CHEMICAL REVIEWS

Review

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Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions

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ABSTRACT: Pd-catalyzed cross-coupling reactions that form C–N bonds have become useful methods to synthesize anilines and aniline derivatives, an important class of compounds throughout chemical research. A key factor in the widespread adoption of these methods has been the continued development of reliable and versatile catalysts that function under operationally simple, user-friendly conditions. This review provides an overview of Pd-catalyzed N-arylation reactions found in both basic and applied chemical research from 2008 to the present. Selected examples of C–N cross-coupling reactions between nine classes of nitrogen-based coupling partners and (pseudo)aryl halides are described for the synthesis of heterocycles, medicinally relevant compounds, natural products, organic materials, and catalysts.

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1. INTRODUCTION

The Pd-catalyzed cross-coupling of amines and aryl halides and pseudohalides to form C−N bonds has emerged as an extremely general technology for the preparation of aromatic amines in numerous areas of basic and applied research.[1−3] Owing to the widespread presence of arylated amines in pharmaceuticals, natural products, organic materials, and catalysts, the application of this process has been exceptionally broad. The continual development of improved ligands and precatalysts has led to increasingly general and reliable protocols.[4−7] In the past 20 years, the utility and versatility of this transformation has been amply demonstrated through literature reports in many fields of chemical research.

Since the first reports of Pd-catalyzed N-arylation reactions, extensive mechanistic investigations, ligand/precatalyst design, and optimization studies have resulted in the discovery of reaction conditions of considerable generality. This generality, combined with the wide availability of amine nucleophiles and (hetero)aryl halides and sulfonates (prepared from the corresponding phenols), renders Pd-catalyzed methods an appealing alternative to more traditional methods for the synthesis of arylamines including nucleophilic aromatic substitution (S_NAr) and Cu-catalyzed Ullmann and Golberg couplings,[8,9] each of which has a more limited substrate scope.

The identification of several families of phosphine ligands of broad utility has contributed to the rapid development of Pd-catalyzed N-arylation reactions.[10] Typically, these phosphine ligands bear alkyl groups, aryl groups, or both as substituents. N-Heterocyclic carbenes (NHC) also have demonstrated utility in these transformations.[11−13] A summary of the most frequently used ligands in the C−N coupling examples presented in this review is shown in Figure 1. Monodentate symmetrical PR_3- or PAr_3-type ligands, as well as ligands containing different alkyl substituents [e.g., *n*-BuP(Ad)$_2$], have often been employed.[14−16] However, BINAP[14,17] and Xantphos[18,19] have become the most often used ligands for N-arylation reactions. Additional bidentate ligands, such as DPEPhos, dppf,[14,20] CyPF-*t*-Bu,[21] and dppp,[14] are also often encountered as supporting ligands. The dialkylbiarylphosphines constitute a third class of commonly employed ligands.[22] Due to their structural variability, dialkylbiarylphosphines can be tuned to promote the desired reactivity or selectivity. Additionally, ligands such as BippyPhos,[23] MorDalPhos,[24] and IPr·HCl[25] are also occasionally utilized in Pd-catalyzed C−N cross-coupling.

Another significant advance has been the development of precatalysts for the rapid generation of active catalyst in the reaction mixture.[26,27] Since the early report of Herrmann, Beller and their co-workers,[28] several research groups have disclosed palladium/ligand complexes bearing phosphines or NHCs.[29] A variety of palladacycles,[30,31] pyridine-containing palladium complexes,[32] and π-allyl palladium complexes[33,34] rapidly activate under the commonly used reaction conditions to release a catalytically active species. Compared to the traditional approach involving the separate addition of ligand and palladium precursor to the reaction mixture, the use of palladium precatalysts simplifies the reaction setup and, in some cases, allows for significantly lower temperatures and/or catalyst loadings to be employed. Our research group first disclosed base-activated cyclometalated precatalysts in 2008.[35]

