analogue for the treatment of glaucoma and ocular hypertension (Scheme 150).³⁵³ The introduction of the arene-bearing side chain on the cyclopentyl ring of travoprost was accomplished through the reaction of higher-order cuprate **608** and polycyclic ketone **609**. Thus, iodide **606** underwent transmetalation with *t*-BuLi in pentane/Et₂O at −70 °C to produce an alkenyllithium intermediate. In a separate vessel, thiophene was treated with *n*-BuLi at −30 °C followed by 1 equiv of CuCN to prepare a solution of cuprate **607**. The subsequent addition of **607** to the preformed alkenyllithium at −70 °C generated the higher-order cuprate **608**, which was then treated with a pre-cooled (−70 °C) solution of polycyclic ketone **609** to form adduct **610** via cyclopropane opening. An aqueous workup and silica pad treatment provided 293 g of **610** (64% yield).

3. CARBON–HETEROATOM BOND FORMATION

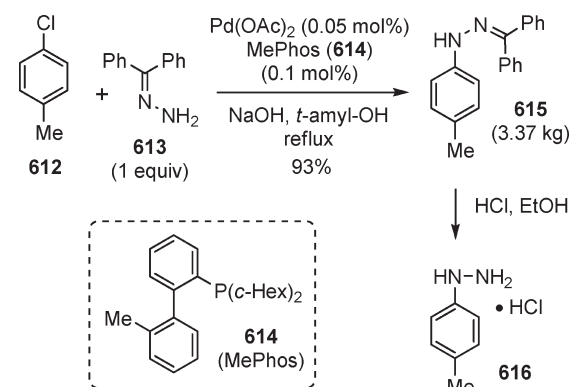
3.1. Buchwald–Hartwig Amination (C–N Bond Formation)

Compounds with *N*-aryl functionality are common to natural products³⁵⁴ and other materials of interest.^{355,356} Classical Ullmann conditions for the amination of aryl halides require stoichiometric copper and very high temperatures.⁷ In 1983, Migita and co-workers reported the first Pd-catalyzed amination of an aryl halide in a procedure using *n*-Bu₃SnNEt₂ for the transfer of a diethylamino group.³⁵⁷ In the years that followed, newer and milder transition metal-catalyzed protocols for the general coupling of amines by Buchwald, Hartwig, and others have impressively advanced the scope of C–N bond forma-

Scheme 150



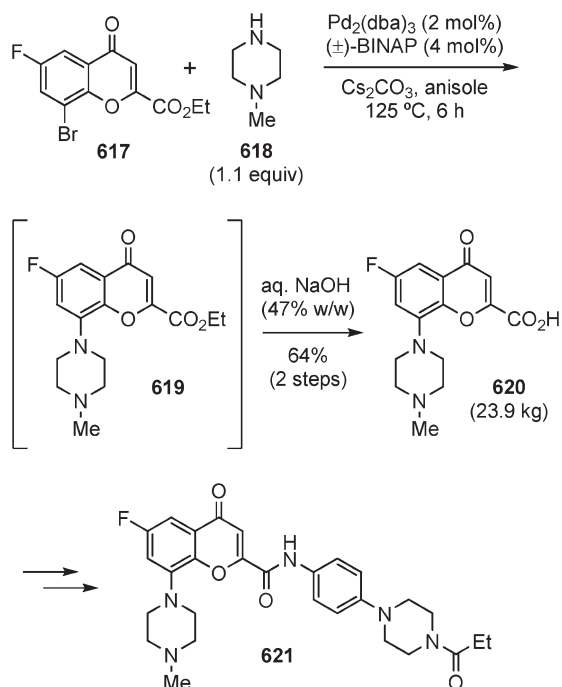
Scheme 151



tion.^{7,358} Modern and reliable methods for the Pd- and Cu-catalyzed couplings of aryl, alkenyl, and alkynyl halides (and sulfonates, etc.) with various nitrogen nucleophiles have provided new tools for the large-scale manufacture of drug candidates.

Mauger and Mignani at Rhodia in France developed an industrial-scale, Pd-catalyzed hydrazone to generate *N*-*p*-tolyl benzophenone hydrazone (**615**), an intermediate for active ingredients in pharmaceutical (and agricultural) products, from 4-chlorotoluene (**612**) and benzophenone hydrazone (**613**) (Scheme 151).³⁵⁹ Original Buchwald conditions (1 mol% Pd(OAc)₂, 3 mol% BINAP, NaOt-Bu, toluene, 110 °C, 24 h)^{358g} suffered from poor conversion on scale-up. An exhaustive screen of Pd catalysts, bases, solvents, and temperatures (80–150 °C) failed to immediately provide acceptable results. The choice of ligand, however, proved key to successful amination. BINAP, dppf, and PPh₃ could not effect the amination; however, Buchwald's biphenylphosphines promoted this coupling very well. Final conditions preformed the catalyst under argon from Pd(OAc)₂ (0.05 mol%) and MePhos (0.1 mol%) in *t*-amyl alcohol at rt. The catalyst solution was then added to a degassed solution of 4-chlorotoluene (**612**) and ground NaOH in *t*-amyl-OH at reflux. Finally, benzophenone hydrazone was added in portions over 2 h. Calorimetric studies revealed the potential for a very large temperature rise if all the benzophenone hydrazone

Scheme 152



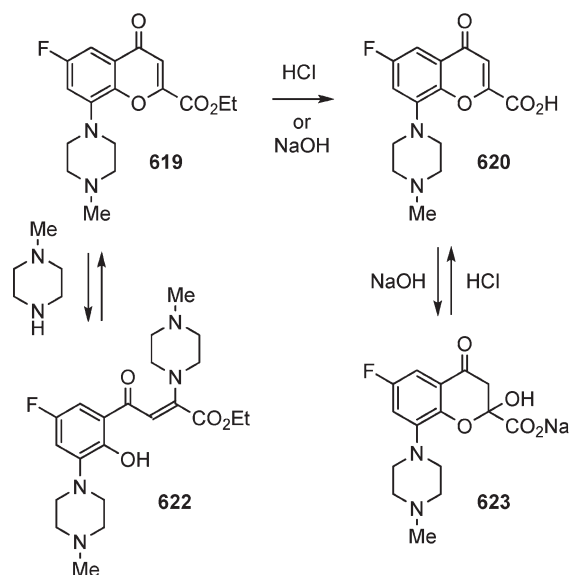
was charged in one portion. Reaction progress was monitored by Raman spectroscopy. Once the coupling reached completion, an aqueous workup extracted salts and the coupled hydrazone **615** crystallized in 93% yield from the organic solution upon cooling. This material was contaminated with 500 ppm Pd, but acid treatment in the subsequent hydrazine deprotection reduced the levels of residual metal in **616**.

Robinson and co-workers at AstraZeneca in the U.K. and India have described the preparation of **621**, a 5-HT receptor antagonist candidate for the treatment of depression and anxiety (Scheme 152).³⁶⁰ The key step in the synthesis was the Pd-catalyzed coupling of bromochromone **617** and *N*-methylpiperazine (**618**) under Buchwald-Hartwig conditions. The original protocol called for $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ and Cs_2CO_3 in toluene at 80°C , which after 138 h afforded the coupling product **619** in 73% yield on 50-g scale following chromatography. Subsequent ester hydrolysis with LiOH provided acid **620** in 95% yield. However, on larger scale (280 g), the yield dropped to 44%, requiring the development of alternative conditions. Because these initial coupling conditions induced partial ester hydrolysis, the researchers decided to avoid the isolation of intermediate **619** and carry out the final hydrolysis step in aqueous NaOH. In addition to the very long reaction times, other issues needing resolution included chromone ring-opening in the presence of *N*-methylpiperazine and the conversion of acid **620** to hydrate **623** during the aqueous alkali hydrolysis (Scheme 153).

The problem associated with the long reaction time on scale was solved by switching to anisole as solvent and running the reaction at higher temperature. In addition, coupling at higher reaction temperature prevented the accumulation of ring-opened byproduct **622** via reversible Michael addition of *N*-methylpiperazine to the α,β -unsaturated ester of **619**. Finally, acidifying the reaction mixture with HCl to pH 3 on workup converted any hydrate **623** to the desired acid **620**.

