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Palladium Catalysis

Biaryl Phosphane Ligands in Palladium-Catalyzed Amination

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Keywords:
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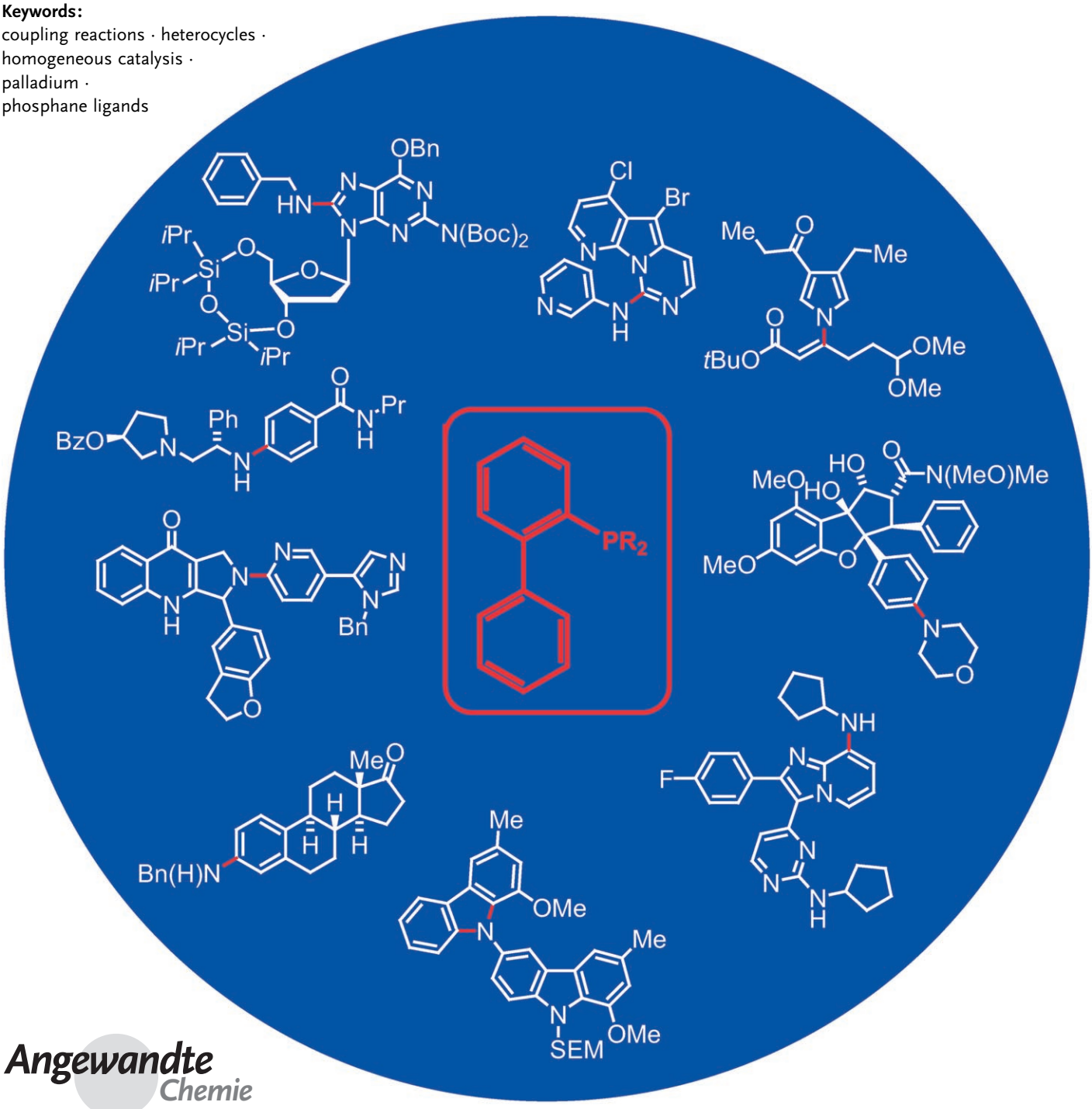


Palladium-catalyzed amination reactions of aryl halides have undergone rapid development in the last 12 years, largely driven by the implementation of new classes of ligands. Biaryl phosphanes have proven to provide especially active catalysts in this context. This Review discusses the application of these catalysts in C–N cross-coupling reactions in the synthesis of heterocycles and pharmaceuticals, in materials science, and in natural product synthesis.

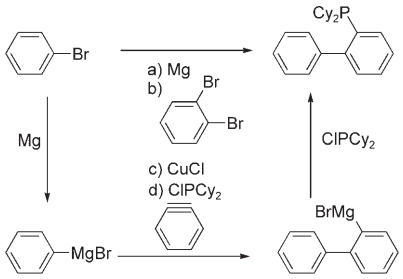
From the Contents

1. Introduction

The development of phosphane ligands has had a huge impact in transition-metal-catalyzed reactions. The steric and electronic properties of phosphanes may be varied readily and independently. This permits the fine-tuning of the coordinated species, thus allowing the desired properties of the complex to be enhanced at different steps of a catalytic cycle. In 1998 we introduced a new class of air-stable[1] phosphane ligands based on the dialkylbiaryl phosphane backbone.[2] These phosphanes have been used as ligands for gold,[3–11] silver,[12] rhodium,[13,14] ruthenium,[15–17] and copper,[18] where they have improved the reactivity and stability of the catalyst. However, that they have had by far the greatest impact on reactions catalyzed by palladium, including the Sonogashira,[19] Negishi,[20] Hiyama,[21–23] Kumada[24] and Suzuki[25–30] cross-coupling reactions, the Heck reaction,[31–33] enolate arylation[34–37] and allylation,[38] reductive cyclization[39] and etherification,[40–43] silylation,[44] borylation,[45–47] cyanation,[48,49] methylation,[50] direct arylation,[51] and dehalogenation[52] of aryl halides.

This Review focuses on the use of dialkylbiaryl phosphane ligands in palladium-catalyzed amination reactions of aryl halides and pseudohalides.[53,54] Palladium-catalyzed amination has rapidly become an important tool in organic synthesis, pharmaceuticals, and materials science.[55–69] Progress in this reaction has been driven largely by the implementation of new classes of ligands. Initial studies made use of tri-*o*-tolylphosphane.[70–72] Later, the scope was improved by the application of chelating ligands, especially binap[73] and dppf.[74] Subsequent research using these and other ligand classes, notably monodentate phosphanes such as trialkyl phosphanes,[75–77] dialkylaryl phosphanes,[78] and QPhos,[79] chelating phosphanes such as JosiPhos derivatives[80] and XantPhos,[81] and other ligand classes such as Verkade's phosphatranes,[82] secondary phosphane oxides[83] and N-heterocyclic carbenes,[84] have widened the substrate scope and resulted in milder reaction conditions.

The synthesis of the dialkylbiaryl phosphane ligands is straightforward and completed in a single operation: An aryl halide is treated with excess magnesium to form the Grignard reagent. A 1,2-dihaloarene is then added, which reacts with more magnesium metal to form benzyne in situ. The aryl magnesium halide then adds to the benzyne and the resulting Grignard reagent is treated with a dialkyl chlorophosphane in the presence of a catalytic quantity of copper(I) chloride to generate the ligand (Scheme 1).[85,86] A significant number of this class are now commercially available, and their large-scale synthesis has been investigated by Rhodia Pharma Solutions and Lanxess[87,88] as well as now at Shasun and Saltigo. The utility of these ligands has resulted in the introduction of structurally related variants,[89–105] and has spawned innovative alternative synthetic routes based on the Diels–Alder reaction[96,106] and a rhodium-catalyzed formal [2+2+2] cycloaddition.[107,108]



Scheme 1. Synthesis of biaryl phosphanes. Cy = cyclohexyl.

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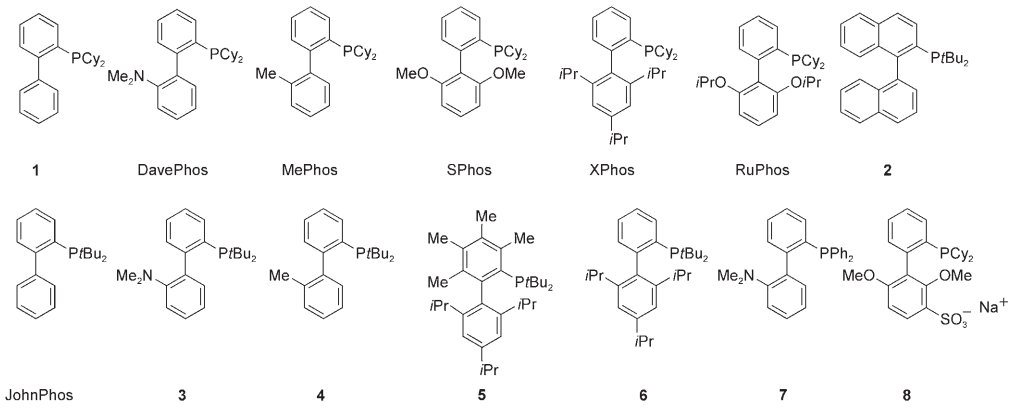
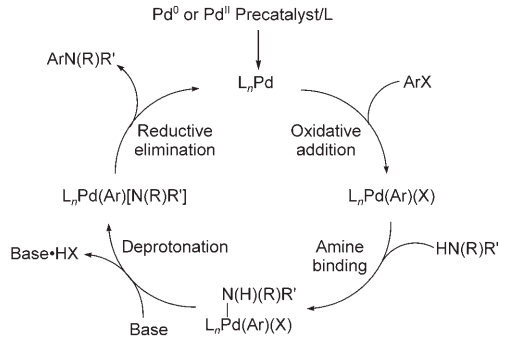


2. Structure of the Dialkylbiaryl Phosphane Ligands

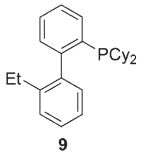
The use of dialkylbiaryl phosphane ligands often allows reactions to proceed with short reaction times, low catalyst loadings, and under mild reaction conditions. A number of studies have been directed towards finding the origin of these effects to further optimize catalyst design. The mechanism of the palladium-catalyzed amination has been the subject of intensive study with numerous ligand systems (Scheme 2).[109–116] In the case of the dialkylbiaryl phosphanes,



Scheme 2. Proposed catalytic cycle.

the catalytically active species is believed to be the monoligated, highly reactive [L_1Pd^0] complex, which exists in equilibrium with the [L_2Pd^0] species.[117] The considerable steric bulk and strong electron-donor ability of the dialkylbiaryl phosphane ligands presumably serves to encourage the formation of this active species, which allows oxidative addition to occur under mild conditions even with unactivated aryl chlorides. Reaction calorimetric measurements have shown that the size of the substituents on the lower ring have a significant effect on the rate of amination of the aryl halide.[118] For example, the metal/ligand (M/L) ratio has a marked effect on the initial reaction rate.

In the case of ligand **9**, the rate of reaction was much lower when a M/L ratio of 1:4 rather than 1:2 was used, while little dependency on the metal/ligand ratio was found with the bulkier XPhos ligand. This finding was taken to suggest that the larger substituents on the lower ring of XPhos played a role in promoting the formation of the reactive [L_1Pd^0] species. Another interesting feature that came to light in this study was that the reaction rate increases with turnover number (TON) for ligands with only one substituent on the lower ring, while it remains essentially constant for 2′,6′-disubstituted ligands. It was later demonstrated through deuterium labeling studies that, in the case of 2′-monosubstituted dialkylbiaryl ligands, the Pd^{II} precatalysts have a tendency to form palladacycles **10**.[119] This effect would serve to reduce the rate of catalyst activation, as such palladacycles are only slowly converted into the active catalyst.[120]



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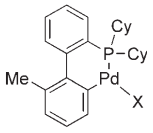

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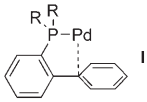
Another characteristic of the dialkylbiaryl phosphane ligands which is believed to promote catalyst stability and increase electron density at the metal center is the possibility of palladium–arene interactions between the metal atom and the lower ring of the ligand (see **I**).[121] Such interactions have been observed in the X-ray crystal structures of a number of palladium–biaryl phosphane complexes[27–29,122–125] and even in an oxidative addition complex with methyl triflate.[126] Obtaining experimental information on the importance of these



I

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David S. Surry completed his undergraduate and PhD studies at the University of Cambridge, UK. During his undergraduate years he worked in the laboratory of Prof. I. Fleming, and carried out PhD research under the supervision of Dr. D. R. Spring. He is currently a Royal Commission for the Exhibition of 1851 Research Fellow with Prof. S. L. Buchwald.

interactions in the catalytically active species has proven more difficult.[127] DFT calculations, however, have underlined the importance of the palladium–arene interactions in intermediates in the catalytic cycle.[128,129]

These studies have also indicated that the lower ring promotes the reductive elimination step. The palladium–arene interaction stabilizes the amidopalladium intermediate and reduces the energy of the transition state when the palladium center is proximal to the lower ring. A further advantage of reductive elimination from such a complex is that the $[L_1Pd^0]$ complex is regenerated directly following reductive elimination and can reenter the catalytic cycle (Figure 1).