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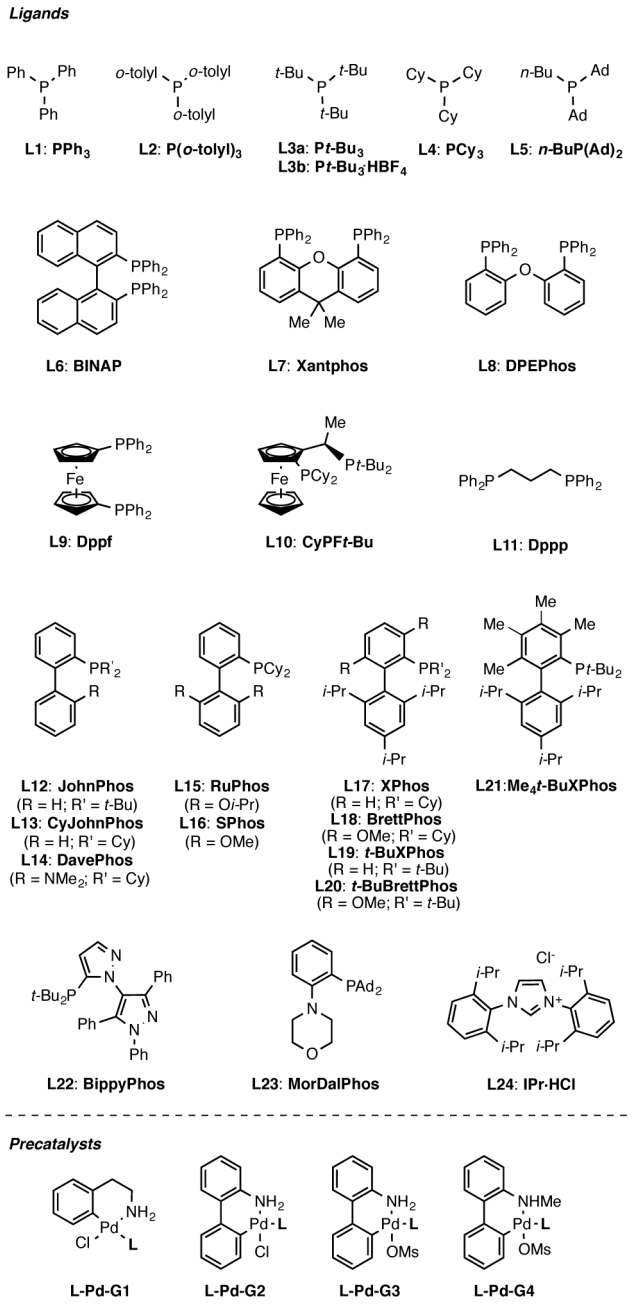

Figure 1. Summary of supporting ligands and palladium precatalysts most frequently encountered in this review.

These air-stable compounds readily form the active catalyst upon exposure to base. Since their discovery, four generations of precatalysts have been reported, with continual improvements to their ease of activation.[36−39] To date, base-activated precatalysts have seen the greatest use in the application of C−N coupling reactions among those available.

The development of C−N coupling reactions has previously been reviewed with a significant emphasis on the evolution of the method.[6,8,12,13,21,22] Given the tremendous utility of Pd-catalyzed C−N cross-coupling reactions, we decided to focus our attention on the applications of Pd-catalyzed C−N coupling reactions across multiple areas of chemical research. As such, only the most widely employed methods of C−N bond-forming reactions are discussed, and then only briefly, at the beginning of each section. This review is organized by class of nitrogen-based coupling partner (with a total of nine), in order to highlight notable differences in their reactivity and properties. Each of these sections is further divided into six different fields of application (vide infra). Within each field, intramolecular reactions are shown first (shown in blue) followed by processes that are intermolecular (shown in red). Finally, all the examples of C−N coupling are grouped by the similarity of the reaction partners involved or products obtained. The major areas of application of Pd-catalyzed C−N cross-coupling are summarized in Figure 2 and include the following.

1.1. Applications of C−N Coupling in the Synthesis of Heterocycles

Nitrogen-based heterocycles are key building blocks in the areas of natural product synthesis, medicinal chemistry (Table 1),[40] and organic materials. Methods for their preparation that utilize Pd-catalyzed C−N coupling chemistry typically provide significant advantages over traditional ones. Often, tandem processes involving at least one C−N bond formation event can readily generate structurally complex heterocycles. Multistep reactions can commonly be carried out in one pot, avoiding the need for isolation or purification of intermediate products. Moreover, processes involving more than one Pd-catalyzed reaction can usually be carried out using a single catalyst. An array of heterocycles, from small compounds to large polycyclic ones that contain several heteroatoms, have been synthesized using this approach.

1.2. Applications of C−N Coupling in Medicinal Chemistry

Arguably, the field of medicinal chemistry is the area in which Pd-catalyzed C−N coupling reactions have had the greatest impact.[41−43] Not surprisingly, given the large number of nitrogen-containing biologically active compounds, the integration of N-arylation reactions in the pharmaceutical industry has been rapid. The simplicity of the synthetic procedures and the versatility of the products obtained have streamlined the creation of compound libraries for use in medicinal chemistry. Recently, high-throughput methods for Pd-catalyzed C−N coupling have even been carried out on nanomolar scale to investigate preparative conditions for complex druglike molecules. Moreover, the functional group tolerance of these processes has enabled the formation of C−N bonds at all stages of synthetic routes.

1.3. Applications of C−N Coupling in Process Chemistry

The applicability of Pd-catalyzed N-arylation reactions in process chemistry has rapidly grown in the past years.[44−46] In many cases, the desired cross-coupling reaction can be optimized to proceed efficiently on a large scale with low catalyst loading, potentially allowing the process to be economically attractive. The development of process-scale C−N cross-coupling reactions for the synthesis of pharmaceuticals has also been aided by new technologies for large-scale metal scavenging,[47] such as the use of functionalized silicas[48] and fixed-bed adsorption processes,[49] which allow isolation of the desired coupling product with low levels of residual palladium, as required by regulatory agencies for active pharmaceutical ingredients. Process chemists often take advantage of C−N cross-coupling reactions when the scalability of the medicinal chemistry route is poor or to avoid a lengthy synthesis or low-yielding steps. Pd-catalyzed strategies are also considered as a viable alternative to the use of toxic reagents or potentially unsafe processes. Ocasionally, identical N-arylation