To this end, the optimized protocol charged a solution of bromide **617** and *N*-methylpiperazine to a mixture of $\text{Pd}_2(\text{dba})_3$

Scheme 153

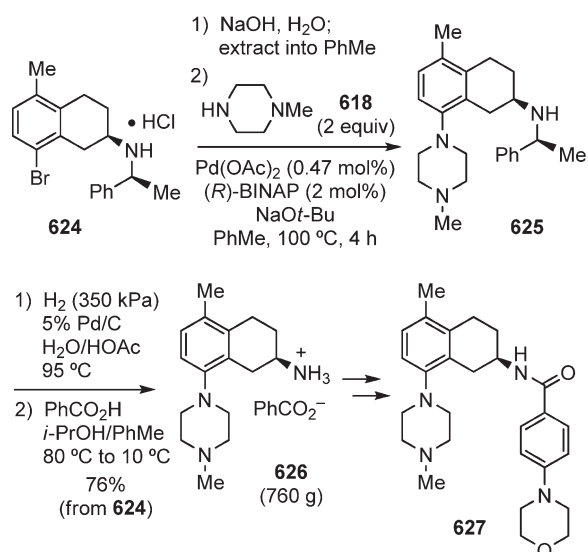


(2 mol%), (\pm)-BINAP (4 mol%), and Cs_2CO_3 in anisole at 125°C and heated at 125°C for 6 h (Scheme 152). Upon cooling, ester hydrolysis of the coupling product **619** was accomplished with 47% w/w NaOH at 45°C . After a carbon treatment and filtration through Harbolite 800 filter aid, the aqueous layer containing **620** and hydrate **623** was acidified with concentrated HCl to pH 3 to effect dehydration. The resulting acid **620** precipitated from solution and was isolated via filtration in 64% yield (average from three batches).

Robinson and co-workers noted that a 5-kg batch afforded little product, most likely due to the presence of oxygen and poor stirring. The latter contributed to the incomplete dissolution of catalyst and ligand, and the insoluble Cs_2CO_3 might have coated the $\text{Pd}_2(\text{dba})_3/(\pm)\text{-BINAP}$ to further prevent these reagents from dissolving into solution. The influence of degassing and mixing on the final outcome was confirmed in subsequent laboratory experiments. Careful degassing and dissolution of $\text{Pd}_2(\text{dba})_3/(\pm)\text{-BINAP}$ prior to the addition of Cs_2CO_3 provided more reliable yields in the 48–63% range. Further coupling optimization prior to subsequent plant-scale campaigns led to an additional improvement in which the NaOH loading was reduced from 2.2 to 1.3 equiv, thus avoiding the formation of hydrate **623** entirely. After all these improvements, 116 kg of bromochromone **617** were converted to acid **620** in three batches, each with >98.5% purity and <5 ppm of residual Pd.

Federsel and co-workers at AstraZeneca in Sweden employed an amination for the pilot plant preparation of novel 5-HT_{1B} receptor antagonist **627** for the treatment of central nervous system disorders such as anxiety and depression.³⁶¹ Key to this project was the development of a robust procedure for installing *N*-methylpiperazine (**618**) onto the aromatic ring of **624** (Scheme 154), and a Buchwald-Hartwig amination approach was immediately identified as the most suitable for scale-up. Prior to this approach, a Smiles rearrangement³⁶² from the phenol was implemented, but this required NaH (undesirable on a large scale) and elevated temperatures to introduce the amino functionality. A second route formed the piperazine from the corresponding aniline and *N,N*-bis-2-chloroethylamine, but the latter is a well-known carcinogen and not ideal for scale-up. These Smiles and alkylation routes also required multistep

Scheme 154

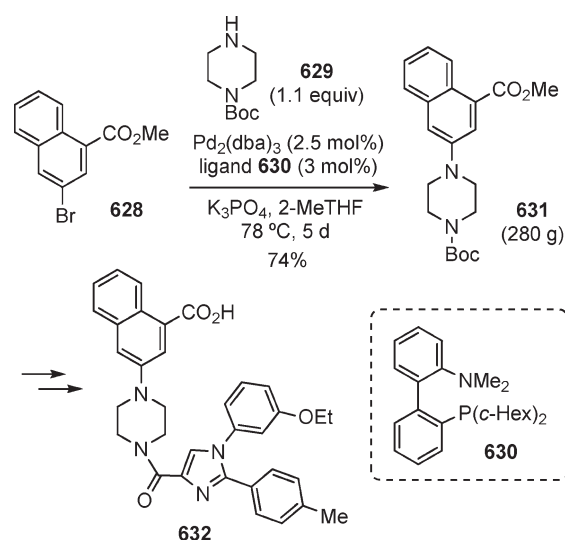


sequences that could be avoided with a more direct coupling reaction.

During the first- and second-generation routes to **627** (not shown), the Buchwald–Hartwig coupling employed the *N,N*-dibenzylprotected analogue of aryl bromide **624** and *N*-methylpiperazine (**618**), which, in the presence of $\text{Pd}(\text{dba})_2$ (1.5–3.1 mol%), (*R*)-BINAP, and NaOt-Bu in toluene, afforded the coupling product in 84–88% yield during laboratory experiments up to 200-g scale. This chemistry could be carried out with catalyst loading as low as 0.1 mol% at the expense of longer reaction times (4 versus 20 h). Surprisingly, these conditions were not reproducible in a third-generation route using aryl bromide **624**, as they led to 11% formation of desbromo-**624** (free base) and Pd-catalyst precipitation as a brownish solid. The ligand/Pd ratio was identified as the major factor contributing to desbromo-**624**; >2.5:1 ligand/Pd was required to minimize byproduct formation, suggesting that dehalogenation was most likely arising from either nonligated Pd or Pd ligated by amine rather than phosphine ligand. Greater excesses of *tert*-butoxide base (above 1.4 equiv) also suppressed debromination, and replacing the $\text{Pd}(\text{dba})_2$ with $\text{Pd}(\text{OAc})_2$ contributed to the overall robustness. Additional findings include the following: (a) The reaction could tolerate up to 0.06% v/v H_2O . (b) The use of higher-boiling xylene had no appreciable effect on the yield but increased the reaction rate. (c) Switching to a noninert atmosphere had essentially no effect. (d) $\text{P}(t\text{-Bu})_3$ as ligand gave the best performance of alternative ligands (Xantphos, $\text{P}(o\text{-tolyl})_3$), but the ratio of desired **625** to desbromo-**624** (free base) was 6:1. One possible alternative to NaOt-Bu was sodium *tert*-pentoxide, which is much more soluble in toluene, but desbromo byproduct was obtained in slightly larger amounts and there was no cost incentive to switch to this base.

In the final process outlined in Scheme 154, the HCl salt **624** was treated with aqueous NaOH and the free base was extracted into toluene and concentrated to remove water via azeotrope. In a second reactor, $\text{Pd}(\text{OAc})_2$ (0.47 mol%) and (*R*)-BINAP (2 mol%) were dissolved in toluene and the mixture was heated to 40 °C. *N*-Methylpiperazine was added, the resulting mixture was transferred to the toluene solution of aryl bromide, and the

Scheme 155

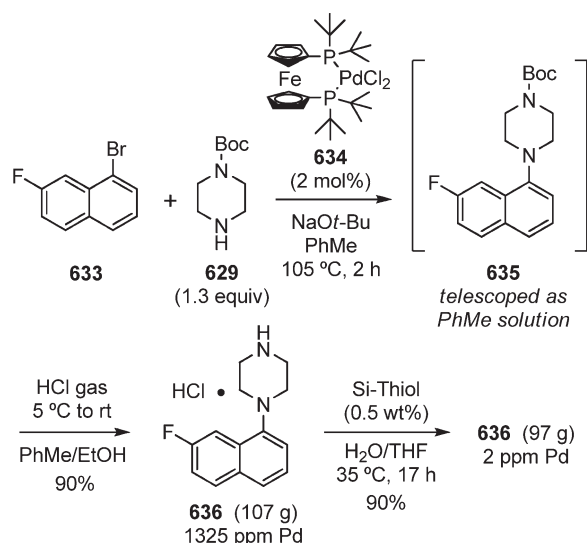


contents of the vessel were heated at 100 °C for 4 h. After an aqueous workup at pH 5 to extract desbromo-**624** from the organic phase, the solution of **625** was subjected to catalytic hydrogenation to cleave the benzyl group followed by salt formation with benzoic acid to furnish **626** in 76% yield. This process was further scaled to 100-kg batch size.