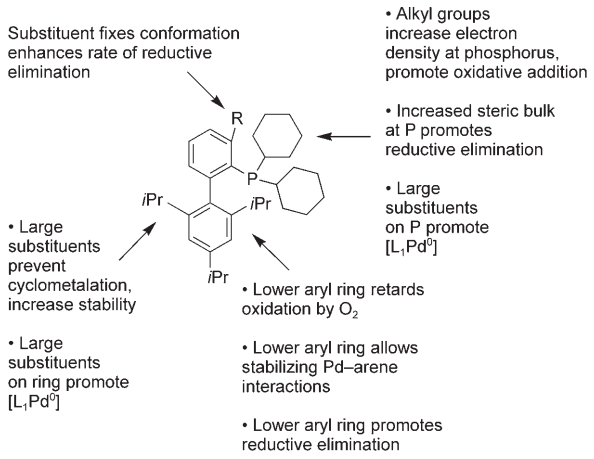
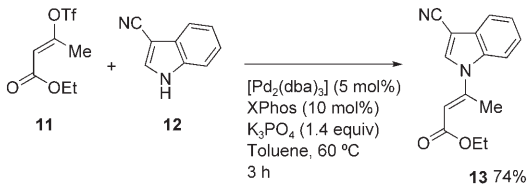


Figure 1. Important structural features of dialkylbiaryl phosphanes.

3. Synthesis of Imines, Enamines, and Enamides

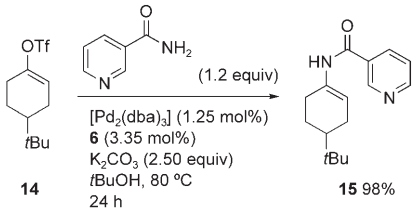
The metal-mediated synthesis of enamines and imines from vinyl halides and pseudohalides has received much attention in recent years, and has been used in the synthesis of heterocycles and natural products.[130,131] The first amination of vinyl halides was documented by Voskoboynikov, Beletskaya, and co-workers, who used azoles and phenothiazines as nucleophiles.[132] The best system required lithium azoles and JohnPhos as the ligand for the palladium. Chelating ligands were less effective, but the cheaper tri-*tert*-butylphosphane resulted in a marginally less efficient catalytic system, and so was used to explore the substrate scope of the reaction. Importantly the process was stereospecific for *cis*- and *trans*-β-bromostyrenes. Movassaghi and Ondrus subsequently extended this reaction to the readily available vinyl triflates by using XPhos as the ligand (Scheme 3).[133] Potassium phosphate was the best base; rigorous drying was essential to minimize the formation of ynoate and β-ketoester by-products.

Willis and Brace found that dialkylbiaryl phosphane ligands such as **1** could be employed to couple vinyl triflates with cyclic aliphatic amines, but that the chelating ligand binap gave superior results with the weaker base cesium carbonate.[134] Chemists at Merck have shown that the chelating ligands XantPhos and dipf (1,1′-bis(diisopropyl-



Scheme 3. Coupling of a vinyl triflate with 3-cyanoindole according to Movassaghi and Ondrus. dba = *trans*,*trans*-dibenzylideneacetone, Tf = trifluoromethanesulfonyl.

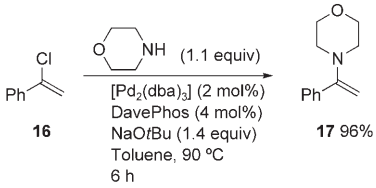
phosphanyl)ferrocene), respectively, are the best systems for coupling amides with vinyl triflates[135] and vinyl tosylates[136] with an activating substituent at the β position. When Willis et al. came to examine the coupling of unactivated vinyl triflates and tosylates, however, ligand **6** proved to be optimal (Scheme 4).[137]



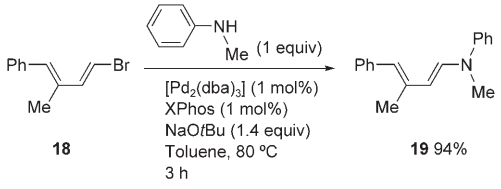
Scheme 4. Coupling of amides with vinyl triflates according to Willis and Brace.

Barluenga et al. showed that binap was a highly effective ligand for the amination of vinyl bromides with alkyl and aromatic amines.[138,139] However, DavePhos was required if vinyl chlorides were to be used as substrates (Scheme 5).[140] The same authors found that XPhos provided the most useful results for 1-halo-1,3-butadienes (Scheme 6).[141]

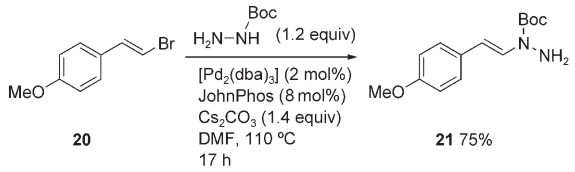
Furthermore, JohnPhos was the best ligand for preparing alkenyl hydrazines (Scheme 7).[142] They discovered that the reaction was very sensitive to the choice of base and solvent,



Scheme 5. Coupling of vinyl chlorides with amines according to Barluenga et al.



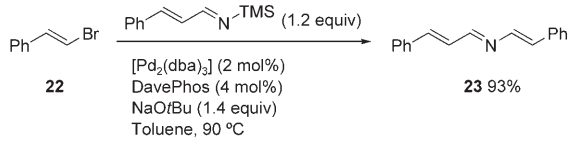
Scheme 6. Coupling of 1-halo-1,3-butadienes with amines according to Barluenga et al.



Scheme 7. Coupling of vinyl bromides with hydrazines according to Barluenga et al. Boc = *tert*-butoxycarbonyl.

and that it was highly selective for coupling at the *N*-Boc-substituted nitrogen atom. These observations were attributed to deprotonation of the *N*-Boc nitrogen atom occurring prior to coordination to palladium.

The best results for coupling *N*-silylimines with vinyl bromides were obtained with DavePhos, although binap showed a superior activity for aryl bromides (Scheme 8).[143]



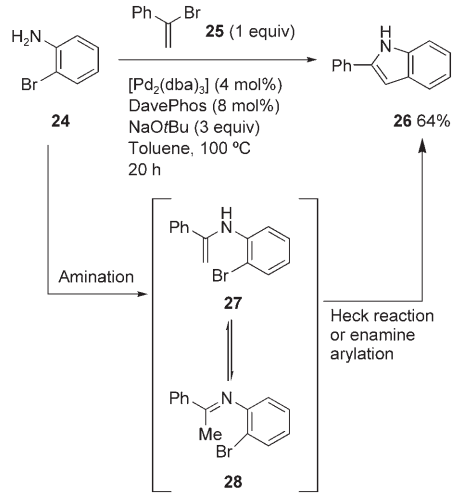
Scheme 8. Coupling of vinyl bromides with trialkylsilylamines according to Barluenga et al. TMS = trimethylsilyl.

4. Construction of Heterocycles

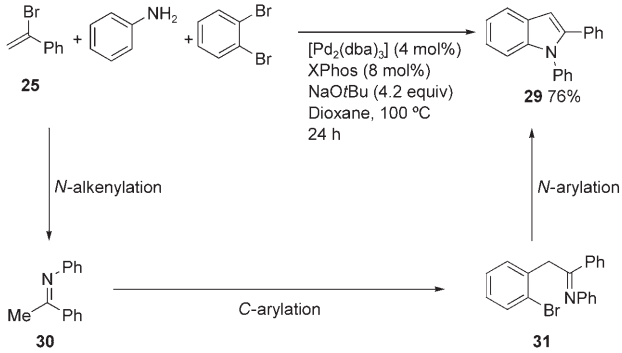
Catalysts based on complexes formed between palladium and dialkylbiaryl phosphane ligands have seen use in several novel heterocycle syntheses.[144–148] The indole system appears in many important compounds, and a number of palladium-based methods have been disclosed for its synthesis and functionalization.[149] The introduction of highly reactive palladium–dialkylbiaryl phosphane complexes, however, has allowed some significant new protocols to be developed.

Barluenga et al.[150] have exploited the large difference in reactivity of 2-aminoaryl halides and vinyl halides towards palladium-catalyzed amination to effect a one-pot synthesis of indoles from *o*-haloanilines and vinyl bromides. It was suggested that ring closure occurs through a Heck reaction; a reasonable alternative mechanism would involve attack of the enamine **27** at the palladium(II) center, followed by reductive elimination (Scheme 9). A range of different ligands can bring about the initial amination of the vinyl bromide, but a bulky dialkylbiaryl phosphane is necesssary for the subsequent cyclization to occur. This process bears a strong mechanistic similarity to the indole synthesis reported by researchers at Merck[151] and to the synthesis of tryptophan derivatives from 2-haloanilies and aldehydes under palladium catalysis with XPhos as the ligand reported by Jia and Zhu.[152]

In a related procedure, *N*-aryl indoles can also be synthesized from *o*-dihaloarenes and imines in the presence of a palladium source and XPhos (Scheme 10).[153] The required imines can be made in situ by the coupling of amines with vinyl bromides. The striking feature of this reaction is once again the selectivity of the process, since the initial coupling of the amine occurs exclusively with the vinyl halide because of its greater reactivity.



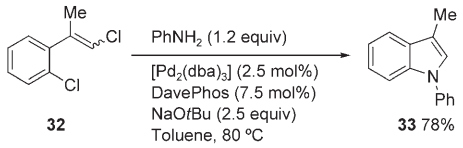
Scheme 9. Synthesis of indoles from vinyl bromides and 2-haloanilines according to Barluenga et al.



Scheme 10. Synthesis of indoles from vinyl bromides, 1,2-dihaloarenes, and anilines according to Barluenga et al.

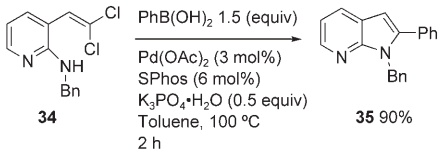
In an alternative route to the indole core, Willis et al. made use of 2-(2-haloalkenyl)aryl halides as coupling partners for primary amines (Scheme 11).[154] Several different dialkylbiaryl phosphane ligands could be used in these reactions, with the exact choice depending on the substrate—although the chelating DPEPhos ligand was more effective for primary alkyl amines. The configuration of the double bond of the alkenyl halide was unimportant, presumably because the intermediate enamine formed in the reaction is able to undergo isomerization.

Lautens and co-workers prepared various substituted indoles by palladium-catalyzed tandem amination and Heck



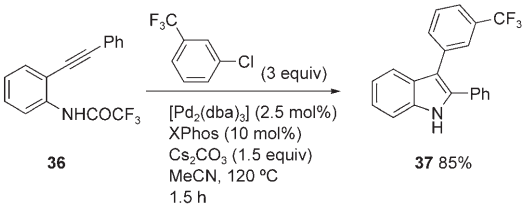
Scheme 11. Synthesis of indoles from 2-(2-haloalkenyl)aryl halides and anilines according to Willis et al.

reactions[155] or amination and Suzuki reactions[156–158] of *ortho-gem*-dihalovinylanilines (Scheme 12). Of particular note is the ability to synthesize azaindoles by this method, a group of compounds of significant interest in pharmaceutical research.



Scheme 12. Heterocycle synthesis by amination and Suzuki coupling according to Lautens and co-workers.

Cacchi et al. employed an alternative route to indoles by taking advantage of the cyclization of *o*-alkynyltrifluoroacetanilides in the presence of aryl chlorides (Scheme 13).[159]

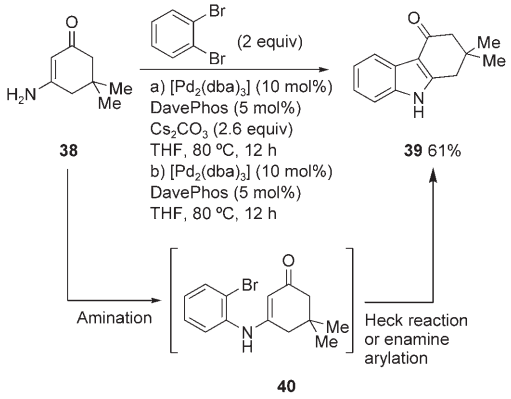


Scheme 13. Synthesis of indoles by cyclization of *o*-alkynyltrifluoroacetanilides in the presence of aryl chlorides according to Cacchi et al.

The use of dialkylbiaryl phosphane ligands allowed aryl chlorides to react. The authors proposed that the mechanism of the reaction involves initial oxidative addition of a palladium(0) species to the aryl halide to form a σ-aryl palladium(II) complex. This then forms a π complex with the alkyne, which is thus activated towards intramolecular nucleophilic attack by the aniline nitrogen atom. The resulting σ-aryl palladium species then undergoes reductive elimination to generate a carbon–carbon bond and furnish the final product. Other ligands such as an N-heterocyclic carbene and a tri-*tert*-butylphosphane proved much less effective.