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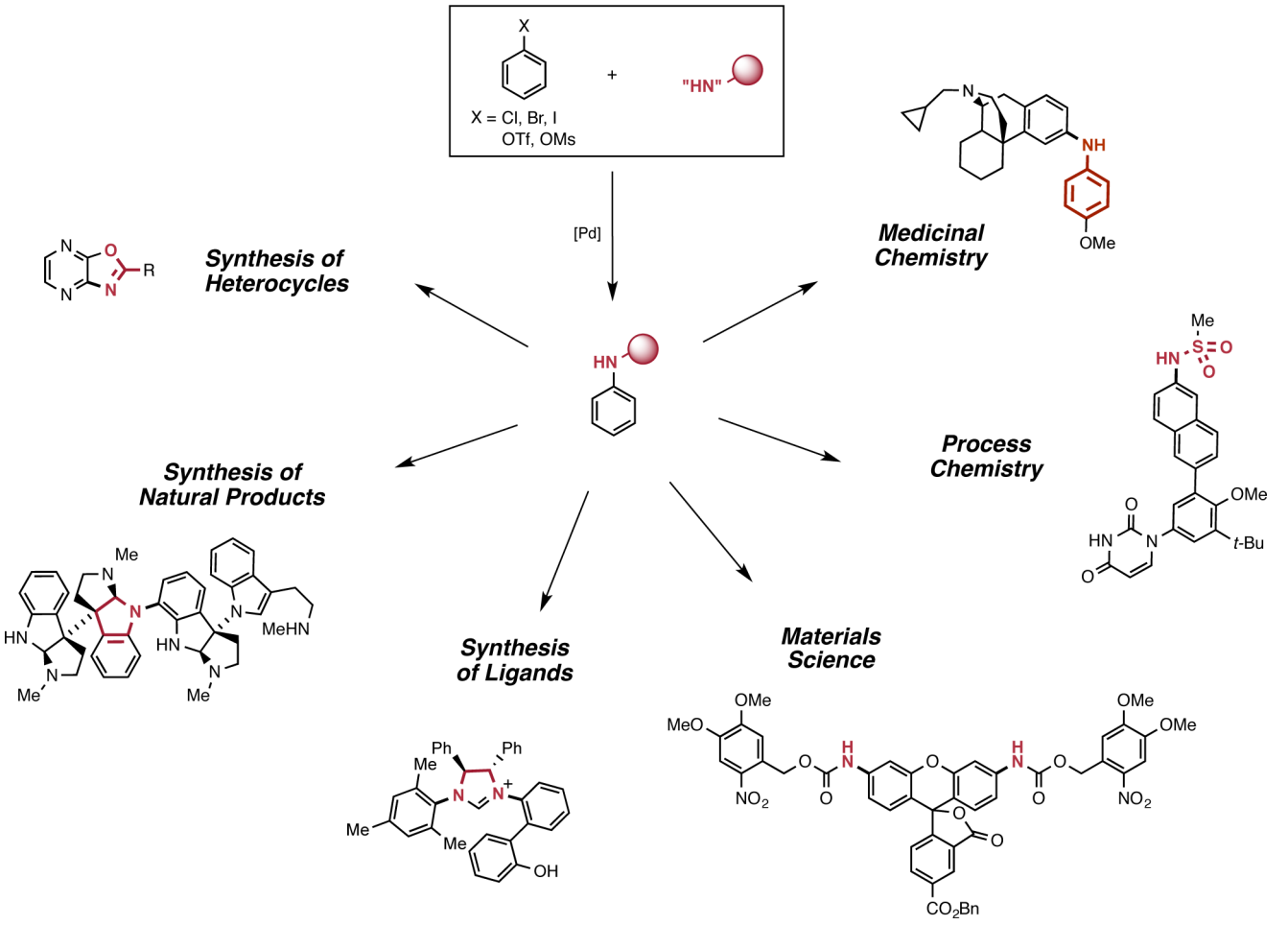

Figure 2. Main fields of application of Pd-catalyzed C−N cross-coupling reactions.

reactions are employed in both the discovery and process routes after optimization of the coupling reaction for manufacturing settings.

1.4. Applications in the Synthesis of Natural Products

Pd-catalyzed C−N coupling reactions in total synthesis often involve particularly challenging transformations. In many cases, these are N-arylations used for the construction of heterocycles embedded in the final natural product structure. Additionally, the versatility of C−N couplings allows for the introduction of nitrogen centers containing protecting groups, which can be required for subsequent steps in the synthesis. Pd-catalyzed C−N couplings have been reported for either late-stage functionalization of complex structures or to establish C−N bonds between two sophisticated fragments in highly convergent synthetic routes.