Kueth and co-workers at Merck reported the large-scale preparation of compound **632**, a potent and selective cholecystokinin 1R receptor agonist candidate for the treatment of obesity (Scheme 155).³⁶³ Original conditions for the conversion of bromonaphthalene **628** and *N*-Boc-piperazine (**629**) to intermediate **631** using $\text{Pd}_2(\text{dba})_3$, ligand **630**, NaOt-Bu , and toluene or dioxane (85 °C, 18 h) proved unreliable for scale-up and provided yields in the 10–50% range. Because of tight timelines that limited progress to find better alternatives, the researchers decided to optimize this original protocol. Whereas mixing all the reagents and catalyst system before heating gave low conversions and variable outcomes, better results were obtained by combining the Pd catalyst and ligand prior to the addition of the aryl bromide and piperazine. This preforming of the active catalyst allowed for coordination of ligand **630** to Pd without competitive ligation of the amine. Process development led to a protocol in which $\text{Pd}_2(\text{dba})_3$ (2.5 mol%) and ligand (**630**, 3 mol%) were mixed with powdered anhydrous K_3PO_4 in 2-MeTHF at 78 °C before adding **628** and **629** over 2 h. Whereas smaller-scale experiments with magnetic stirring were complete within 18–24 h (presumably because of the grinding effect of the stirring bar),³⁶⁴ mechanically stirred, larger-scale runs (>100 g) required up to 5 days but had no other effect on reaction outcome. On workup, the mixture was filtered and treated with a 2,4,6-trimercaptotriazine polystyrene-based resin (MP-TMT)^{13,365} to scavenge Pd from this coupling (and Hg from a previous step). After recrystallization from heptane/*i*-PrOAc, coupling product **631** was obtained in 74% yield with 37 ppm Pd (and <3 ppm Hg).

Magano and co-workers at Pfizer have reported the preparation of naphthalenylpiperazine **636**, a key intermediate in the synthesis of a drug candidate (Scheme 156).³⁶⁶ This material had been previously prepared in gram quantities through the classical reaction of 1-amino-7-fluoronaphthalene and bis-(2-chloroethyl)amine in chlorobenzene (solvent) at 135 °C for

Scheme 156

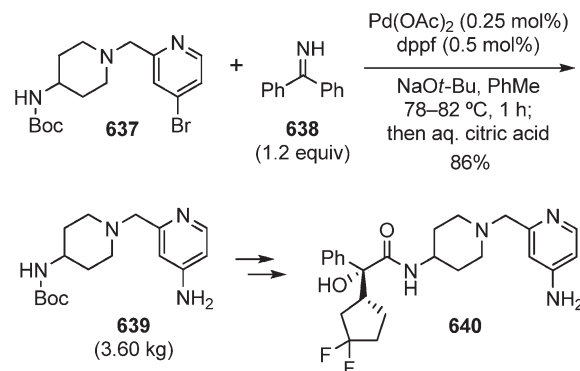


15 h.³⁶⁷ Drawbacks of this alkylation approach include the toxicity of both reagents (of which the former is OEB 5), the formation of dark impurities that complicate the purification of piperazine **636**, and low yields (30–40%). For the production of larger batches, the chemists turned to the Pd-catalyzed coupling of piperazine and aryl halide. A scalable protocol was developed that called for the reaction of bromonaphthalene **633** and *N*-Boc-piperazine (**629**) using 1,1'-bis(di-*tert*-butylphosphino)ferrocene)PdCl₂ and NaOt-Bu in toluene at 105 °C. After an aqueous workup and concentration, the *N*-Boc-protected coupling product **635** was telescoped as a toluene solution into the next step. (During process development, **635** was isolated as a waxy solid that was difficult to purify by recrystallization.) Cleavage of the Boc group was effected by treating the toluene solution of **635** with EtOH and bubbling HCl gas for 2 h, which caused the precipitation of HCl salt **636** in 90% yield. Crude **636** contained 1325 ppm of residual Pd and was treated with Si-Thiol (0.5 wt%) in H₂O/THF at 35 °C for 17 h. After filtration and concentration, purified **636** was crystallized from water with 90% recovery and only 2 ppm Pd. This protocol was implemented in a kilo-lab facility to produce multikilogram quantities of HCl salt **636**.

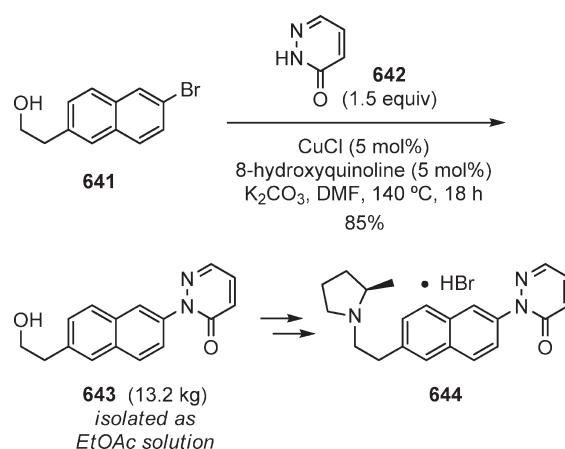
Researchers at Banyu Pharmaceutical in Japan and Merck in the U.S.A. described the amination of bromopyridine **637** to aminopyridine **639** for their preparation of muscarinic receptor antagonist candidate **640**, a treatment for chronic obstructive pulmonary diseases and urinary incontinence (Scheme 157).³⁶⁸ Installing amino groups via the direct coupling of NH₃ and aryl halides such as **637** is often difficult, and so amine surrogates were considered for the preparation of **639** using Pd, Ni, and Cu catalysts. Allylamine and diallylamine were avoided because of both sluggish cleavage and toxicity, whereas benzophenone imine (**638**)³⁶⁹ performed well and was easily hydrolyzed to the desired amine after coupling. Thus, bromopyridine **637** was treated with imine **638**, Pd(OAc)₂/dppf, and NaOt-Bu in toluene at 78–82 °C for 1 h. On workup, P(*n*-Bu)₃ was added to the mixture as a metal scavenger.⁴⁷ After imine hydrolysis via citric acid (also a Pd scavenger) and recrystallization from *n*-heptane/*i*-PrOAc, analytically pure aminoaniline **639** was obtained in 86% yield on kilogram-scale.

Researchers at Abbott have reported the multikilogram preparation of naphthalenyl pyridazinone **643** as an intermediate to

Scheme 157



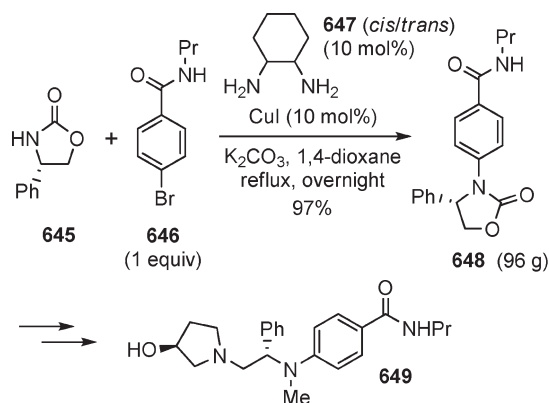
Scheme 158



naphthalenoid H₃ antagonist **644**, a compound for the treatment of CNS conditions such as memory and cognitive disorders (Scheme 158).³⁷⁰ Initial attempts to couple bromonaphthalene **641** with pyridazinone **642** via Pd-catalyzed *N*-arylation³⁷¹ failed despite an extensive screening of catalyst, ligand, base, and solvent. The chemists proposed that the low nucleophilicity of the pyridazinone anion (pK_a = 10.5) prevented coordination to the catalyst or, alternatively, decreased the propensity for reductive elimination of the intermediate aryl–Pd–pyridazinone complex. Better results were obtained from Cu-catalyzed coupling.³⁷² A copper and ligand screen revealed that CuCl in combination with 8-hydroxyquinoline provided the best catalyst system.³⁷³ Optimized conditions treated bromonaphthalene **641** and pyridazinone **642** with CuCl (5 mol%), 8-hydroxyquinoline (5 mol%), and K₂CO₃ in DMF at 140 °C for 18 h, which provided coupling product **643** in 85% yield without any *O*-arylation byproduct. Residual copper could be removed by successive washes of the organic phase with aqueous NH₃ and Na₂EDTA. Product **643** was isolated as an EtOAc solution and used in the next step without any further purification.