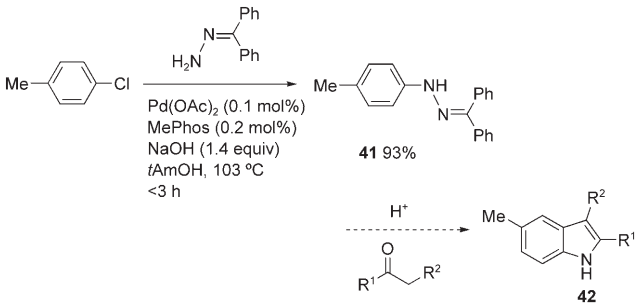
Researchers at Merck have developed an approach to 2,3-disubstituted indoles based on a palladium-catalyzed C–N coupling reaction followed by an intramolecular Heck reaction or enamine arylation between a vinylogous amide and 1,2-dibromobenzene (Scheme 14).[151] It was necessary to add a second equivalent of the palladium source and the ligand for the proposed second step to occur. Other ligands such as binap, tri-*tert*-butylphosphane, and a JosiPhos derivative were ineffective in this reaction.

The preparation of indoles is often achieved by the Fischer indole synthesis in which an *N*-aryl hydrazone undergoes an acid-catalyzed or thermal sigmatropic rearrangement to yield an indole after elimination of ammonia.[160] In 1998 Buchwald and co-workers showed that *N*-aryl benzophenone hydrazones could be made for the Fischer indolization by palladium-catalyzed amination of aryl bromides by using the chelating phosphanes binap or XantPhos.[161,162] This process



Scheme 14. Merck synthesis of indoles from vinylogous amides and 1,2-dihaloarenes.

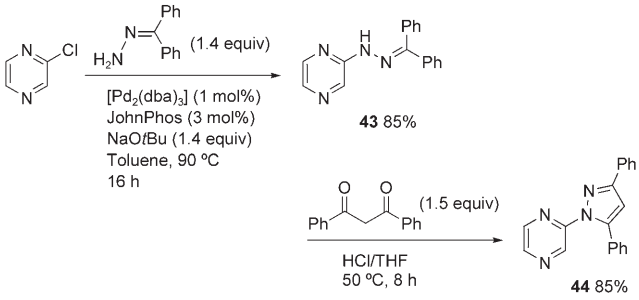
has subsequently been extended to aryl chlorides by the application of dialkylbiaryl phosphane ligands,[163] and has been studied in detail on a larger scale at Rhodia (Scheme 15).[164,165]



Scheme 15. Synthesis of indoles by arylation of benzophenone hydrazones followed by cyclization.

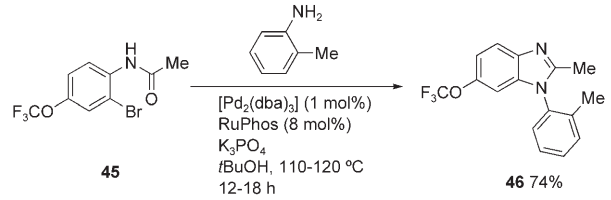
Analogously, researchers at Boehringer Ingelheim demonstrated that heterocyclic aryl halides such as 2-chloropyrazine and 2-bromopyrimidine can be coupled with hydrazones by using dialkylbiaryl phosphane ligands.[166] The intermediate heteroaryl hydrazones were then converted into heteroaryl pyrazoles (Scheme 16).

Buchwald and co-workers have demonstrated that *N*-aryl benzimidazoles may be constructed by the coupling of



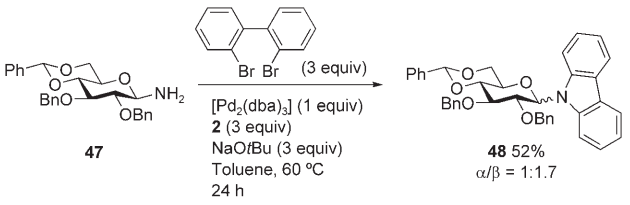
Scheme 16. Boehringer Ingelheim synthesis of heterocycles by arylation of benzophenone hydrazones.

anilines with *o*-haloacetanilides, with cyclization occurring under the reaction conditions (Scheme 17).[167] This is a valuable method as it allows benzimidazoles to be synthesized in regioisomerically pure form, which can otherwise be difficult to access.



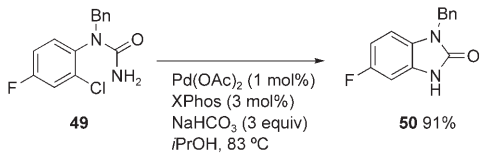
Scheme 17. Synthesis of benzimidazoles from *o*-haloacetanilides and anilines according to Buchwald and co-workers.

In 2003 Nozaki and co-workers introduced the palladium-catalyzed double amination of primary amines with 2,2′-dihalobiphenyl derivatives as a route to carbazoles.[168,169] It was subsequently shown by Chida and co-workers that significantly improved yields of product could be obtained with alkyl amines by using dialkylbiaryl phosphane ligands.[170] In particular, it was necessary to use ligand **2** for the coupling of the glucopyranosylamine derivative **47** to afford reasonable yields of product (Scheme 18). This is a challenging reaction because of the limited stability of the amine substrate.



Scheme 18. Synthesis of carbazoles from 2,2′-dihalobiphenyls and amines according to Nozaki and co-workers.

Researchers at Merck have employed XPhos as the ligand in the palladium-catalyzed cyclization of urea derivatives to synthesize benzoimidazolones (Scheme 19).[171] The dialkylbiaryl phosphane catalyst facilitated the use of chloroaniline substrates, although 2-chloropyridines could be activated by the chelating ligands XantPhos or dppb.

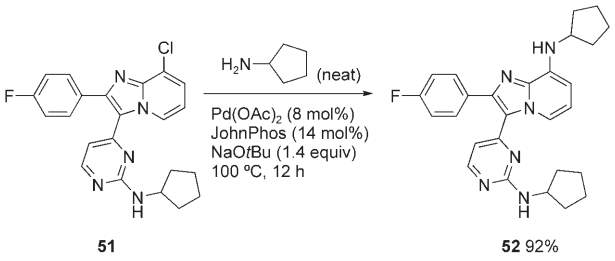


Scheme 19. Merck synthesis of benzoimidazolones by cyclization of ureas.

5. Applications in Pharmaceutical Synthesis

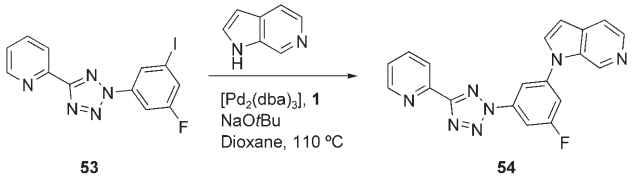
Palladium-catalyzed amination has had a large impact on the manufacture of pharmaceuticals,[172,173] and it is perhaps in this area that dialkylbiaryl phosphane ligands have seen the most use.

Scientists from GlaxoSmithKline utilized a palladium catalyst with the ligand JohnPhos for the coupling of cyclopentylamine with an 8-chloroimidazopyridine **51** in the synthesis of novel imidazo[1,2-*a*]pyridines, which have demonstrated potent activity against the herpes virus (Scheme 20).[174] They noted that the reaction did not proceed in the absence of catalyst and that other ligands, such as binap, afforded significantly lower yields of product.



Scheme 20. GlaxoSmithKline synthesis of antiherpes agents.

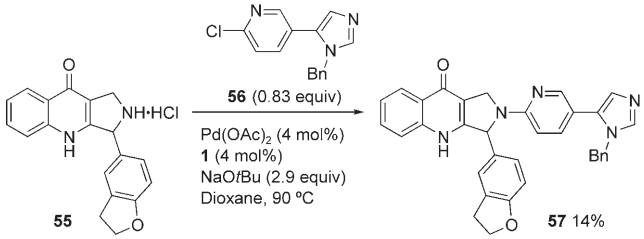
Chemists at Merck have used a palladium-catalyzed cross-coupling reaction of aryl iodides with aromatic amines in the synthesis of a series of substituted tetrazoles for structure–activity studies relating to the design of an antagonist for the metabotropic glutamate subtype 5 receptor (Scheme 21).[175]



Scheme 21. Merck synthesis of mGlu5 receptor antagonists.

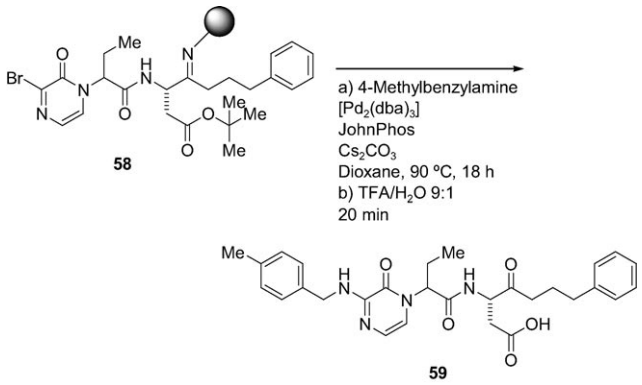
Johnson & Johnson[176] have used **1** as the ligand in the low-yielding synthesis of PDE 5 inhibitors for the treatment of erectile dysfunction (Scheme 22).

The solid-phase synthesis of caspase-3 inhibitors was achieved at Merck Frosst by utilizing JohnPhos as the ligand



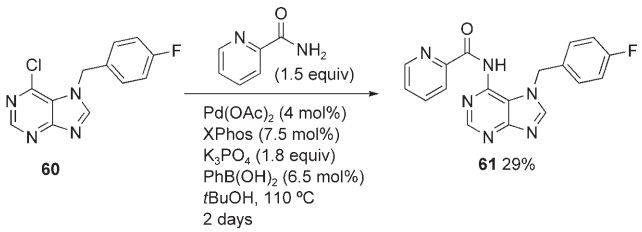
Scheme 22. Johnson & Johnson synthesis of PDE5 inhibitors.

(Scheme 23).[177] This is the first example of the coupling of bromopyrazinones. The use of a mild base such as cesium carbonate was crucial; stronger bases gave only products of ester hydrolysis.



Scheme 23. Merck Frosst synthesis of caspase-3 inhibitors.

Li and Vince employed XPhos as the ligand in a key step of the synthesis of HIV integrase inhibitors (Scheme 24).[178]

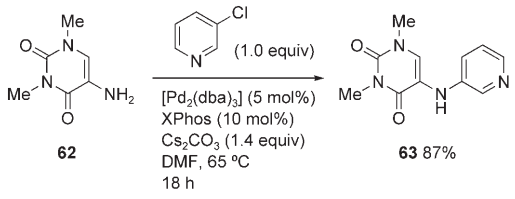


Scheme 24. Synthesis of HIV integrase inhibitors according to Li and Vince.

The coupling of picolinamide was found to be extremely challenging, with a careful choice of conditions required to obtain any of the desired product. Protocols with the chelating ligand dppf gave none of the product. The choice of the palladium source and base were also key to ensuring that the desired reaction occurred.

Kobayashi and co-workers used XPhos as the ligand in the coupling of 3-chloropyridine with 5-amino-1,3-dimethyluracil (**62**) in the syntheses of hybrids of caffeine and eudistomin D to modulate adenosine receptor activity (Scheme 25).[179]

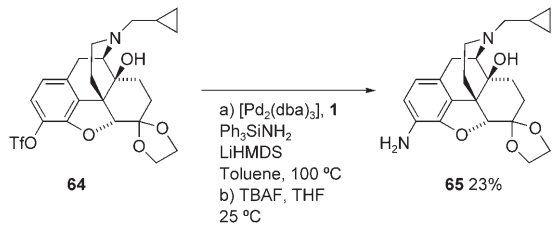
During efforts to define the structure–activity relationships of 2,6-methano-3-benzazocines,[180] Wentland et al. used a coupling reaction between triphenylsilylamide and the aryl



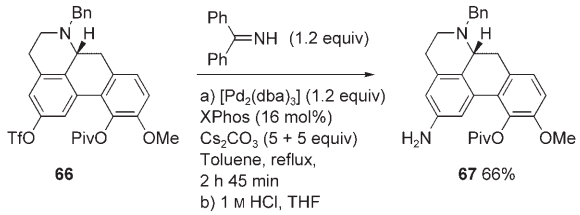
Scheme 25. Coupling step in the synthesis of hybrids of caffeine and eudistomin D by Kobayashi and co-workers.

triflate **64**; subsequent proteolysis of the amine yielded the aniline (Scheme 26).

In a related series, Begtrup and co-workers used benzophenone imine as an ammonia surrogate (Scheme 27).[181]



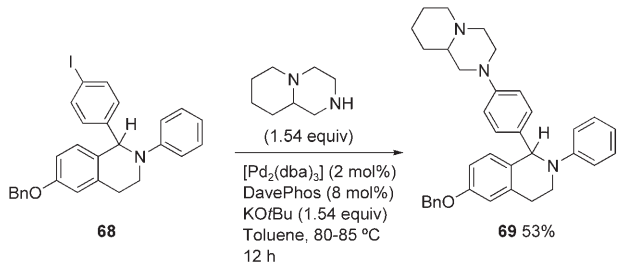
Scheme 26. Synthesis of benzazocine analogues according to Wentland et al. HMDS = 1,1,1,3,3,3-hexamethyldisilazane.