1.5. Applications in Materials Chemistry and Chemical Biology

Due to the prevalence of highly conjugated systems in organic materials and the donor ability of nitrogen-containing functional groups, N-arylation reactions are widely employed in materials research. In addition, many functional materials for chemical biology applications (e.g., biological probes) are also prepared via C−N cross-coupling reactions. Frequently, multiple C−N couplings are carried out in one operation using either aryl halides with several reactive sites or employing coupling partners with more than one nucleophilic nitrogen.

1.6. Applications in the Synthesis of Ligands and Catalysts

Because of their ability to coordinate to transition metals, nitrogen atoms are often present in ligands for new catalytic processes. Pd-catalyzed N-arylation reactions are exploited in the synthesis of ligands to assemble heterocycles or to introduce chelating functional groups into an existing framework. Multiple nitrogen atoms can be attached to the core of the structure in order to access multidentate ligands. Examples of C−N coupling reactions performed both on free ligands or on ligands that are already bound to a metal have also been described. Lastly, the use of N-arylation for the synthesis of amine-containing organocatalysts for enantioselective catalysis is also an emerging application.

Over the course of our analysis, we identified several trends regarding the application of Pd-catalyzed C−N coupling reactions. (1) There is a significant delay in the implementation of new methods after their disclosure. Even though improved and highly efficient precatalysts and novel ligands have become available, chemists typically continue to use older catalyst systems to enable C−N bond-forming reactions. (2) Similarly, while published methods report comparatively mild, optimized reaction conditions, N-arylation reactions are often carried out under significantly harsher conditions (e.g., higher catalyst loading and temperatures) in practice. This is especially true for applications where the primary goal is the rapid generation of the target compound and synthetic efficiency is a secondary consideration. (3) The chemoselectivity of C−N couplings has

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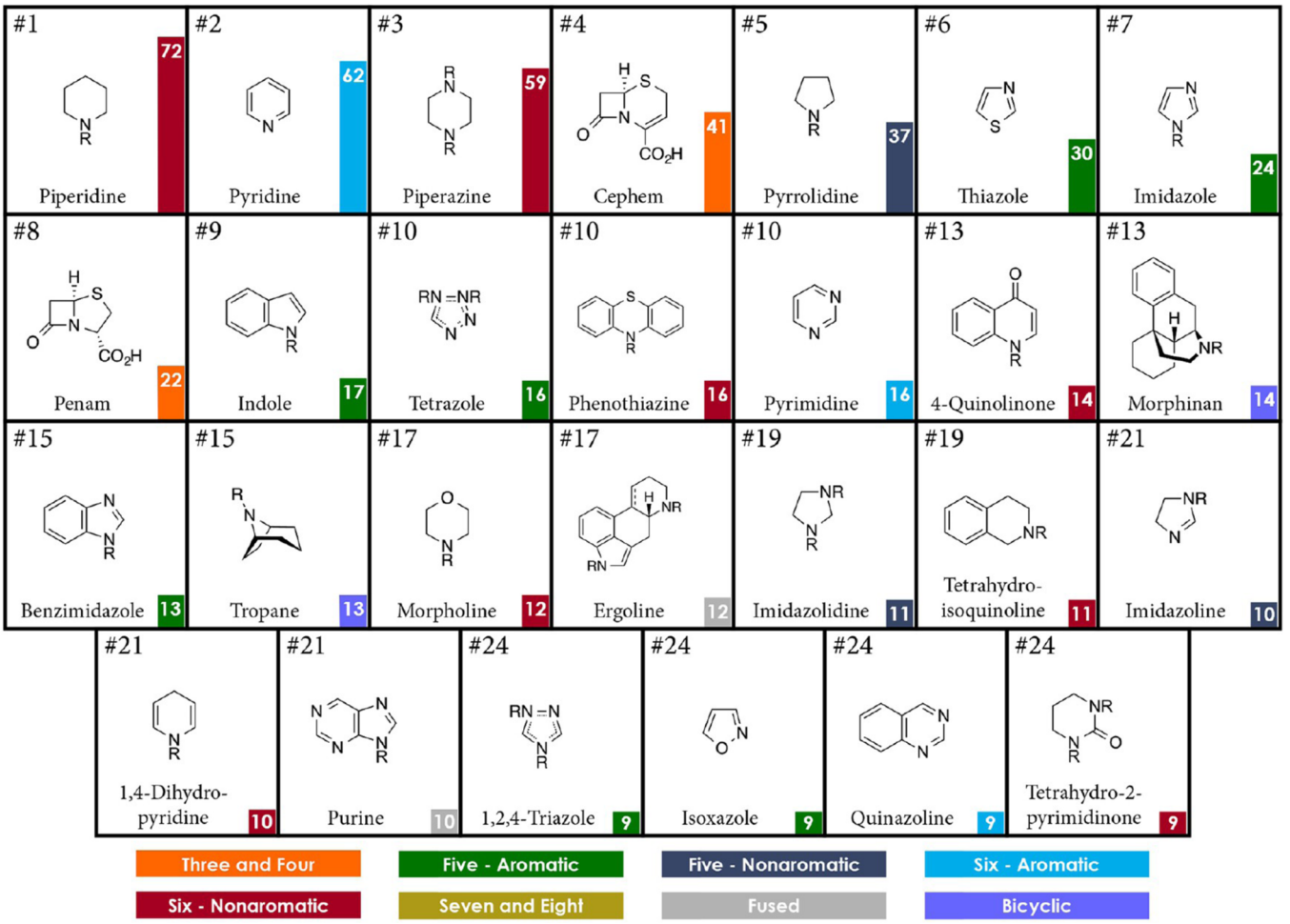
Table 1. Top 25 Most Frequent Nitrogen Heterocycles in U.S. FDA Approved Drugs