Ghosh and co-workers at Pfizer have reported the synthesis of κ -opioid receptor agonist **649** (Scheme 159).³⁷⁴ On the basis of reports from the Buchwald group on optimized Cu-catalyzed couplings under Goldberg-type conditions,³⁷² the researchers carried out the reaction of oxazolidinone **645** and aryl bromide **646** in the presence of catalytic CuI and 1,2-diaminocyclohexane (*cis*/*trans* mixture) in 1,4-dioxane at reflux to afford *N*-arylated oxazolidinone **648** in 97% yield. This coupling proved general for

Scheme 159

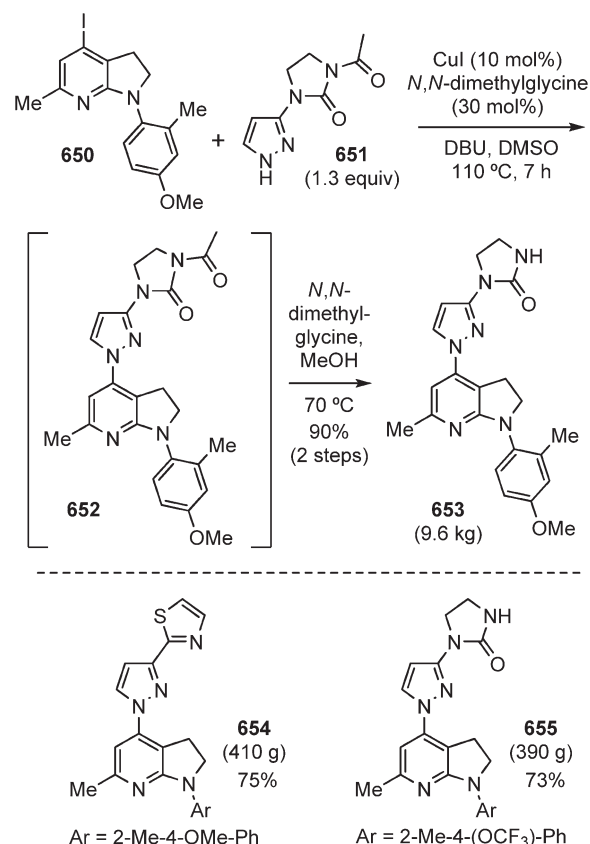


various substrates regardless of the electronic nature of the aryl halide or the oxidation state of the Cu catalyst. It was proposed that the diamine ligand could facilitate the dissolution of the catalyst as well as Cu(I)/(II) disproportionation and subsequent stabilization of the active Cu(I) species.

Ribecai and co-workers at GlaxoSmithKline in Italy prepared compounds **653**–**655** as novel corticotropin releasing factor antagonists for the treatment of stress-related conditions such as anxiety and depression (Scheme 160).³⁷⁵ The final synthetic step to **653** entailed the Cu-catalyzed coupling of iodide **650** and pyrazole **651**. Original conditions employed CuI as catalyst, (1*R*,2*R*)-*N,N'*-dimethylcyclohexane-1,2-diamine as ligand, and K_2CO_3 in DMF at 90 °C for 15 h to give coupling product **652** in 90% yield. Because this protocol generated a number of byproducts, a screen of copper catalysts, ligands, bases, and solvents was carried out with the additional goal of finding a cheaper ligand. As a result, CuI (10 mol%), *N,N*-dimethylglycine (30 mol%), and DBU as base in DMSO at 110 °C was identified as the combination of choice. The advantages of this new set of conditions were that *N,N*-dimethylglycine is considerably cheaper than (1*R*,2*R*)-*N,N'*-dimethylcyclohexane-1,2-diamine and that DBU gave a homogeneous reaction. In addition, the protection of the imidazolidinone nitrogen as the acetamide prevented the formation of additional coupling byproducts. After reaction completion, the mixture was treated with MeOH and 1 equiv of *N,N*-dimethylglycine and heated to 70 °C for 30 min to cleave the acetamide and sequester residual copper. After cooling to 25 °C, **653** was isolated by filtration in 90% yield with 5–45 ppm Cu. Analogues **654** and **655** were prepared in a similar fashion on a smaller scale; however, the trifluoromethoxy group of **655** changed the physical properties of the compound relative to **653**. As a result, **655** was an oil, rather than a solid, that could only be purified by chromatography.

Wallace and co-workers at Merck applied Pd-catalyzed amidation to the preparation of taranabant (**491**), a cannabinoid-1 receptor inverse agonist for the treatment of obesity (Scheme 161).²⁶⁷ During process development for the coupling of tosylate **656** and amide **657**, the researchers employed the corresponding triflate with $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 in dioxane at 50 °C to afford the coupling product in 90% yield without olefin isomerization. The triflate was prepared from the ketone precursor via $PhNTf_2$, but this triflating reagent was expensive and not widely available in bulk. Thus, the amidation of tosylate **656** was evaluated as a less expensive alternative. The tosylate was easily prepared as a single olefin isomer from the ketone precursor via *p*-toluenesulfonic anhydride, and **656** performed well in the coupling reaction despite being less

Scheme 160



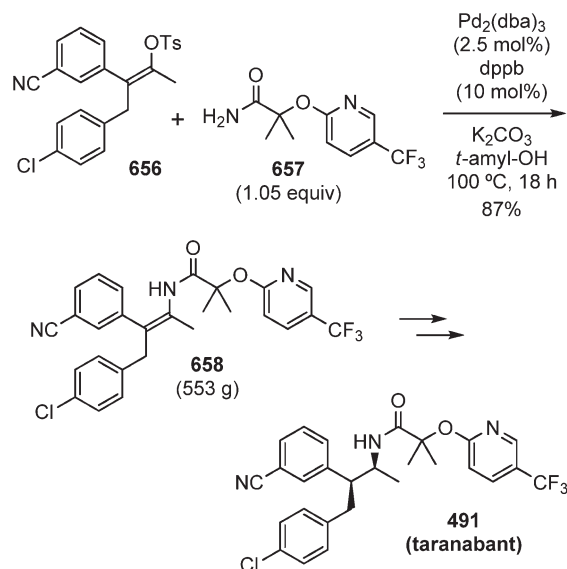
reactive than the triflate. After some minor modifications to the original protocol, the reaction of tosylate **656** and amide **657** was effected by $Pd_2(dba)_3$ (2.5 mol%), dppb (10 mol%), and K_2CO_3 in *t*-amyl alcohol at 100 °C for 18 h. After diluting with MTBE and a Darco treatment, enamide **658** was isolated via recrystallization from heptane/MTBE in 87% yield.

3.2. Ullmann Ether Synthesis (C–O Bond Formation)

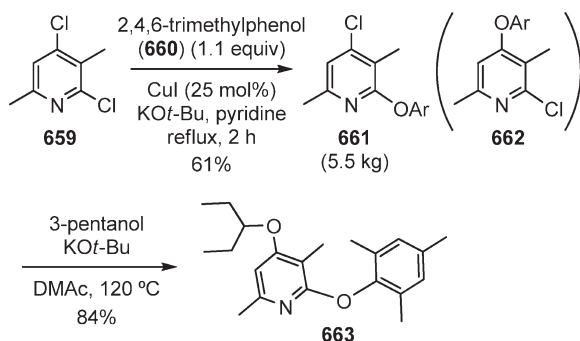
Traditional conditions for the Ullmann ether synthesis (coupling of aryl alcohols and aryl halides) require excess copper and very high temperatures. Recent advances in the design of new catalyst/ligand systems have allowed for Cu-catalyzed C–O bond formation via substoichiometric copper at lower temperatures, thus expanding the versatility of this venerable reaction.^{7,376}

Ruggeri and co-workers at Pfizer developed the selective addition of 2,4,6-trimethylphenol (**660**) to dichloropyridine **659** for the synthesis of corticotropin-releasing factor (CRF) antagonist **663**, a potential treatment in therapeutic areas including depression, anxiety, and stress-related diseases (Scheme 162).³⁷⁷ The base-promoted coupling of the phenol to dichloride **659** produced mixtures of the desired diaryl ether **661** and isomer **662**, with copper-free conditions favoring undesired **662**. Introducing copper salts to the reaction mixture reversed the selectivity to favor the desired adduct, and the optimized conditions furnished **661** without any **662** (although <5% of bis-adduct was formed). Thus, the Ullmann coupling of phenol and chloride was catalyzed by 25 mol% CuI and $KOt-Bu$ in pyridine at reflux; after 2 h, the mixture was cooled to 0 °C for aqueous workup (including ammonium hydroxide washes to