Scheme 27. Use of benzophenone imine in the synthesis of 2-fluoronorapomorphine according to Begtrup and co-workers.

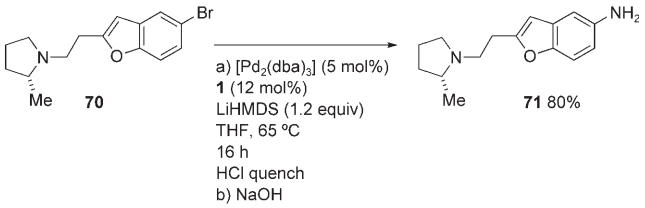
Interestingly, a range of chelating phosphanes proved unsuccessful in this system. It was also found that a large excess of base was necessary to effect a successful reaction, and that the addition of a second batch of base to the reaction after 75 minutes was necessary to reach full conversion.

Chemists at Novartis used a palladium-catalyzed amination in the synthesis of selective estrogen receptor modulators with potential for the treatment of postmenopausal osteoporosis (Scheme 28).[182] The use of binap gave unsatisfactorily low yields, but DavePhos and the carbene SIPr led to product in acceptable yields.



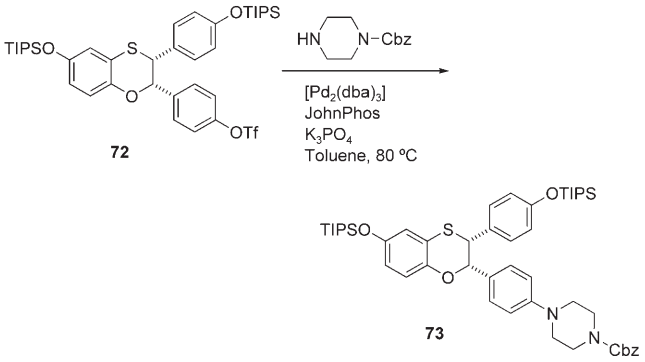
Scheme 28. Novartis synthesis of estrogen receptor modulators.

In the syntheis of histamine H_3 receptor antagonists at Abbott, LiHMDS was coupled with aryl bromide **70** by making use of **1** as the ligand (Scheme 29).[183] Subsequent deprotection allowed a more efficient access to the aniline **71** than an alternative route which involved reduction of an aromatic nitro group.



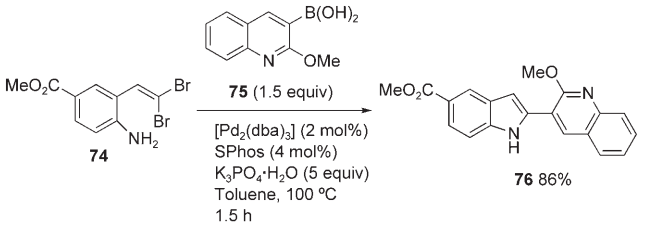
Scheme 29. Abbott synthesis of histamine receptor H_3 antagonists.

The synthesis of estrogen receptor ligands at Merck involved the coupling of aryl triflate **72** with Cbz-protected piperazine (Scheme 30). This is a challenging substrate because of the risk of epimerizing the benzylic chiral centers, but this was not reported to be a problem when the reaction was mediated by the weak base potassium phosphate.[184]



Scheme 30. Merck synthesis of estrogen receptor ligands. Cbz = benzyloxycarbonyl, TIPS = triisopropylsilyl.

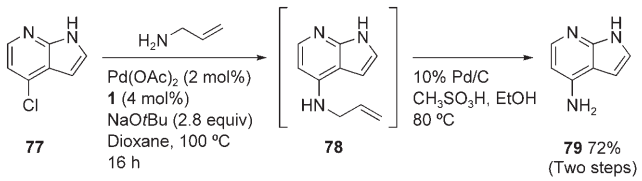
In the construction of KDR kinase inhibitors, which have potential as cancer therapeutic agents, Lautens and co-workers employed a palladium-catalyzed tandem amination and Suzuki coupling reaction as a key step (Scheme 31).[185] This approach was significantly more efficient than other published routes.



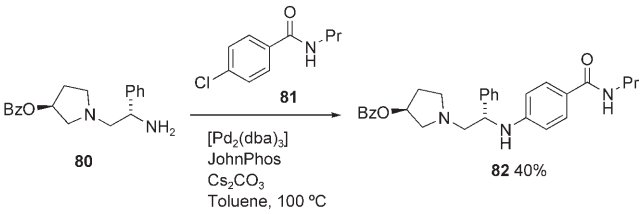
Scheme 31. Synthesis of KDR kinase inhibitors according to Lautens and co-workers.

Researchers at Bristol–Myers Squibb described a palladium-catalyzed amination in the synthesis of substituted 7-aza-indoles (Scheme 32).[186] The reaction was carried out on a 20 g scale. Consistent with other results, the presence of the free NH group of the azaindole **77** was not problematic.[187]

Scientists at Pfizer used JohnPhos as the ligand in one approach to the κ-opiod receptor agonist CJ-15,161 drug candidate, which has applications as a potential non-addictive analgesic (Scheme 33).[188,189] Although the coupling reaction could also be performed on the corresponding aryl bromide by using binap, JohnPhos allowed the chloride to be employed.

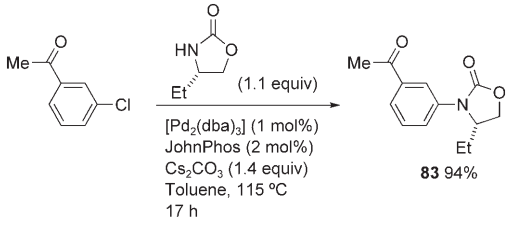


Scheme 32. Bristol–Myers Squibb synthesis of substituted 7-aza-indoles.



Scheme 33. Pfizer synthesis of a κ-opiod receptor agonist.

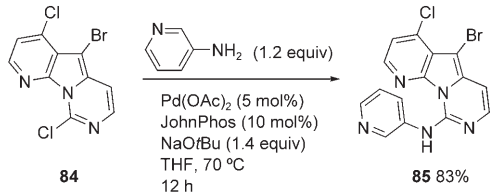
Pfizer chemists have also reported a palladium-catalyzed synthesis of *N*-aryl oxazolidinones from aryl chlorides (Scheme 34).[190] Dialkylbiaryl phosphane ligands generally gave a much faster reaction than did chelating ligands such as binap, XantPhos, DPEPhos, or dppf, although the reaction is only efficient with electron-poor aryl chlorides.



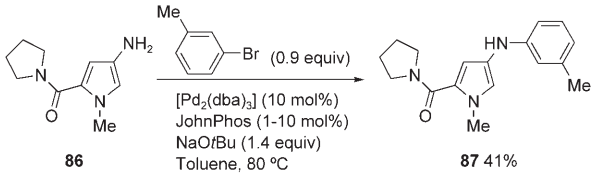
Scheme 34. Pfizer synthesis of *N*-aryl oxazolidinones.

In studies on the derivatization of the variolin core (a heterocyclic family of natural products isolated from an Antarctic sponge) Burgos, Vaquero, and co-workers used JohnPhos as the ligand in the coupling of the aryl chloride substrate **84** with a series of amines; attempts to do the reaction by direct nucleophilic substitution in the absence of a catalyst were unsuccessful (Scheme 35).[191] These coupling reactions are challenging due to the large number of heteroatoms and selectivity issues between the three halogen atoms present in the heteroaromatic core.

Tanatani and co-workers utilized a palladium-catalyzed C–N coupling process during the synthesis of a nonsteroidal and non-anilide-type androgen antagonist (Scheme 36).[192]



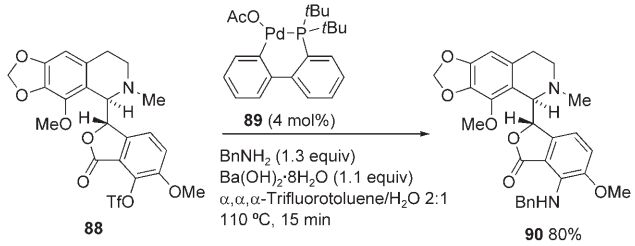
Scheme 35. Synthesis of variolin derivatives according to Burgos, Vaquero, and co-workers.



Scheme 36. Synthesis of a nonsteroidal and non-anilide-type androgen antagonist according to Tanatani and co-workers.

JohnPhos (and in some cases binap) was useful for the transformation of a wide range of aryl halides.

Scientists at Athersys performed a C–N coupling in their synthesis of a series of noscapine analogues with improved antimitotic action (Scheme 37).[193] They found that it was

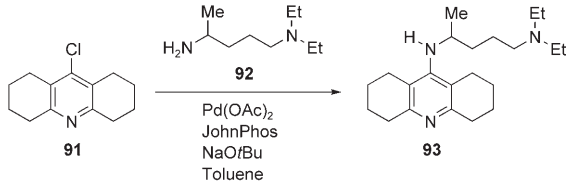


Scheme 37. Athersys synthesis of noscapine analogues.

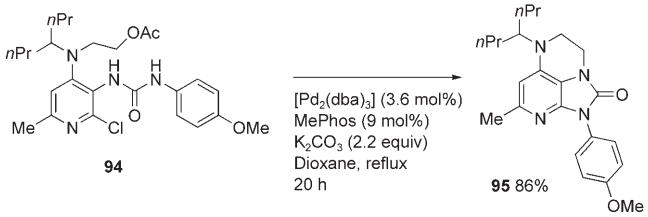
essential to employ a weak base to avoid epimerization of the phthalide center. The use of K_2CO_3, Cs_2CO_3, and KOH all gave poor conversion, as did other ammonia equivalents such as benzophenone imine, LiHMDS, and *tert*-butyl carbamate. Eventually it was discovered that the desired reaction of benzylamine could be effected by barium hydroxide as the base in a biphasic solvent system of toluene and water, although α,α,α-trifluorotoluene and water proved more practical on a large scale because of problems of foaming with other solvents. Noteworthy, is the use of air-stable palladacycle **89** which was introduced by Zim and Buchwald.[194] This was found to be a highly efficient catalyst, giving complete reaction on a 5 gram scale in only 15 minutes. It is tempting to speculate that the reason for the alacrity of this process is that it occurs by a sequence involving aminolysis of the lactone, intramolecular lactam formation, and lactam alcoholysis.

At Merck, JohnPhos was applied as the ligand for the coupling of primary amine **92** with octahydrochloroacridine **91** during the synthesis of analogues of ligands for voltage-gated calcium channels as potential anticonvulsants (Scheme 38).[195]

GlaxoSmithKline scientists used a bisannulation process in a new approach to the potent CRF_1 antagonist GW808990 (Scheme 39).[196] The chelating ligand DPEPhos was also found to be capable of mediating the reaction, but in significantly lower yield than observed with MePhos.

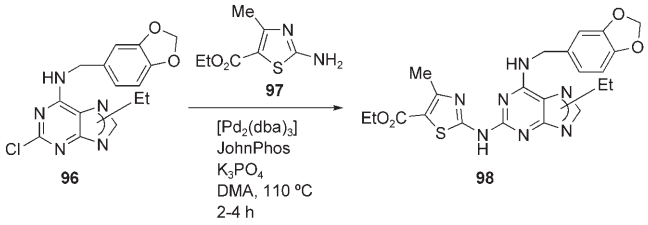


Scheme 38. Merck synthesis of calcium channel ligands



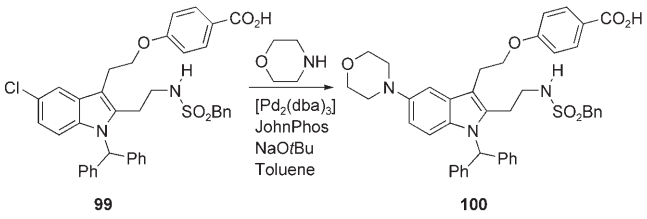
Scheme 39. GlaxoSmithKline syntheis of CRF_1 receptor antagonists.

At Bristol–Myers Squibb, researchers used JohnPhos as the ligand in the coupling of purines with thiazoles in the synthesis of a library of phosphodiesterase 7 inhibitors (Scheme 40).[197] A wide range of conditions were examined, and dialkylbiaryl phosphane ligands gave the best yields and reproducibility (earlier solid-phase studies showed tolbinap to give optimal results).



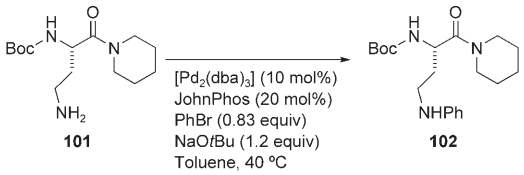
Scheme 40. Bristol–Myers Squibb synthesis of phosphodiesterase 7 inhibitors.