[a]Reproduced from ref 40. Copyright 2014 American Chemical Society.

been exploited many times by synthetic chemists. The ability to selectively functionalize aryl chlorides, bromides, iodides, and sulfonates greatly expands their applicability, since two reaction sites can be independently modified. (4) The number of N-arylation reactions performed under continuous flow conditions has gradually increased in recent years. This technology not only enables challenging reactions to be carried out at high temperatures with short reaction times but also allows for safer handling of inconvenient or potentially unsafe reagents.[50]

In the process of writing this review, more than 1000 scientific publications since 2008 were examined. The inclusion of every example of C−N coupling was thus deemed to be unfeasible. However, we believe that this report is comprehensive given the large number of representative examples shown. To limit the scope of this report, we applied the following selection criteria: We have attempted to be as inclusive as possible with respect to reports of the synthesis of heterocycles and natural products, as well as applications in process chemistry. In the remaining fields, the number of examples was considerably larger. Only medicinal chemistry publications in which a C−N coupling reaction was used to generate the lead compound were included. In the case of encountering similar processes, we chose those of higher levels of complexity, with respect to either the transformation or the product being formed. The syntheses of functional organic materials as well as ligands and catalysts were examined case by case on the basis of the difficulty of the C−N coupling reaction or the applicability of the target molecule. Thus, we believe that the selected examples included in this review are representative of the types of transformations that Pd-catalyzed C−N coupling has made possible in recent years and should be informative for the design and implementation of new applications of coupling processes.

2. ALKYLAMINES

2.1. Primary Alkylamines

The N-arylation of primary alkylamines is one of the most extensively developed Pd-catalyzed C−N cross-coupling reactions. The main challenge of this transformation is avoiding the formation of undesired tertiary anilines as a result of the competing diarylation reaction. Thus, the judicious choice of supporting ligand is key for achieving the desired reaction selectivity. Numerous Pd catalysts have been shown to accomplish the C−N coupling of primary alkylamines, with early ones reported by Wolfe and Buchwald[17] and Hartwig and co-workers[51,52] based on **L6** and **L10**, respectively, demonstrating the broadest generality. A dialkylbiarylphosphine, **L18**,[53] has since emerged as a powerful ligand showing excellent activity and selectivity for a broad range of aryl halides, including aryl chlorides and (pseudo)aryl halides, at very low catalyst loadings.[54] Additional catalysts have been reported by

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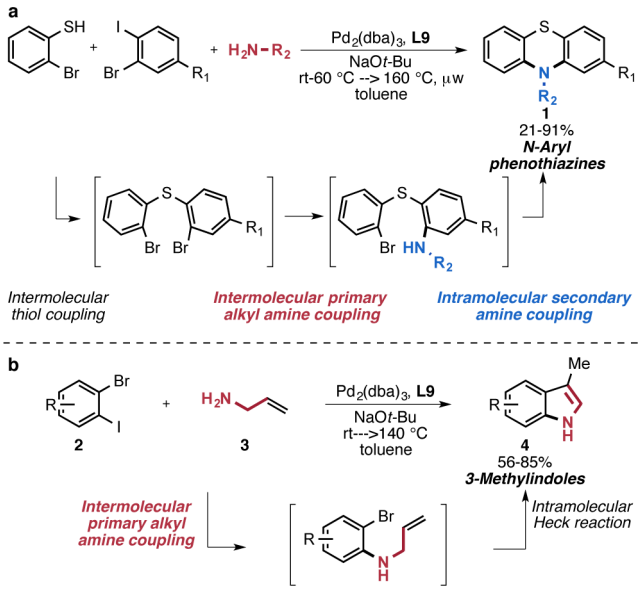
Organ and colleagues,[55] who employed NHCs for this transformation, while Stradiotto's group showed that **L22**-[23] and **L23**-based[24] catalysts also enabled the coupling of primary amines with great selectivity for the monoarylation product. More recently, specialized conditions for the N-arylation of more challenging primary amines, such as fluoroalkylamines[56] and very hindered aliphatic amines,[57] have further expanded the scope of nucleophiles that can be employed in this reaction.