Scheme 161



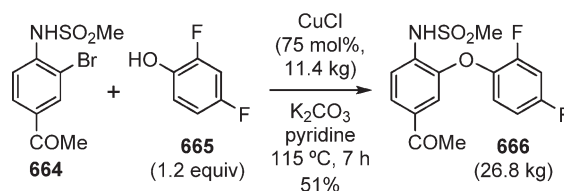
Scheme 162



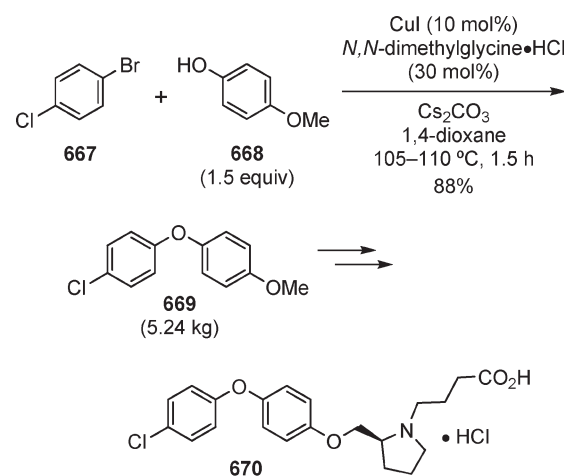
remove copper via complexation to NH_3) and concentrated to a brown oil that was passed through silica gel. The filtered oil was stirred over MeOH to precipitate diaryl ether 661, and a second crop was crystallized from the mother liquor to provide the coupling product in combined 61% yield as >99% pure (with only 0.6% bis-adduct). Isolated 661 was converted to pharmaceutical ingredient 663 via $\text{S}_{\text{N}}\text{Ar}$ reaction with 3-pentanol and KOt-Bu in hot DMAc.

Zanka and co-workers at Fujisawa Pharmaceuticals completed their synthesis of COX-II selective inhibitor 666, an anti-inflammatory agent, with the Ullmann coupling of bromide 664 and phenol 665 (Scheme 163).³⁷⁸ Of the various copper catalysts, bases, and solvents surveyed for this coupling, only CuCl , K_2CO_3 , and pyridine (as solvent) generated the API 666 in >11% yield. The CuCl stoichiometry was fine-tuned to 0.75 equiv; lower catalyst loadings led to sluggish couplings, whereas higher loadings promoted the degradation of 664 to desbromo-664. The coupling rate and yield increased when using an excess of K_2CO_3 (2.4 equiv), although too large an excess (4.8 equiv) led to viscous reaction mixtures that were difficult to scale. Finely granulated K_2CO_3 (<10 μm) had increased surface area and exposure to the reaction mixture and led to the most efficient couplings. Yields increased moderately with an excess of phenol 665; however, the expense of this reagent ensured that only a slight excess could be used for large-scale coupling. Also, Zanka

Scheme 163



Scheme 164

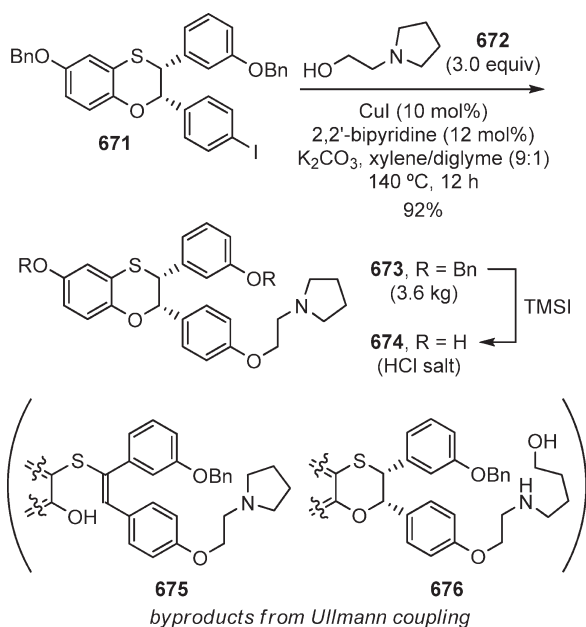


and co-workers rationalized that water in the reaction mixture might coordinate to the active copper–pyridine complex³⁷⁹ and interfere with Ullmann coupling. Thus, the coupling was performed under dehydrating conditions in which trace water was distilled continuously with pyridine (while replacing with fresh pyridine to maintain constant volume).

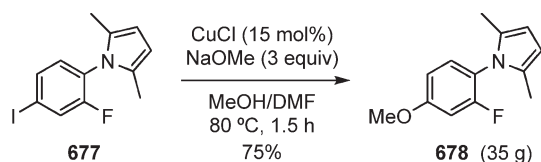
After reaction completion, an extensive series of extractions, crystallizations, and filtrations were required to purge copper and impurities from the drug substrate 666 (11.4 kg CuCl used in this coupling). To this end, the mixture at room temperature was partitioned between CH_2Cl_2 and aqueous HCl. The organic layer was passed through a column of alumina to remove residual copper, and the filtrate was washed with aqueous NaOH solution to precipitate the sodium salt of 666. After protonating with aqueous HCl, the API was extracted into CH_2Cl_2 and washed with aqueous KOH solution, thus returning the API to the aqueous phase as the more soluble potassium salt. The product-containing aqueous KOH solution was treated with activated charcoal, filtered, acidified to pH 6.0, and held overnight at 3°C to precipitate 26.8 kg of diaryl ether 666. A portion of this API was recrystallized from EtOH to provide higher-purity drug substrate with 94% recovery.

Enache and co-workers at deCODE Chemistry in Illinois initiated their synthesis of leukotriene A4 hydrolase inhibitor 670 with the Ullmann coupling of 1-bromo-4-chlorobenzene (667) and 4-methoxyphenol (668) (Scheme 164).³⁸⁰ This coupling was catalyzed by 10 mol% CuI , 30 mol% N,N -dimethylglycine hydrochloride,³⁸¹ and Cs_2CO_3 in dioxane heated at reflux. After reaction completion, the mixture was cooled to room temperature, subjected to aqueous workup, and concentrated to provide diaryl ether 669 as an oil that solidified upon standing. Residual copper was purged via downstream crystallizations later in the synthesis.

Scheme 165



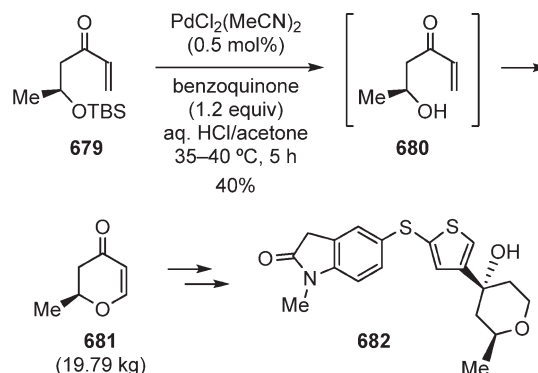
Scheme 166



Song and co-workers at Merck installed the side chain of **674**, a selective estrogen receptor modulator, via Ullmann coupling of aryl iodide **671** and aminoethanol **672** (Scheme 165).³⁸² The initial application of Buchwald conditions³⁸³ to **671** and **672** (CuI, 1,10-phenanthroline, Cs₂CO₃, toluene, 110 °C) led to <10% conversion after 2 days, and heating to 140 °C in a sealed tube provided ether **673** in 85% assay yield but with byproducts **675** and **676**. Switching to K₂CO₃ prevented the formation of these byproducts, and ligand screening revealed 2,2'-bipyridine as a superior alternative to 1,10-phenanthroline. Replacing toluene with xylene allowed for heating at 140 °C without an autoclave, and the azeotropic removal of any water under these conditions helped maintain a consistent reaction rate. Diglyme cosolvent prevented solids from coating the walls of the reaction vessel, a problem that led to incomplete conversion in diglyme-free couplings. The reaction mixture was degassed via vacuum/nitrogen purges before the optimized conditions coupled iodide **671** and alcohol **672** with only 10 mol% CuI. After completion, the mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated, diluted with 2-butanol, and seeded to effect the crystallization of Ullmann product **673** with >99% purity (>99% ee).