At Wyeth, studies have been made towards the development of cytosolic phospholipase $A_2\alpha$ inhibitors which have promise in the treatment of multiple indications including asthma, arthritis, and pain. During the course of the study of the structure–activity relationship, which eventually led to the compound ecopladib, a C–N coupling with JohnPhos was employed (Scheme 41).[198] It is notable that the presence of multiple acidic hydrogen atoms in the aryl halide substrate did not interfere with the coupling reaction, which had previously been applied successfully in the transformation of simpler members of the series.[199]



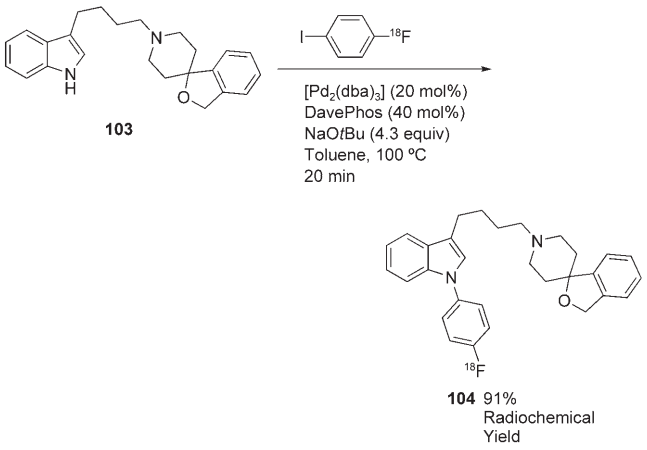
Scheme 41. Wyeth synthesis of ecopladib.

Augustyns and co-workers utilized the coupling of a primary amine and bromobenzene during the course of work on the synthesis of selective dipeptidyl peptidase II inhibitors which have potential for the treatment of a range of diseases (Scheme 42).[200]



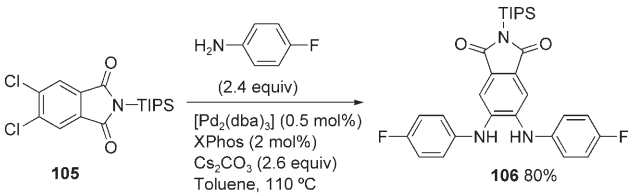
Scheme 42. Synthesis of dipeptidyl peptidase II inhibitors according to Augustyns and co-workers.

For the synthesis of radiolabeled compounds, the reaction time for a cross-coupling reaction is an important factor when dealing with isotopes with a short half-life. During studies aimed at the synthesis of ^{18}F-labeled σ_2-receptor ligands for positron emission tomography studies Wüst and Kniess employed a coupling reaction between indole **103** and 4-[^{18}F]fluoroiodobenzene (Scheme 43).[201] The reaction times have to be short because of the short half-life of ^{18}F ($t_{1/2}$ = 109.6 min). Copper-mediated arylation proved too slow, as did a palladium–XantPhos system. When DavePhos was used as the ligand,[202] however, a satisfactory radiochemical yield of the product could be obtained with a reaction time of just 20 minutes.



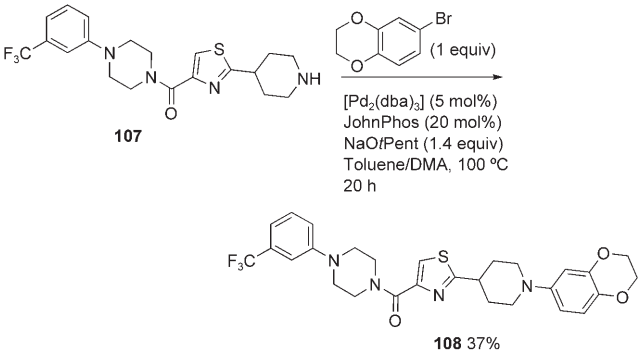
Scheme 43. Synthesis of radiolabeled ligands according to Wüst and Kniess.

In 2005, Hennessy and Buchwald made use of XPhos as the ligand in the synthesis of DAPH analogues which have potential for the treatment of Alzheimer's disease (Scheme 44).[203] A palladium-catalyzed coupling between a 4,5-dihalophthalimide and anilines resulted in a more efficient route to these compounds which was also more amenable to diversification.



Scheme 44. Synthesis of DAPH analogues according to Hennessy and Buchwald.

Scientists at 4SC investigated aromatic amination reactions on a range of substrates (Scheme 45).[204] JohnPhos was the most versatile ligand, but dppf, binap, and XantPhos were most successful for particular substrate classes. The JohnPhos system could be used in synthesizing a library of compounds in a parrallel synthesizer.



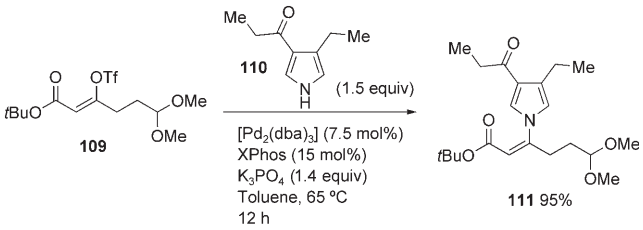
Scheme 45. 4SC study of aromatic amination.

6. Natural Product Synthesis

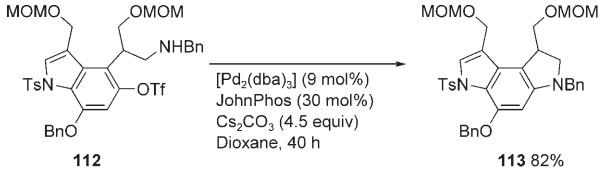
Catalyst systems with dialkylbiaryl phosphane ligands have also been applied in the synthesis of natural products. Movassaghi and Ondrus exploited a coupling reaction between a functionalized pyrrole **110** and vinyl triflate **109** on a 7 gram scale in the synthesis of tricyclic myrmicarin alkaloids (Scheme 46). Attempts to perform a copper-based coupling on these substrates were unsuccessful.[205]

Ganton and Kerr[206] carried out an intramolecular amination of aryl triflate **112** with a [Pd_2dba_3]/JohnPhos catalyst combination to form a dihydropyrrolo[3,2-*e*]indole as part of their studies on the synthesis of the CC-1065 CPI subunit. Such natural products have been studied intensively for their antitumor properties (Scheme 47).

Hosokawa, Tatsuka, and co-workers[207] used the coupling of a functionalized aryl bromide and dimethylamine during the synthesis of the actinomycete natural product trichostatin

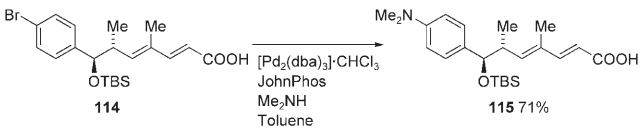


Scheme 46. Pyrrole coupling reactions according to Movassaghi and Ondrus.



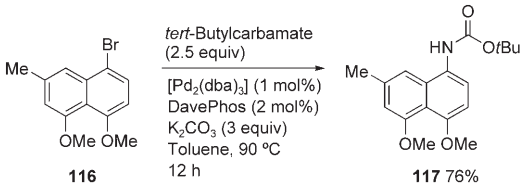
Scheme 47. Studies on the CC-1065 CPI subunit according to Ganton and Kerr. Bn = benzyl, MOM = methoxymethyl, Ts = toluene-4-sulfonyl.

(Scheme 48). This is an interesting transformation as examples of palladium-catalyzed arylation of dimethylamine are rare.



Scheme 48. Synthesis of trichostatin according to Hosokowa, Tatsuka, and co-workers. TBS = *tert*-butyldimethylsilyl.

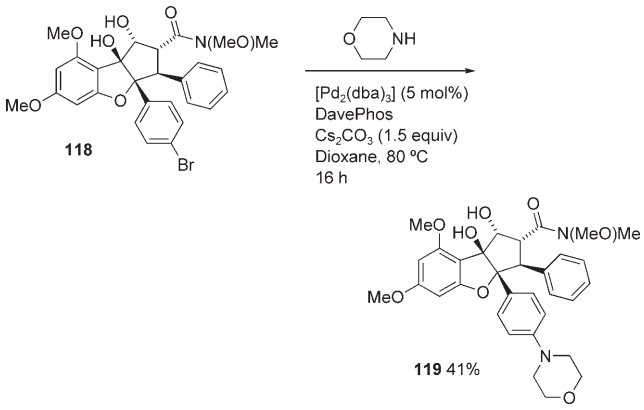
Bringmann et al.[208] utilized the coupling of *tert*-butylcarbamate with aryl bromide **116** in the course of synthesizing the N,C-napthylisoquinoline alkaloid anchisheynine (Scheme 49). This synthesis allowed the separation of the two atropoisomeric products and assignment of their absolute configurations.



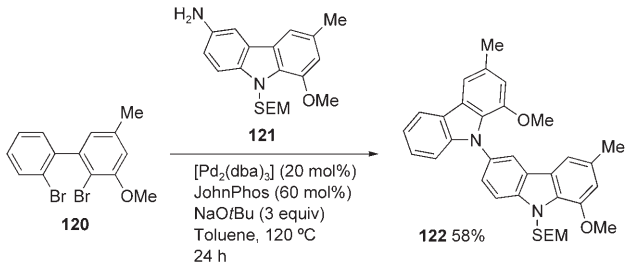
Scheme 49. Synthesis of anchisheynine according to Bringmann et al.

During the synthesis of analogues of the insecticidal natural product rocaglamide, researchers at Novartis employed a palladium-catalyzed amination between morpholine and the complex aryl bromide **118** by using DavePhos as the ligand (Scheme 50).[209]

In the synthesis of the carbazole natural product murrastifoline A, Chida and co-workers used the double N-arylation[168,169] of primary amine **121** with 2,2′-dihalobiphenyl **120** as a key step (Scheme 51).[170]

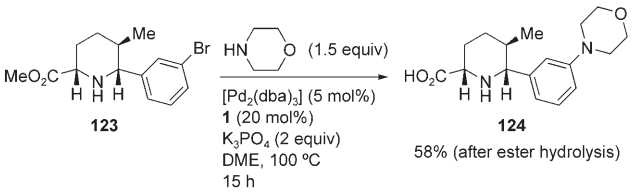


Scheme 50. Novartis synthesis of rocaglamide analogues.



Scheme 51. Synthesis of murrastifoline A according to Chida and co-workers. SEM = trimethylsilylethoxymethyl.

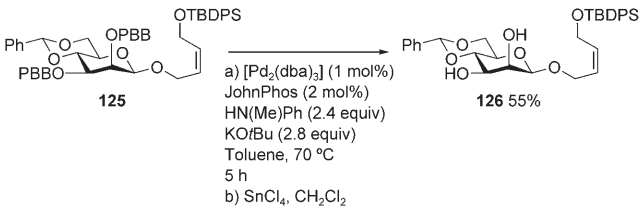
During construction of a library of natural product like diketopiperazines for biological screening Porco, Panek, and co-workers used ligand **1** in the coupling of morpholine with the complex aryl bromide **123** (Scheme 52).[210]



Scheme 52. Synthesis of a library of diketopiperazines according to Porco, Panek, and co-workers. DME = 1,2-dimethoxyethane.

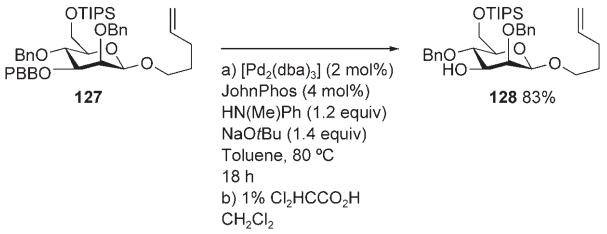
In 2000, Plante, Buchwald, and Seeberger introduced halobenzyl ethers as protecting groups for hydroxy groups in organic synthesis.[211] Such ethers can undergo amination in the presence of a suitable combination of a palladium source and ligand. The resulting aryl amines can then be removed by brief exposure to acid or oxidant. These protecting groups, in particular the *p*-bromobenzyl (PBB) group, have been applied in the synthesis of saccharides. Crich et al. used this method in the synthesis of mannosylerythritol lipid A, an unusual biosurfactant produced by *Candida antarctica*.[212] The PBB groups were selectively removed from the inter-

mediate **125** in the presence of a benzylidene acetal, thus allowing subsequent installation of the key alkyl ester groups at the 2- and 3-positions (Scheme 53).



Scheme 53. Synthesis of mannosylerythritol lipid A according to Crich et al. TBDPS = *tert*-butyldiphenylsilyl.

Seeberger and co-workers also used this protecting group in the synthesis of branched mannose-rich oligosaccharides from the HIV-1 viral surface envelope glycoprotein gp120; such oligosaccharides are important in the binding of the virus to human CD4 lymphocyte receptors (Scheme 54).[213] Here the PBB group could be removed in the presence of two benzyl ethers, thus allowing subsequent glycosylation of the free hydroxy group.