2.1.1. Applications of the Coupling of Primary Alkylamines in the Synthesis of Heterocycles. Jørgensen and co-workers described two methods for the preparation of nitrogen-based heterocycles via the Pd-catalyzed cross-coupling of primary alkylamines. The first protocol consisted of a one-pot process that transformed 2-bromothiophenol, a primary amine, and a functionalized 1-bromo-2-iodobenzene into biologically interesting *N*-alkyl- and *N*-arylphenothiazines (**1**, Scheme 1a) using a single catalyst.[58] Given the strong

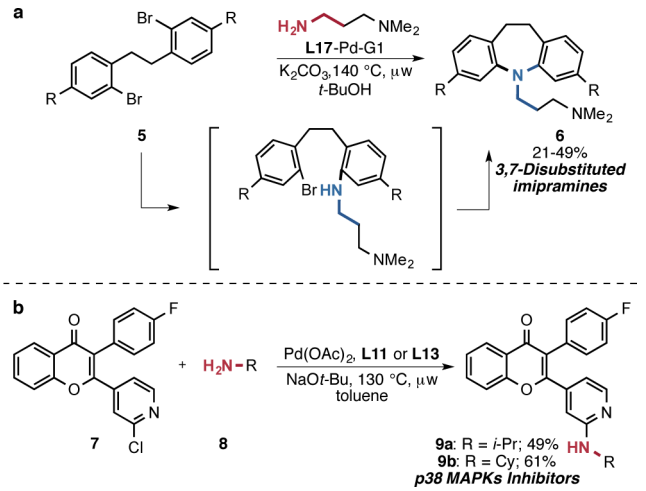
Scheme 1. Synthesis of Heterocycles via the Coupling of Primary Alkylamines



nucleophilic character of thiols, a C−S bond-forming step with the more activated aryl iodide preceded the sequential inter- and intramolecular N-arylation steps. The use of catalysts based on triaryl- or trialkylphosphines (**L1**, **L2**, **L3a**) only gave trace amounts of the desired product, and those based on dialkylbiarylphosphines (**L14**, **L17**) promoted the undesired intermolecular coupling between the amine and the aryl iodide. With **L9** as the supporting ligand, heterocycles **1** were obtained in 21−91% yield. Interestingly, when allylamine was employed as the nucleophile, the formation of 3-methylindole **4** was observed instead of the expected phenothiazine (Scheme 1b).[59] This outcome arose from the C−N coupling reaction between allylamine and the aryl iodide followed by an intramolecular Heck cyclization. Given the value of indoles in the pharmaceutical industry, the fortuitous transformation was optimized and a series of 3-methylindoles were prepared from 1-bromo-2-iodoarenes **2** and allylamine (**3**).

2.1.2. Applications of the Coupling of Primary Alkylamines in Medicinal Chemistry. Examples of the N-arylation of linear alkyl primary amines in the synthesis of drug candidates are shown in Schemes 2 and 3a,b. Building on

Scheme 2. Synthesis of Biologically Active Compounds via the Coupling of Primary Alkylamines



Jørgensen's method for the synthesis of phenothiazines (**1**, Scheme 1a),[58] Jensen and co-workers prepared a series of 3,7-disubstituted analogues of the tricyclic antidepressant imipramine (R = H) (**6**, Scheme 2a).[60] The dibenzazepines were generated in a one-pot procedure from bisaryl bromides **5**. The two N-arylation steps were enabled by a first-generation **L17** palladium precatalyst with a weak base in *t*-BuOH. However, the inherent difficulty of accessing seven-membered ring compounds via eight-membered ring intermediates[61] led to the formation of significant amounts of monoaminated and reduced products. The use of microwave heating improved the reaction yields to 21−49%. Grøtli and colleagues also synthesized several chromone derivatives via the coupling of primary alkylamines under microwave heating (Scheme 2b).[62] **L11** or **L13** were suitable supporting ligands for promoting the reaction between aryl chloride **7** and primary amines **8** to afford compounds **9a** and **9b**, which were investigated as candidates for the treatment of human breast cancer.

Additional examples of the N-arylation of primary linear alkylamines are shown in Scheme 3. Gopalsamy and co-workers (Wyeth) prepared Hsp90 inhibitor **11** as a potential antitumor agent by selectively coupling 1-(2-aminoethyl)piperidine with aryl iodide **10** in 35% yield.[63] Dow and colleagues (Pfizer) employed $Pd(OAc)_2$/**L17** in the synthesis of DGAT-1 inhibitor **13** for studies on the treatment of obesity or type II diabetes.[64] In this manner, enantioenriched aryl triflate **12** was successfully coupled to the O-protected primary amine in 70% yield.

Likewise, primary aminocycloalkanes are common units in pharmaceutical targets (Scheme 3c−f). George and co-workers (AbbVie) arrived at compound **16**, a promising protein kinase Cθ inhibitor for autoimmune disease therapy, by coupling aryl bromide **14** with aminoazetidine **15** in excellent yield (91%, Scheme 3c).[65] Additionally, Huang and co-workers (Pfizer) prepared a series of indazol-4-one-derived Hsp90 inhibitors **18** via S_NAr or, alternatively, Pd-catalyzed cross-coupling reactions such as the N-arylation of cyclohexyl amine **17** (Scheme 3d).[66] Furthermore, the 4-aminopiperidine structure is found in biologically active candidates such as **20** and **22** (Scheme 3e,f). In Griffin and co-workers (AstraZeneca) synthetic route to δ-opioid agonist **20**, two C−N bond-forming reactions of alkylamines were key steps (Scheme 3e).[67] Sequential N-arylation reactions of 4-aminopiperidine **19** readily delivered a series of alkyldiarylamine analogues **20**. Catalysts based on two