Ragan and co-workers at Pfizer developed the Cu(I)-mediated, Ullmann methoxylation of pyrrole-protected iodoanilines such as **677** for the synthesis of pharmaceutical intermediates (Scheme 166).^{384,385} Heating iodide **677** with 15 mol% CuCl and 3 equiv of NaOMe at reflux in MeOH/DMF provided methoxyaniline **678**. These conditions proved general for the

Scheme 167



methoxylation of various pyrrole-protected iodoanilines, including substrates with ortho or meta regiochemistries between the iodide and aniline nitrogen. The Cu(I) source was not found to be critical, as CuI (99.999%) and CuCl (98%) performed equally well. Carboxy substituents on the aniline, however, hindered the coupling, as did replacing aryl iodide with aryl bromide. Furthermore, protecting the aniline nitrogen as a phthalate (unstable) or benzophenone imine (competitive fluorine displacement) proved to be unsuitable for this coupling.

After the conversion of iodide **677** to **678**, the mixture was partitioned between aqueous NH₄Cl solution and diisopropyl ether. Phase separation and Celite filtration of the organic layer provided a solution of **678** in ether. Subsequent washing with aqueous NH₄OH solution, filtration through silica gel, and concentration furnished crude **678** as a free-flowing brown solid in 92% yield. Recrystallization from hot hexanes then provided the methoxy coupling product in 75% yield.³⁸⁴

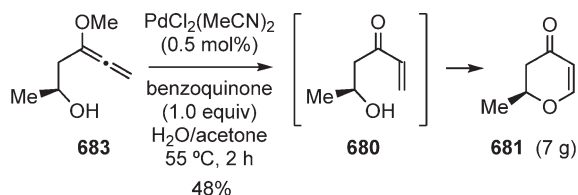
3.3. Oxidative Wacker-type Cyclization (C–O Bond Formation)

The Wacker oxidation is the aerobic, PdCl₂-catalyzed, Cu-mediated, aqueous oxidation of an olefin to a carbonyl. The oxidation step has been known for over a century,³⁸⁶ and Smidt and co-workers at Wacker Chemie elucidated the mechanism by discovering that the active Pd(II) catalyst is regenerated from Pd(0) via oxidation by CuCl₂.³⁸⁷ Molecular oxygen, peroxide, or benzoquinone can also serve as oxidants for Pd.³⁸⁸ The Wacker oxidation is a very important industrial process for the conversion of ethylene to acetaldehyde.

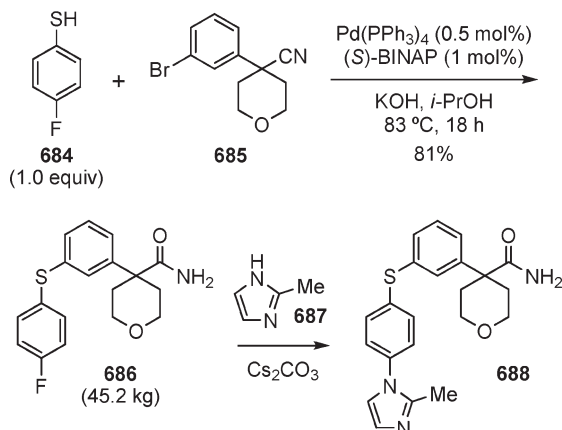
A variation of this process is the intramolecular Pd-catalyzed coupling of an alcohol onto an alkene. Several reviews have been published on the history and recent variations of the Wacker reaction.^{388,389}

Merifield and co-workers at AstraZeneca employed an oxidative, Wacker-type cyclization to prepare a key intermediate in their synthesis of **682**, a 5-lipoxygenase inhibitor and potential treatment for various inflammation conditions.³⁹⁰ As outlined in Scheme 167, key intermediate dihydropyranone **681** was accessed via Pd-catalyzed cyclization of hydroxy enone **680**, which in turn was unmasked from silyl ether **679** under acidic reaction conditions. In this one-pot, desilylation–cyclization sequence, treatment of **679** with aqueous HCl cleaved the silyl ether, and then Pd(II) catalyst mediated the cyclization of liberated alcohol onto the enone followed by β-elimination to generate the desired **681**. Stoichiometric benzoquinone promoted the complete conversion of hydroxy enone **680** by oxidizing the resulting Pd(0)

Scheme 168



Scheme 169



species to Pd(II), thus regenerating the active catalyst.³⁹¹ The high water solubility of product **681** facilitated workup and purification, as silyl protecting group residues were removed by washing the aqueous solution of dihydropyranone with heptane. The product was extracted into toluene and isolated by distillation in 40% yield with >99% ee (19.79 kg).

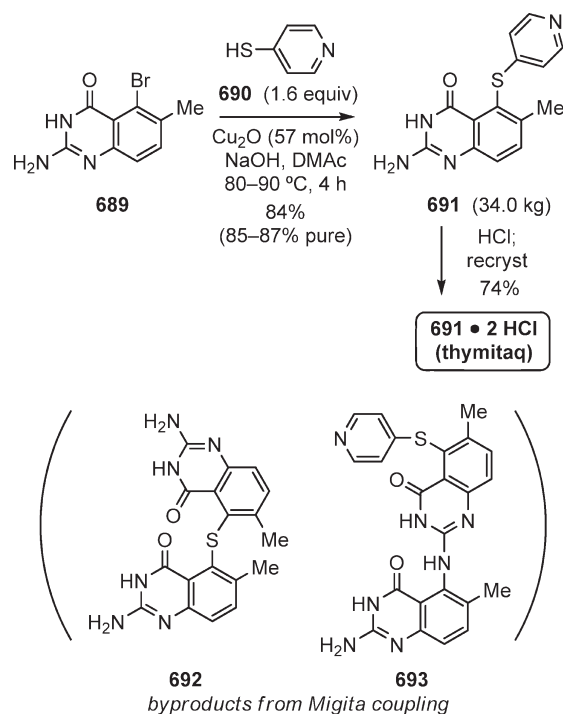
Merifield and co-workers explored an alternative oxidative Wacker-type cyclization to dihydropyranone **681** from methoxyallene **683** (Scheme 168).³⁹⁰ Under reaction conditions, the methoxyallene was converted to hydroxy enone **680**, and then the Pd(II) catalyst mediated the cyclization of alcohol onto the enone.

3.4. Migita Thioether Synthesis (C–S Bond Formation)

In the late 1970s and early 1980s, Migita and co-workers developed the Pd-catalyzed coupling of thiols and aryl iodides/bromides for the synthesis of thioethers.³⁹² Numerous improvements have been implemented in recent years to increase catalyst TON and the efficiency of coupling.⁷ In particular, Buchwald and Murata³⁹³ and Hartwig and co-workers³⁹⁴ have used phosphine ligands in combination with either $\text{Pd}(\text{OAc})_2$ or $\text{Pd}(\text{dba})_2$ to increase the scope and generality of this transformation to include aryl chlorides and both aliphatic and aromatic thiols.

Norris and Leeman at Pfizer developed a variant of the Migita reaction for the manufacture of antiasthma drug candidate **688**.³⁹⁵ Whereas the original Migita conditions³⁹² for the coupling of thiophenols and aryl iodides employed $\text{Pd}(\text{PPh}_3)_4$ without additional ligand, couplings with aryl bromides were generally sluggish and provided product in lower yield. Norris and Leeman found that incorporating bidentate phosphorus ligands such as BINAP into the reaction mixture substantially increased the coupling rate of aryl bromides in Migita reactions, and they developed the conditions shown in Scheme 169 to prepare 45 kg of diaryl thioether **686** from thiophenol **684** and