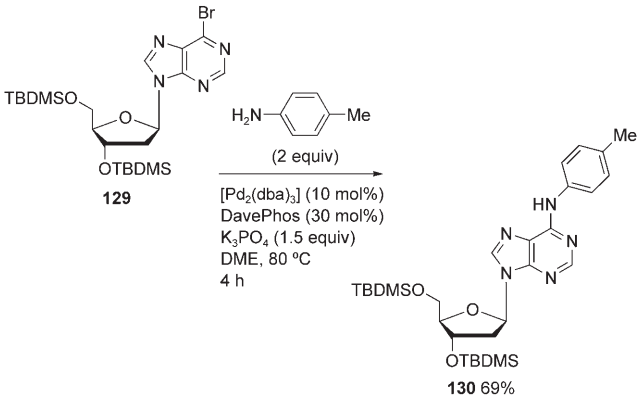


Scheme 54. Synthesis of gp120 oligosaccharide according to Seeberger and co-workers.

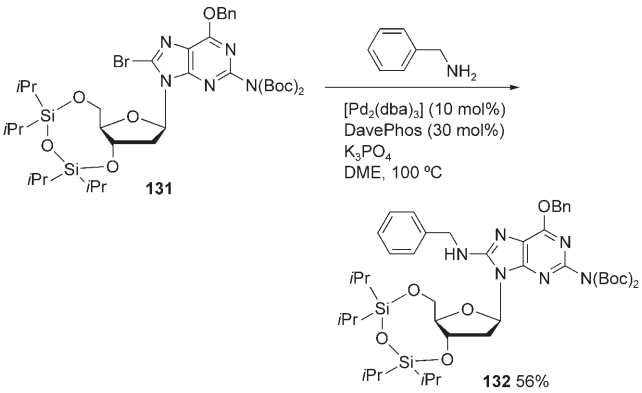
7. Modification of Biomolecules

Another important area where dialkylbiaryl phosphane ligands have been applied in C–N coupling reactions is in the chemical modification of 2′-deoxynucleosides.[214,215] Such N^6-modified adenine and N^2-modified guanine derivatives have a range of interesting biological activities and have also been implicated in the alterations to DNA that lead to mutagenesis. Lakshman et al. were able to synthesize N^6-aryl 2′-deoxyadenosine analogues by using DavePhos in combination with K_3PO_4 as the base (Scheme 55).[216]

Similar conditions were used in the synthesis of N^2-modified guanine derivatives.[217] The method was subsequently extended to nucleoside aryl sulfonates.[218] This represented an important advance, as O^6-aryl sulfonate nucleosides of purine are readily available. The same ligand system has also been employed in the synthesis of C^8-nucleoside adducts (Scheme 56).[219] Such compounds are of significance because of their carcinogenicity and their occurrence in cooked meats. The authors found that although the dialkylbiaryl phosphane ligand system was useful, binap could effect similar results under the same conditions.

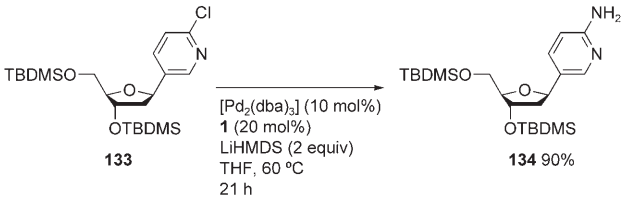


Scheme 55. Modification of 2′-deoxyadenosine derivatives according to Lakshman et al. TBDMS = *tert*-butyldimethylsilyl.



Scheme 56. C^8-modified nucleosides according to Wang and Rizzo.

Hocek and co-workers took advantage of a palladium-catalyzed amination in the synthesis of 6-substituted pyridin-2-yl and pyridin-3-yl C-nucleosides (Scheme 57).[220,221] The best ligand seemed to depend strongly on the substrates, with JohnPhos, ligand **1**, JosiPhos, and tri-*tert*-butylphosphane being preferred for different combinations of amines and halides.

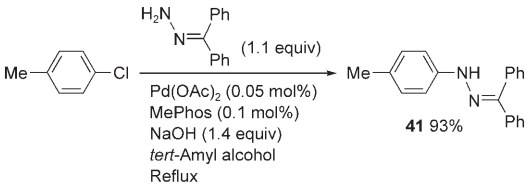


Scheme 57. Synthesis of pyridin-3-yl C nucleosides according to Hocek and co-workers.

8. Process Development

The palladium-catalyzed arylation of hydrazones by using dialkylbiaryl phosphane ligands has been investigated extensively on a large scale by Rhodia Pharma Solutions and Lanxess.[87,88,164,165] The progress of the reaction was followed by both calorimetry and in situ Raman spectroscopy. The

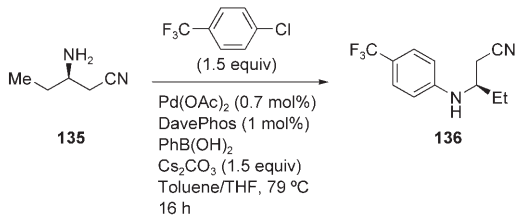
structure of the ligand was crucial in the coupling of the model system of 4-bromotoluene with benzophenone hydrazone (Scheme 58). The nature of the base and solvent was also important in determining the outcome of the reaction and



Scheme 58. Rhodia study of benzophenone hydrazone arylation.

controlling the formation of unwanted by-products. For example, sodium *tert*-butoxide gave much higher yields than did potassium *tert*-butoxide, and the choice of solvent had a significant influence on the formation of the by-product diphenylmethane. The low catalyst loadings are of particular note.

The palladium-catalyzed amination of aryl halides with dialkylbiaryl phosphane ligands has also been performed on a larger scale. Chemists at Pfizer reported such a reaction on a 3 kg scale during the manufacture of the cholesteryl ester transfer protein inhibitor torcetrapib, which can lower blood cholesterol levels (Scheme 59).[222] A number of conditions



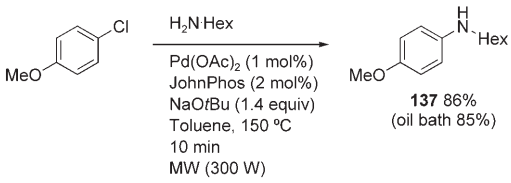
Scheme 59. Pfizer synthesis of torcetrapib.

were examined, but the combination of DavePhos and cesium carbonate as the base proved best. The reaction temperature was important—if the temperature was raised above 80 °C, slight erosion of the enantiomeric purity was observed.

9. Reaction Conditions

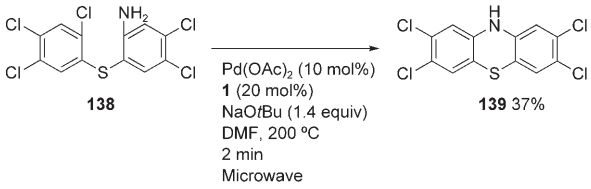
Microwave (MW) heating in organic synthesis is becoming an increasingly important area.[223] Maes et al. have shown that temperature-controlled microwave heating allows the reaction time of palladium-catalyzed aryl chloride amination reactions with dialkylbiaryl phosphane ligands to be reduced to just 10 minutes, with yields comparable to those obtained with conventional heating (Scheme 60).[224,225] The same authors were later able to increase the scale of these reactions in an appropriate microwave reactor.[226]

A modified version of these conditions was subsequently employed in an intramolecular reaction by Rozman and co-workers in the synthesis of chlorinated phenothiazines as



Scheme 60. Coupling under microwave conditions according to Maes et al.

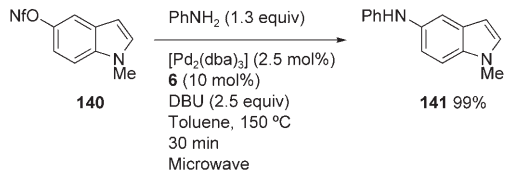
models for dioxin-like compounds (Scheme 61).[227] The copper-mediated Ullmann conditions usually used for these cyclizations were unsatisfactory in this case because of decomposition of the product.



Scheme 61. Synthesis of phenothiazines under microwave conditions according to Rozman and co-workers.

Subsequent studies by Skjaerbaek and co-workers in the course of synthesizing p38 MAP kinase inhibitors have illustrated that XPhos can be an even more effective ligand under microwave irradiation and that the process can be extended to the use of aryl triflates as electrophiles.[228] Heo et al. have demonstrated that, under similar conditions, halopyridines can be used as substrates for the amination during the synthesis of amino-substituted 2-pyridones.[229,230]

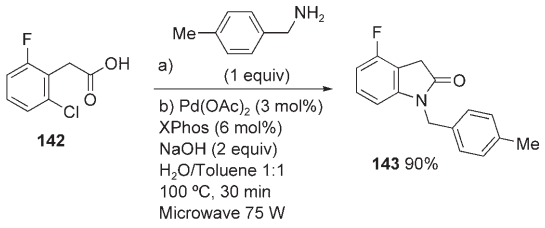
Buchwald and co-workers have shown that the soluble, organic amine bases DBU and MTBD can be advantageous for the palladium-catalyzed amination of aryl nonaflates under microwave heating (Scheme 62).[231] It was suggested



Scheme 62. Buchwald's amination of aryl nonaflates under microwave conditions. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

that this had the benefit of rendering the reactions homogeneous, which has advantages for heat transfer and stirring. As is often observed with microwave irradiation, reaction times were significantly reduced compared to conventional thermal reactions.[232]

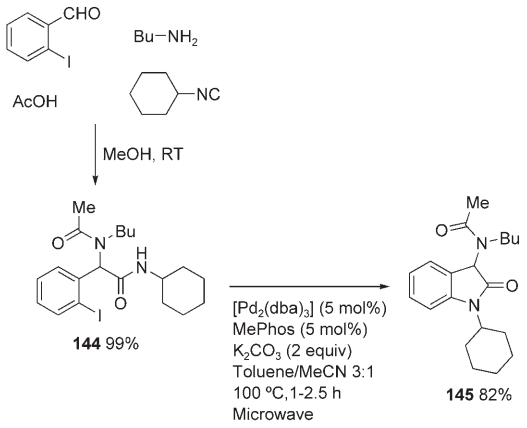
Intramolecular amidation was used by Poondra and Turner in a palladium-catalyzed synthesis of oxindoles (Scheme 63).[233] In this approach an amide was initially generated from an amine and 2-haloarylacetic acid with microwave heating under solvent-free conditions. The crude



Scheme 63. Synthesis of oxindoles by cyclization according to Poondra and Turner.

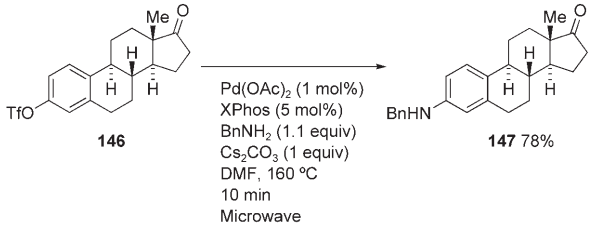
product was then subjected to a palladium-XPhos catalyst system to effect the cyclization. These conditions led to a significant decrease in the reaction time to 30 minutes. Reaction times of 20–48 hours had previously been reported for such palladium-catalyzed intramolecular amidations under thermal conditions and with chelating ligands,[234] while reaction times of 3 hours have been reported by van den Hoogenband et al. for such oxindole formation with XPhos under thermal conditions.[235,236]

Microwave heating was also employed by Zhu and co-workers in an Ugi four-component reaction/intramolecular amidation sequence to synthesize oxindoles for diversity-oriented synthesis (Scheme 64).[237]



Scheme 64. Synthesis of oxindoles by Ugi four-component coupling according to Zhu and co-workers.

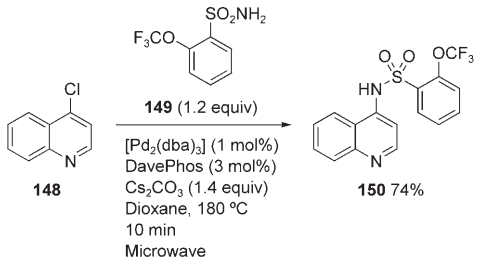
Scientists at Solvay have also applied microwave heating in an improved route to 3-aminoestrone, a key intermediate in the synthesis of biologically active steroids (Scheme 65).[238] Although the reaction could also be performed in similar yield under thermal conditions, reaction times were longer



Scheme 65. Solvay 3-aminoestrone synthesis.

(15 h compared to 10 min) and much higher loadings of the palladium source (10 compared to 1 mol%) and ligand (10 compared to 5 mol%) were required.

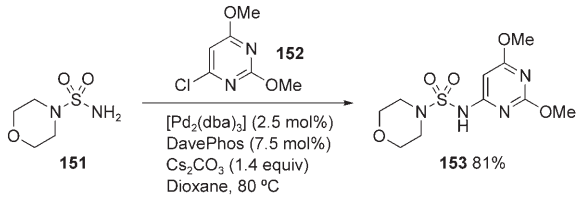
At GlaxoSmithKline, microwave heating has been found useful in the synthesis of *N*-aryl sulfonamides from aryl chlorides and sulfonamides (Scheme 66).[239] A range of



Scheme 66. GlaxoSmithKline sulfonamide synthesis under microwave conditions.

ligands were suitable for the transformation, including a monodentate N-heterocyclic carbene and chelating phosphanes, but the dialkylbiaryl phosphane DavePhos gave the most consistent results under these conditions. Lower conversion was observed under thermal conditions, even after prolonged heating.