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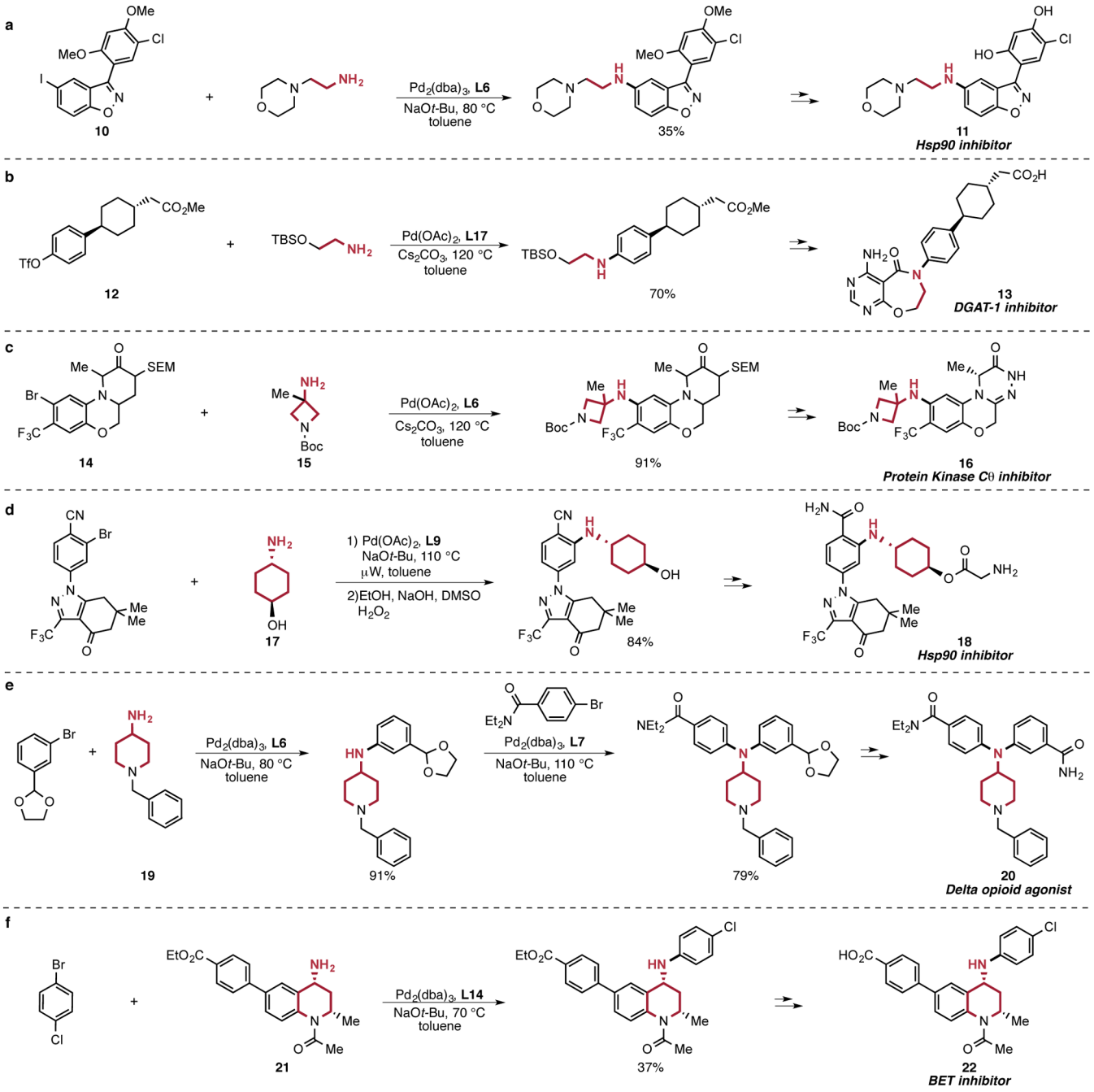
Scheme 3. Applications of the Coupling of Primary Alkylamines in Medicinal Chemistry



different ligands, **L6** and **L7**, were utilized. Similarly, but employing an **L14**-based catalyst, Bamborough, Prinjha, and their co-workers (GlaxoSmithKline) described the N-arylation of chiral aminopiperidine **21** to access anti-inflammatory compound **22** (Scheme 3f).[68] It was important for the success of the reaction that the NaO-*t*-Bu used as the base be dry, since undesired hydrolysis of the ester in **21** led to the formation of the carboxylic acid, which was unreactive in the C−N coupling reaction.