Scheme 170



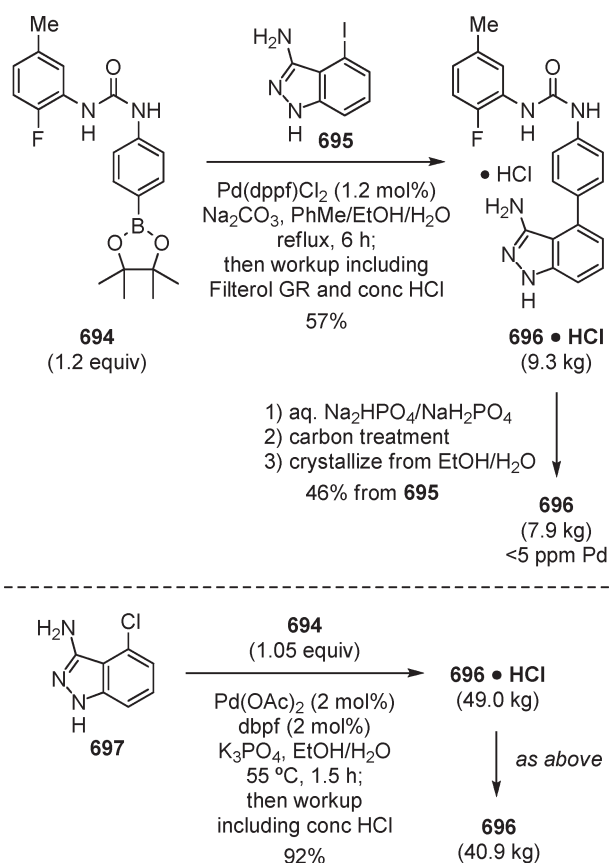
aryl bromide **685**. The nitrile of **685** was also hydrolyzed to the desired amide under these reaction conditions. For the pilot plant production of **686**, the Migita reaction was conducted under a nitrogen atmosphere but did not require thorough degassing of the reaction mixture to purge oxygen. The coupling partners were heated in *i*-PrOH for 18 h with 0.5 mol% catalyst, 1 mol% (*S*)-BINAP, and excess KOH. After reaction completion, the mixture was cooled to room temperature, diluted with water, and transferred onto a horizontal plate pressure filter. Crude thioether **686** was isolated from the filter and treated with activated charcoal in AcOH at $95\text{--}100\text{ }^\circ\text{C}$. The mixture was passed through a horizontal plate pressure filter and diluted with water to crystallize Migita product in 81% yield.

Surprisingly, racemic BINAP led to slower couplings for this reaction than enantiopure BINAP. A mechanistic study revealed that thioether formation is faster than nitrile hydrolysis in the presence of enantiopure BINAP, whereas the nitrile hydrolysis of **685** is faster than thioether formation with racemic BINAP. It is possible that the product from nitrile hydrolysis of **685** is a less reactive substrate for this Migita coupling than **685**, and thus racemic BINAP leading to nitrile hydrolysis slows the rate of thioether formation.

Wennerberg and co-workers at DuPont Chemoswed developed the Cu-catalyzed Migita coupling of aryl bromide **689** and 4-mercaptopyrindine (**690**) for the large-scale preparation of thymitaq (**691**·2HCl), a thymidylate synthetase inhibitor for the treatment of inoperable primary liver cancer (Scheme 170).³⁹⁶ The coupling of **689** and **690** with Cu_2O and NaOH in DMAc at $80\text{--}90\text{ }^\circ\text{C}$ proceeded to completion within 4 h. Sodium hydroxide replaced the NaH used in earlier development efforts, as NaH poses a safety hazard in solvents such as DMF and DMAc.³²⁸

After reaction completion, an extensive workup was required to purge the catalyst from pharmaceutical ingredient that behaves as a ligand for heavy metals and retains copper. To this end, the

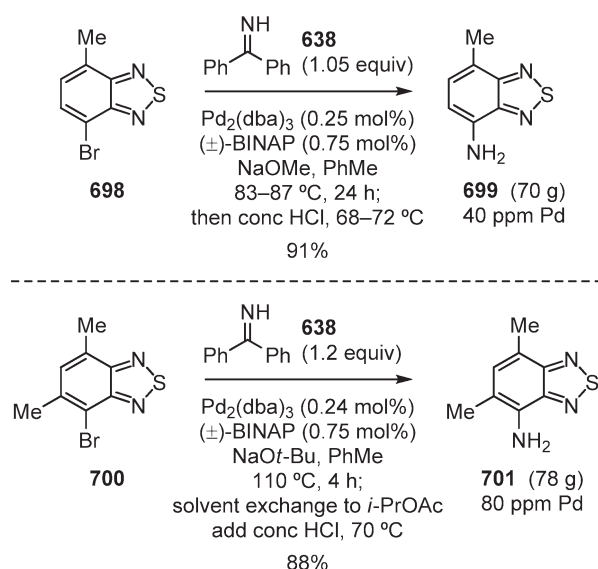
Scheme 171



cooled reaction mixture was diluted with aqueous HCl and passed through a series of bag and cartridge filters to remove bulk quantities of copper. Migita product **691** was precipitated from the filtrate with the addition of aqueous NH_3 and isolated via centrifugation. The collected solids were redissolved in aqueous HCl and precipitated once more with the addition of aqueous NH_3 . The solids were collected again via centrifugation and treated with metal scavenger TMT-15, an aqueous 15% sodium salt solution of 2,4,6-trimercaptotriazine.¹³ It was necessary to charge the TMT-15 in portions in 20 min intervals while maintaining low pH with aqueous HCl. During TMT-15 treatment, compressed air was bubbled into the mixture to oxidize Cu(I) chelated with **691** to Cu(II), the divalent ion able to coordinate more preferentially with the metal scavenger. After copper removal (verified by the lack of precipitate upon dosing a solution aliquot with hydrogen sulfide), the TMT–Cu complex was removed by treating the solution with activated charcoal and Celite and passing it through a series of bag and cartridge filters. Dilution with aqueous NH_3 precipitated crude thymitaq (**691**) as the free base in 84% yield with 85–87% purity and 15–25 ppm Cu.

The free base **691** was converted to the pure dihydrochloride salt through a series of crystallizations that purged major byproducts **692** (2–3%) and **693** (4–5%). Ultimately, **691 • 2HCl** was isolated with >99.5% purity in 74% yield from the free base. Even after extensive purification, the chelating nature of the API ensured that traces of several metals would be carried into the final API, including 2–6 ppm Cu, 13–15

Scheme 172



ppm Fe, and, surprisingly, 5–9 ppm Pb (<10 ppm Pb required). Copper(I) oxide was uncovered as the source of lead contamination, and a survey of Cu_2O from different suppliers revealed Pb levels ranging from 10 to 3000 ppm. Although some Pb was purged upon purification, it was necessary to use low-Pb copper catalyst to obtain API with low lead content.

4. ADDENDUM

Our careful survey of the non-patent literature uncovered over 170 examples of large-scale (>100 mmol) transition metal couplings for the synthesis of pharmaceuticals through August, 2010 (as specified in the Introduction). In reviewing such an expansive field, however, it is regrettable that despite our best efforts a few examples might be overlooked. Fortunately, we discovered the following examples before this manuscript went to press.³⁹⁷

Kruger and co-workers at Abbott reported two variations of a Suzuki coupling for the synthesis of **696**, a potent tyrosine kinase receptor inhibitor for the possible treatment of cancer (Scheme 171).³⁹⁸ The first-generation Suzuki reaction of boronic ester **694** and iodoindazole **695** was effected with Pd(dppf)Cl_2 after a screen revealed this catalyst as superior with respect to highest coupling rate and stability to oxygen. Although this catalyst system offered the greatest resistance to oxygen contamination, it was still necessary to control oxygen levels by sparging the reaction mixture with nitrogen for 30 min prior to heating. After coupling, the boron-related byproducts and inorganic base were extracted into aqueous washes and the crude **696** was crystallized from toluene with typically >500 ppm Pd. Treatment with Filterol GR and salt formation provided **696 • HCl** in 57% yield. Subsequent basification, Darco treatment, and crystallization from aqueous EtOH provided **696** in 46% overall yield and >99.8% purity.

The preparation of iodoindazole **695** caused glass etching of the reactors, which was attributed to displaced fluoride generated from the reaction of 2-fluoro-6-iodobenzonitrile and hydrazine. Thus, chloroindazole **697**, readily available from the reaction of 2,6-dichlorobenzonitrile and hydrazine (thus avoiding fluoride

generation), was developed as an alternative coupling partner for boronic ester **694** in a second-generation Suzuki reaction (Scheme 171).³⁹⁸ Kruper and co-workers identified Pd(OAc)₂/dbpf as optimal for the conversion of chloroindazole **697** to API; however, this catalyst system proved even more sensitive to oxygen than the Pd(dppf)Cl₂ used in the first-generation approach. The complexation of Pd to ligand was found to be the most oxygen-sensitive phase of the reaction, and the Pd(OAc)₂ and dbpf were premixed in EtOH after first degassing the solvent to <10 ppm O₂ (as measured via headspace oxygen monitor). After heating the catalyst/ligand solution at 55 °C for 45 min, the preformed catalyst was transferred to a degassed mixture of **694**, **697**, and K₃PO₄ containing <100 ppm O₂. Once the Suzuki coupling of **694** and **697** was complete, aqueous workup and salt formation provided 49.0 kg of **696**·HCl (92% yield). Basification, carbon treatment, and crystallization then provided the free base **696** in 84% overall yield.