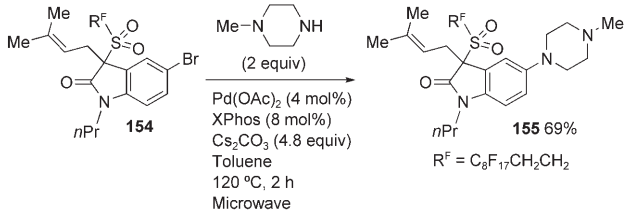
In a related study by AstraZeneca, *N*-heteroaryl sulfamides were prepared from heteroaryl chlorides and activated aryl bromides under thermal conditions by using either XPhos, DavePhos, or XantPhos (Scheme 67).[240]



Scheme 67. AstraZeneca synthesis of *N*-aryl sulfamides.

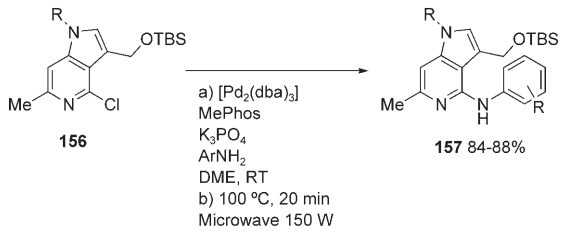
Procter and co-workers showed that microwave heating promoted the amination of oxindole aryl bromides bearing a fluorous tag, which could later undergo traceless removal (Scheme 68).[241]

Microwave irradiation was used by researchers at GlaxoSmithKline in a key coupling step in the synthesis of analogues of CRF_1 receptor antagonists for the treatment of



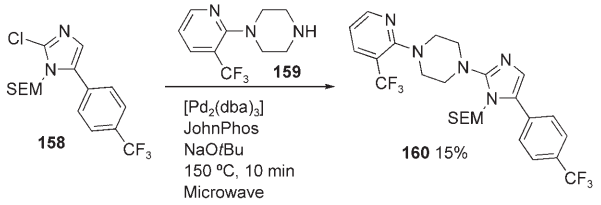
Scheme 68. Synthesis of fluorous-tagged heterocycles according to Procter and co-workers.

stress-related disorders (Scheme 69).[242] It was found that reaction times were minimized and yields maximized by using microwave irradiation and MePhos as the ligand.



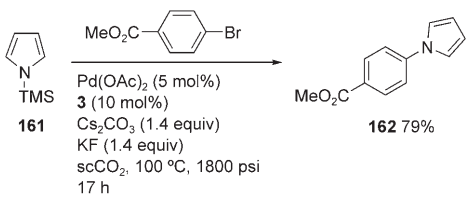
Scheme 69. GlaxoSmithKline synthesis of CRF_1 receptor antagonists.

In a recent example from Amgen, microwave heating was also used in the palladium-catalyzed amination of a protected imidazole in the synthesis of vanilloid receptor antagonists, which have potential use an analgesics (Scheme 70).[243]



Scheme 70. Amgen synthesis of vanilloid receptor antagonists.

Another area of development has been in the application of supercritical carbon dioxide ($scCO_2$) as the solvent for the palladium-catalyzed amination of aryl halides in the presence of biaryl phosphane ligands (Scheme 71).[244,245] Holmes and



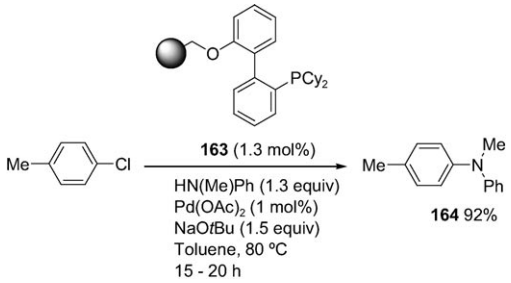
Scheme 71. Amination of aryl halides in supercritical carbon dioxide according to Holmes and co-workers.

co-workers showed that it is necessary to protect the amine with a trimethylsilyl group for successful reaction to occur in this medium so as to prevent carbamate formation from occurring. A range of aryl bromides and chlorides could be coupled using a variety of different dialkylbiaryl phosphane ligands.

At Rhodia, efforts have been made to apply palladium-catalyzed reactions in continuous microreactors.[246] A ligand system composed of $Pd(OAc)_2$ and DavePhos was highly efficient in the model reaction of 4-bromotoluene and piperidine at 110 °C with residence times around 10 minutes, and led to 100 % conversion of the aryl halide with greater than 99 % selectivity.

10. Solid-Supported Catalysts

Phosphane-functionalized polymers have become increasingly common in organic synthesis.[247,248] Such immobilized catalysts are of interest because of the possibility of recovering the catalyst and the minimization of metal impurities in the product.[249] In 2001, Parrish and Buchwald reported dialkylbiaryl phosphane ligands supported on a Merrifield resin for amination and Suzuki cross-coupling reactions (Scheme 72).[250] This represented the first example of an amination of an aryl chloride with solid-supported ligands.

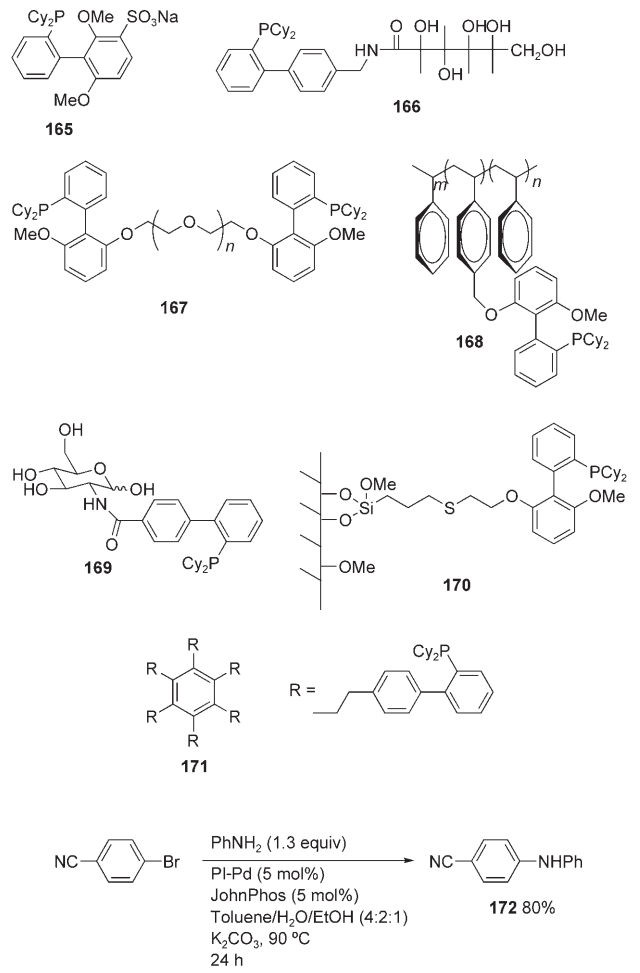


Scheme 72. Application of a solid-supported dialkylbiaryl phosphane in the amination of aryl chlorides according to Parrish and Buchwald.

García and co-workers have prepared a dialkylbiaryl phosphane ligand on a high surface area silica **170**, but this material was found to be inactive in amination and Suzuki reactions. The same researchers also prepared SPhos anchored on soluble supports such as non-cross-linked polystyrene (in **168**) and poly(ethylene glycol) (PEG; in **167**). These complexes were active in amination reactions of aryl chlorides.[251] The PEG-SPhos ligand **167** could be recovered at the end of the reaction by precipitation and retained activity through four runs. A similar ligand was employed by an der Heiden and Plenio[252] as well as by Framery, Sinou, and co-workers[253] (with a PEG-polystyrene copolymer) for biphasic Suzuki reactions. Similarly, a water-soluble dialkylbiaryl phosphane has been prepared by Miyaura and co-workers[89] (**166**) and by Framery, Sinou, and co-workers[254] (**169**) by attachment of a carbohydrate side chain, and by Anderson and Buchwald by sulfonation.[255] Another approach pioneered by Lemo, Heuzé, and Astruc has been to use dendrimer phosphane derivatives **171**, which may be recovered at the end of the reaction by precipitation.[256]

An alternative way of rendering these reactions heterogeneous is to employ an polymer-incarcerated palladium source. Kobayashi and co-workers showed that the amination of aryl halides could be performed by using a range of dialkylbiaryl phosphane ligands; minimal palladium leaching was observed if the solvent was chosen correctly (Scheme 73).[257]

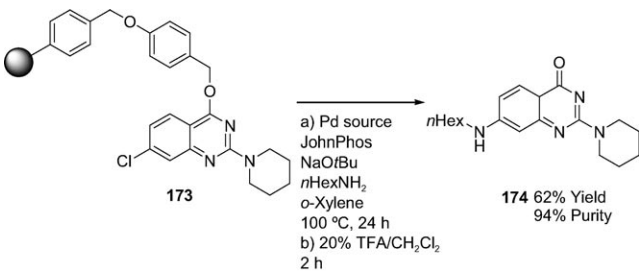
Chemists at Elan Pharmaceuticals have shown that unmodified JohnPhos may be recovered from palladium-catalyzed reactions by a catch and release approach by using sulfonic acid groups bound to cross-linked polystyrene, or by using sulfonic acid functionalized silica gel (Silicycle) in a variety of solvents.[258] The phosphane could subsequently be



Scheme 73. Use of polymer-incarcerated palladium with dialkylbiaryl phosphane ligands according to Kobayashi and co-workers.

released in pure form from the solid support by treatment with a solution of ammonia in methanol

Substituted quinazolines can be synthesized by making use of substrates supported on Wang resin (Scheme 74).[259] For this class of substrate, aryl bromides could be coupled successfully using binap as the ligand, but aryl chlorides required JohnPhos or tri-*tert*-butylphosphane. Interestingly the latter ligand proved more effective for secondary amines, but for primary amines JohnPhos was better because of the lower amount of diarylation.

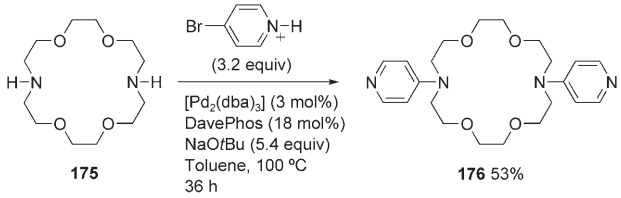


Scheme 74. Amination of solid-supported heteroaryl chlorides. TFA = trifluoroacetic acid.

11. Synthesis of Ligands and Sensors

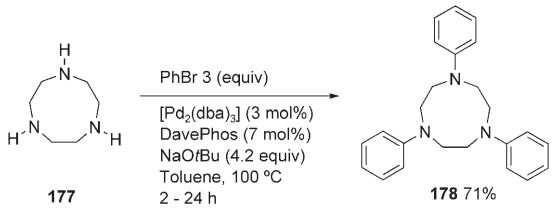
The amination of aryl halides with palladium-dialkylbiaryl phosphane catalysts has also been applied in the synthesis of ligands for other metals.

The development of methods for the palladium-catalyzed arylation of macrocyclic amines[260–262] has served to significantly improve the synthesis of this class of ionophore over more traditional synthetic routes.[263] Stang and co-workers used DavePhos as the ligand in the palladium-catalyzed arylation of **175** during the synthesis of precursors for the assembly of supramolecules by coordination-driven self-assembly (Scheme 75).[264]



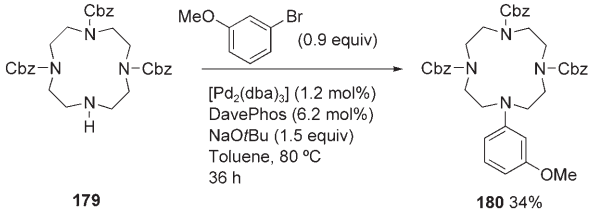
Scheme 75. Synthesis of precursors for self-assembling supramolecules according to Stang and co-workers.

Nakanishi and Bolm employed similar conditions in the arylation of 1,4,7-triazacyclononanes, which can act as chelating ligands in bioorganic chemistry (Scheme 76).[265] Chelating phosphane ligands were ineffective in this reaction.

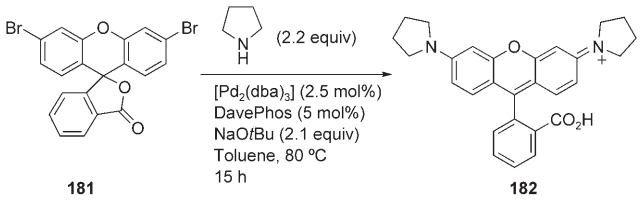


Scheme 76. Synthesis of triazacyclononane derivatives according to Nakanishi and Bolm.

Burdette and Lippard used this method in the synthesis of fluorescent sensors for zinc ions; once again the dialkylbiaryl phosphane DavePhos was the ligand of choice (Scheme 77).[266] The same research group used a palladium-catalyzed amination in one approach to a rhodamine fluorophore (Scheme 78).[267] The synthetic route allowed access



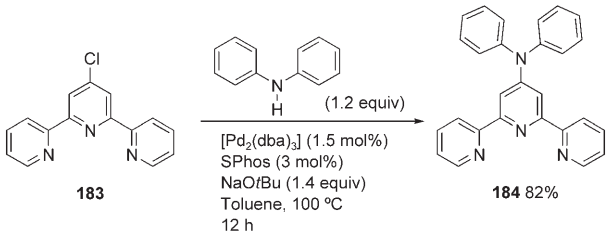
Scheme 77. Synthesis of fluorescent zinc sensors according to Burdette and Lippard.



Scheme 78. Synthesis of substituted rhodamine fluorophores according to Lippard and co-workers.

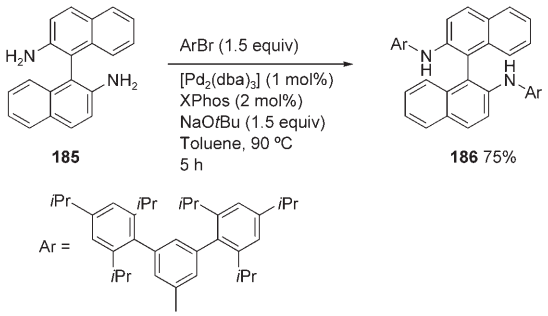
to isomerically pure material; such dyes are of interest because of their biocompatibility as well as their high brightness and quantum yields.

Johansson enlisted a palladium-catalyzed amination with SPhos as the ligand in the synthesis of terpyridine ligands, with the ultimate goal of synthesizing ruthenium(II) complexes (Scheme 79).[268] A range of amines were coupled with 4′-chloro-tpy (**183**) in high yield, this is an important result considering the strong metal-coordinating ability of this heteroaryl chloride.



Scheme 79. Johansson's synthesis of ruthenium(II) ligands.

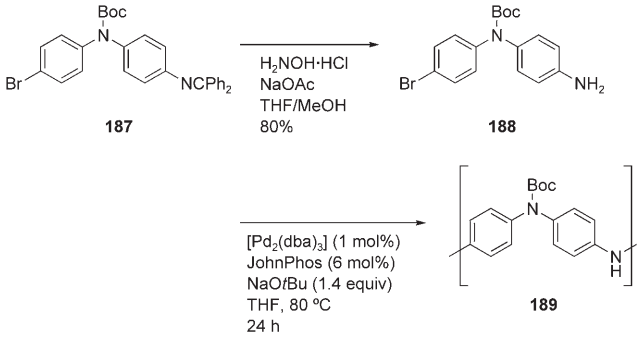
In 2006, Tonzetich and Schrock performed a palladium-catalyzed amination of binam during the synthesis of ligands for Group IV metals that would act as potential catalysts for alkene polymerization (Scheme 80).[269] This reaction provided over 13 g of purified product.



Scheme 80. Synthesis of alkene polymerization catalysts according to Tonzetich and Schrock.

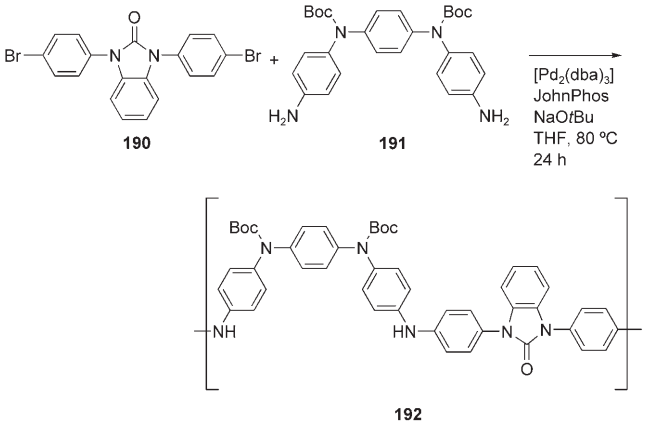
12. Applications in Materials Science

The palladium-catalyzed amination of aryl halides also lends itself to polymerization processes for the formation of polyaniline (PANI). *p*-Polyaniline has tunable electrical conductivity and high environmental stability. Buchwald and co-workers have demonstrated that dialkylbiaryl phosphane ligands allow high-molecular-weight polyaniline **189** to be synthesized from a suitable aryl bromide precursor (Scheme 81).[270] This protected polymer is readily processed, as it is soluble in organic solvents, and can be fabricated into thin films.



Scheme 81. Synthesis of polyaniline according to Buchwald and co-workers.

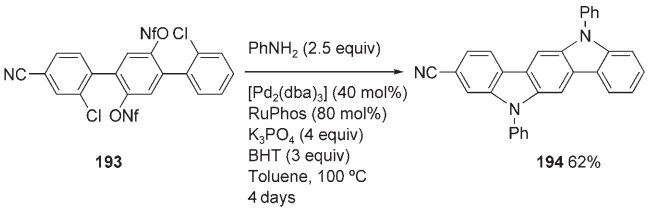
In a similar way, Ward and Meyer generated copolymers of *ortho*- and *para*-substituted polyaniline **192** (Scheme 82).[271] This material exhibited comparable conductivity and oxidation properties to polyaniline.



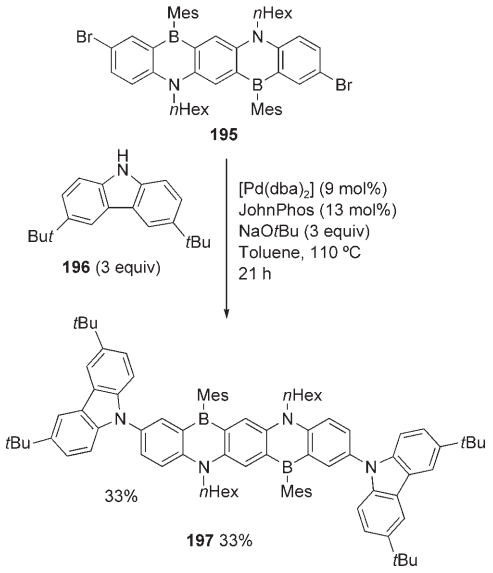
Scheme 82. Synthesis of a polyaniline copolymer according to Ward and Meyer.

The research group of Nozaki has exploited the palladium-catalyzed double N-arylation of primary amines to synthesize ladder-type π-conjugated heteroacenes which show potential as organic semiconductors in field-effect transistors (Scheme 83).[272] The dialkylbiaryl phosphane ligand RuPhos was found essential to obtain good yields of product.

Kawashima and co-workers used a palladium-catalyzed amination to functionalize ladder-type azaborines; such aminated compounds exhibit enhanced photoluminescence (Scheme 84). Hexylamine and diphenylamine could be cou-



Scheme 83. Synthesis of heteroacenes according to Nozaki and co-workers. BHT = butylated hydroxytoluene.

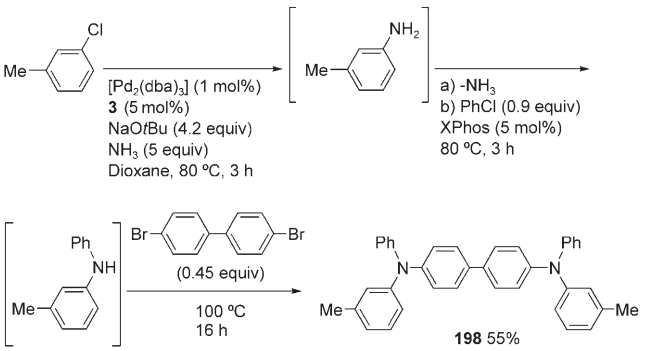


Scheme 84. Synthesis of azaborines according to Kawashima and co-workers.

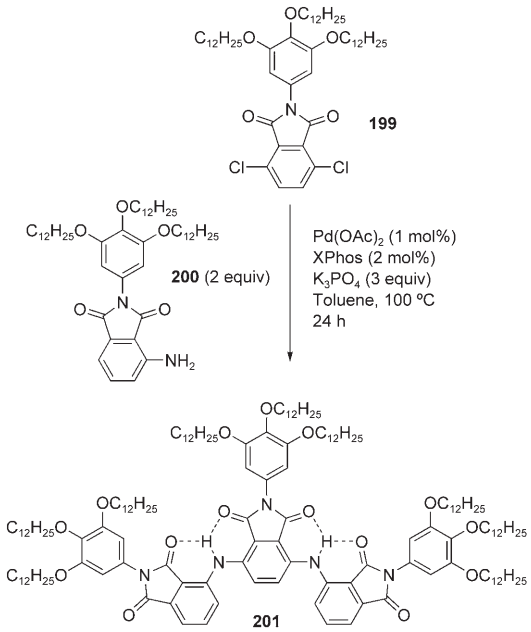
pled with this aryl bromide by using a Pd/binap system, but JohnPhos was required to effect the reaction of carbazole **196**.[273]

Triarylamines have been the subject of continuing research because of their optoelectronic properties.[274,275] Numerous methods have been disclosed for their synthesis by the palladium-catalyzed arylation of diarylamines. Harris and Buchwald demonstrated that under suitable conditions with dialkylbiaryl phosphane ligands it is possible to synthesize these molecules from anilines and an aryl chloride and an aryl bromide by exploiting the difference in the reactivity of the two halides.[276] Subsequently, it was discovered that the selective arylation of ammonia[277] with three different aryl halides could be achieved by sequential addition.[278] In this way, the important triarylamine *N*,*N*′-bis(3-methylphenyl)-*N*,*N*′-diphenylbenzidine (TPD, **198**) could be made in a one-pot procedure from three aryl halides and ammonia (Scheme 85).

Meijer and co-workers showed that a palladium-catalyzed amination can be used successfully in the synthesis of poly(aminophthalimide) dimers and trimers (Scheme 86).[279] The choice of the base and palladium source was essential in obtaining an optimal yield of the product, with aryl chlorides giving higher yields of the desired oligomers than either aryl bromides or iodides as coupling partners.



Scheme 85. Synthesis of TPD by selective arylation of ammonia.

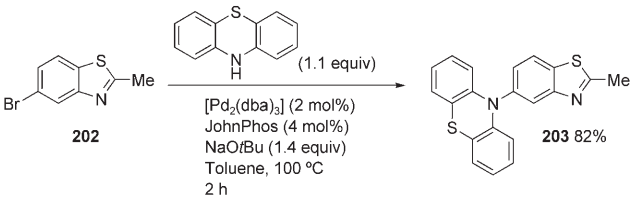


Scheme 86. Synthesis of poly(aminophthalimide) oligomers according to Meijer and co-workers.

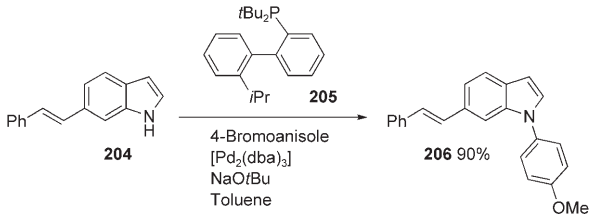
Burgess and co-workers disclosed a palladium-catalyzed amination with JohnPhos in the synthesis of energy-transfer systems based on squaraines (Scheme 87).[280]

Yang et al. used a palladium-catalyzed arylation of an indole during the synthesis of aminostilbenes for studies on torsional motion during photoinduced intramolecular charge transfer (Scheme 88).[281]

The palladium-catalyzed amination of 2,2′-dibromo-9,9′-spirobifluorene (**207**) with LiHMDS and using **1** as the ligand

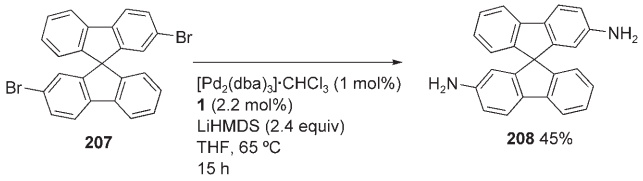


Scheme 87. Synthesis of squaraine-based energy-transfer systems according to Burgess and co-workers.



Scheme 88. Synthesis of aminostilbenes for studies on charge transfer according to Yang et al.

has been reported by Lützen and co-workers in the synthesis of 9,9′-spirobifluorene derivatives, with a view to applications in macromolecular chemistry (Scheme 89).[282]



Scheme 89. Synthesis of 9,9′-spirobifluorene derivatives according to Lützen and co-workers.

Conclusions and Outlook

Dialkylbiaryl phosphane ligands have found a wide range of practical applications in palladium-catalyzed aryl and vinyl halide amination reactions. Catalyst systems with other ligands can provide highly active catalysts, especially for the amination of aryl bromides, but none have as many applications in reactions of the more economically attractive aryl chlorides. A noticeable trend in this field is the increasing use of microwave heating because of the resulting short reaction times. Challenges remain, in particular in the design of ligands which allow low catalyst loadings with substrates bearing multiple heteroatoms. A more detailed understanding of the subtle effects imparted by different ligand substituents will be important, as at present the choice of dialkylbiaryl phosphane used for a particular reaction is still often empirical. It is hoped that this Review inspires further uses of amination reactions with these ligands, and spurs further developments in ligand design.

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