For the preparation of aminobenzothiadiazoles as pharmaceutical intermediates, Liu and co-workers at Novartis³⁹⁹ developed the Pd-catalyzed amination of bromobenzothiadiazoles **698** and **700** using benzophenone imine (**638**)³⁶⁹ as an ammonia equivalent. As shown in Scheme 172, the coupling of bromobenzothiadiazoles and benzophenone imine was demonstrated in heated toluene using Pd₂(dba)₃/BINAP and either NaOMe or NaOt-Bu as base. After aqueous workup, the immediate imine coupling products were hydrolyzed to the HCl salts of aminobenzothiadiazoles **699** and **701** by heating in concentrated HCl. Free bases **699** and **701** were obtained with 40 and 80 ppm Pd, respectively, by washing their HCl salts with NaOH solution. Liu and co-workers did not discuss additional efforts to purge Pd but noted that the levels were reduced to <2 ppm downstream. This amination protocol was performed in the pilot plant to convert 14.0 kg of **698** to **699** in 86% yield; however, a detailed procedure for this scale-up was not provided.

Finally, several recent pharmaceutical examples of large-scale transition metal-catalyzed couplings appeared in the literature after this manuscript was submitted for review.^{400–403}

5. CONCLUSIONS

As this review has attempted to demonstrate, advancements in transition metal-catalyzed couplings over the past four decades have given rise to process methods that can provide kilogram quantities of pharmaceuticals. The mildness and functional group compatibility of modern protocols allow for transition metal couplings late in synthetic routes for more convergent approaches to pharmaceutical ingredients. To develop reliable and scalable processes, these couplings must often be optimized for catalyst, ligand, base, solvent, temperature, and concentration. In addition, the process chemist now has a variety of tools for the efficient scavenging of metals^{11–13} routinely employed in these reactions, such as the commonly used 2,4,6-trimercaptotriazine¹³ or more sophisticated functionalized resins,⁹² and the ability to purge metals further allows the placement of transition metal couplings near the end of a synthetic sequence.

The development of high turnover catalysts is another factor that has been very beneficial for large-scale applications due to the importance of cost reduction during process development for the manufacture of clinical batches. Some of the examples presented herein used as little as 0.1 mol% catalyst, but >1 mol% loadings are more common to ensure robustness. However, continuing research is developing more active catalyst systems to further reduce costs, as is

exemplified by the work of Santelli and co-workers, who have reported a turnover number of 28×10^6 for a Suzuki–Miyaura coupling reaction.⁴⁰⁴ As the cost of precious metals rises from higher demands and lower availability,⁴⁰⁵ high turnover numbers and catalyst recycling will be of primary importance to future applications of these technologies. Part of the answer may come from polymer-anchored catalysts, which are more easily recycled,⁴⁰⁶ and solid supports have already been used for Suzuki, Heck, and Stille reactions.⁴⁰⁷

The continued development of new ligands for the coupling of less-reactive substrates such as aryl chlorides^{6h} and sulfonates (cheaper than bromo or iodo counterparts), or previously incompatible substrates such as alkyl halides, has expanded the versatility of transition metal-catalyzed transformations. An excellent example is the progress that has been made in the couplings of unactivated secondary alkyl halides.⁴⁰⁸ Other advancements in substrate scope involve pioneering Pd-, Cu-, and Ru-catalyzed methods for the introduction of aromatic fluorine^{409,410} and trifluoromethyl⁴¹⁰ groups, which are very common functional groups in active pharmaceutical ingredients. Other highlights such as new redox couplings for the diastereoselective formation of quaternary carbon centers⁴¹¹ continue to expand the versatility of transition metal catalysis in organic synthesis.

Furthermore, metal alternatives to Pd are being explored for coupling reactions. For example, nickel has been the metal of choice in recent, highly enantioselective Negishi,⁴¹² Hiyama,⁴¹³ Suzuki–Miyaura,⁴¹⁴ and Kumada⁴¹⁵ reactions. Cobalt has been used to form sp²–sp² carbon bonds.^{6b} Iron catalyzes the reaction of alkyl Grignard reagents with aryl chlorides, tosylates, and triflates.⁴¹⁶ Gold has emerged as a new player for Suzuki and Sonogashira reactions due to Au–Pd synergy.⁴¹⁷

The use of noble metal nanocatalysts in coupling reactions is an exciting new area of research as well, since noble metal nanoparticles display a large surface-to-volume ratio and, therefore, are more active than their bulk counterparts.⁴¹⁸ The nanoparticle shape, the type of solid support employed to load the active metal (fluorous silica gel, ZnO nanopowder, magnetic nanoparticles, nanometer-scale platelets of montmorillonite, among others) and the use of bimetallic (Pd–Ag, Pd–Cu, Pd–Ni), trimetallic (Cu–Pd–Ru), and tetrametallic (Cu–Pd–Pt–Ru) nanoparticles are factors currently investigated for applications in Heck and Suzuki reactions. The higher activity and recyclability of these nanocatalysts are important factors that should help them find a niche in industry, where cost is a fundamental factor.

In conclusion, the chemistry of transition metal-catalyzed couplings has had a brilliant past and promises to have an even brighter future. The well-deserved awarding of the 2010 Nobel Prize in Chemistry to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi⁴¹⁹ for their work in this area clearly demonstrates the importance of this research, particularly as a tool for the manufacture of drug candidates. In addition, the number of publications in this fast-paced arena increases exponentially each year, and many new discoveries should find their way into the process chemist's toolbox of practical and reliable methods for the large-scale manufacturing of pharmaceuticals.

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BIOGRAPHIES



Javier Magano was born in Madrid, Spain. He received his B.S. degree in Organic Chemistry from Complutense University in Madrid and his M.S. degree in Chemistry from the University of Michigan. After working for the oil industry in Spain for 3 years, he obtained his M.S. degree in Rubber and Polymer Science from the School of Plastics and Rubber at the Center for Advanced Scientific Research in Madrid. In 1995 he moved back to the United States to carry out graduate work at the University of Michigan, and in 1998 he joined Pfizer Inc. to work in the early process group in Ann Arbor, MI, and currently in Groton, CT. He has also worked in the area of biologics for 1.5 years.



Joshua R. Dunetz received his B.A. degree in Chemistry from Haverford College in 2000 under the guidance of Professor Karin S. Åkerfeldt and his Ph.D. degree in Organic Chemistry from MIT in 2005 under the direction of Professor Rick L. Danheiser. His graduate research focused on the synthesis of ynamides and their cycloadditions with conjugated enynes in a strategy for the synthesis of indoles and indolines. His other graduate studies included the synthesis of nitrogen heterocycles in environmentally friendly reaction media such as supercritical carbon dioxide. After graduate school, Joshua conducted postdoctoral studies with Professor William R. Roush at Scripps Florida and completed the total synthesis of tedanotide, a macrolide natural product with potent cytotoxicity against several cancer cell lines. In early 2008, Joshua assumed his current position at Pfizer in Groton, CT, with the early process development group (Research API).

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ABBREVIATIONS

API	active pharmaceutical ingredient
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -butoxycarbonyl
CAP	ϵ -caprolactam
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	bis(dibenzylideneacetone)
dbpf	1,1'-di- <i>tert</i> -butylphosphinoferrocene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAC	<i>N,N</i> -dimethylacetamide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dpppe	1,5-bis(diphenylphosphino)pentane
dr	diastereomeric ratio
DTTA	(+)-di- <i>p</i> -toluoyl-D-tartaric acid
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
er	enantiomeric ratio
EM	effective molarity
HMPA	hexamethylphosphoramide
IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene
IMS	industrial methylated spirits
IPA	isopropanol
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
MEK	methyl ethyl ketone
MEM	methoxyethoxymethyl
2-MeTHF	2-methyltetrahydrofuran
Ms	methanesulfonyl
MTBE	methyl <i>t</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
NMDA	<i>N</i> -methyl-D-aspartic acid
NMP	2-methylpyrrolidinone
OEB	occupational exposure band
PhMe	toluene
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
PNB	<i>p</i> -nitrobenzyl
RCM	ring-closing metathesis
RSM	response surface methodology
rt	room temperature
TBAB	tetra- <i>n</i> -butylammonium bromide
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
Ts	<i>p</i> -toluenesulfonyl
VEGFR	vascular endothelial growth factor receptor
vol	volumes

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