2.1.3. Applications of the Coupling of Primary Alkylamines in the Synthesis of Natural Products. In order to access (+)-epi-indolacatam V (**24**, Scheme 4a), Piersanti and co-workers carried out an intramolecular N-arylation with compound **23**.[69] Although there is less precedent for the Pd-catalyzed construction of nine-membered rings than of smaller cycles, the cyclization step was successfully accomplished in 72% yield using **L17**, a first-generation precatalyst. The reaction afforded the desired macrocycle as nearly a single diastereomer. Additionally, Bringmann and co-workers prepared ancistrocladinium A (**28**), an alkaloid with antiparasitic properties and activity against tropical diseases (Scheme 4b).[70] The target compound was obtained as a 2.5:1 mixture of atropo-diastereomers **28a** and **28b** through a concise synthesis with Pd-catalyzed N-arylation and Bischler−Napieralski cyclization as key steps. Bromonaphthalene **25** and chiral primary amine **26** were subjected to cross-coupling conditions, providing intermediate **27** in 63% yield. Scheme 4c shows Chida and co-workers' total synthesis of biologically active alkaloid murrayazoline **31** via the double N-arylation of primary amine **30**,[71] a practical method for the construction of N-

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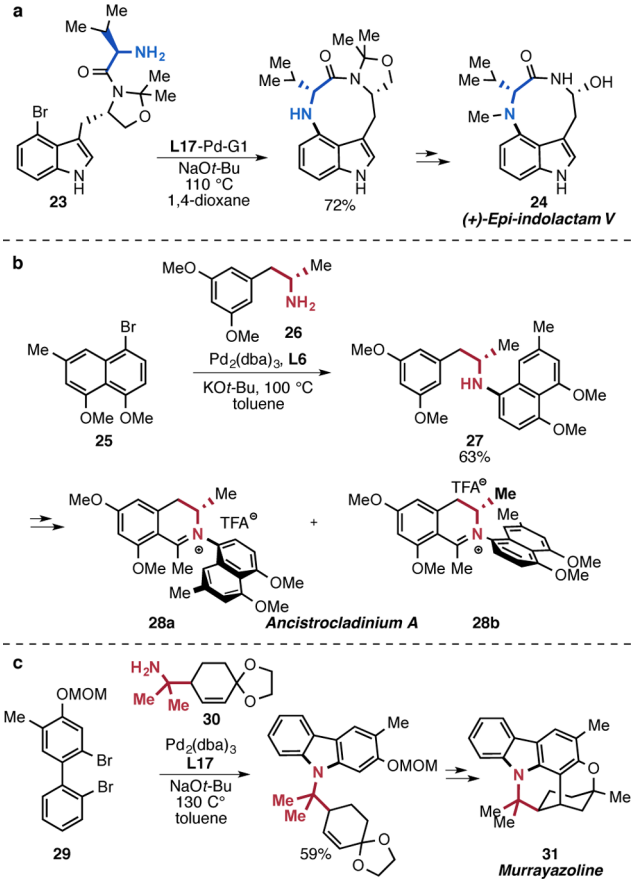
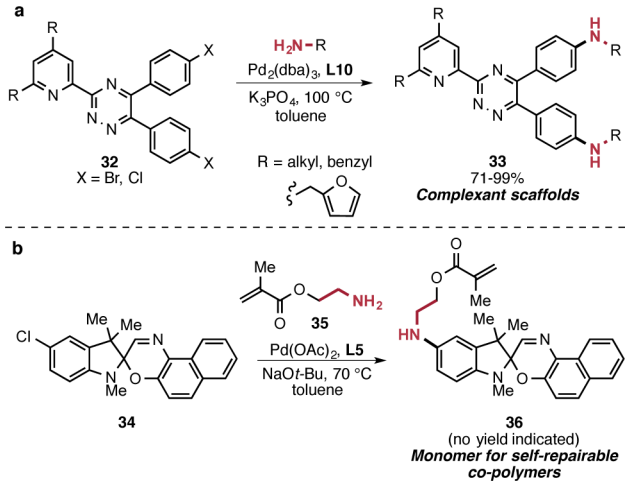
Scheme 4. N-Arylation of Primary Alkylamines in the Synthesis of Natural Products



Scheme 5. Synthesis of Organic Materials via the Coupling of Primary Alkylamines



substituted carbazoles (see Scheme 28, section 3.1.1). Accordingly, 2,2′-dibromobiphenyl **29** reacted twice with the alkylamine using an **L17**-based catalyst in 59% yield. The title fused heterocycle was then assembled via Friedel−Crafts and Pd-catalyzed C−O coupling reactions.

2.1.4. Applications of the Coupling of Primary Alkylamines in Materials Chemistry. Carrick and colleagues reported the use of C−N coupling reactions to prepare polydentate complexants **33**, applicable to the extraction of actinides from nuclear fuel (Scheme 5a).[72] In order to investigate the effects on ligand behavior, a number of structurally varied analogues based on a 1,2,4-triazinylpyridine framework were synthesized and examined. From precursors **32**, a two-step N-arylation reaction with various primary alkylamines gave rise to 16 novel complexants. Although the multiheteroatom-containing starting material could potentially bind to the Pd center and poison the catalyst, the coupling proceeded smoothly using **L10** as the supporting ligand. The use of a weak base was crucial for the success of the reaction, since attempts to use NaO-*t*-Bu as the base resulted in decomposition of the aryl bromide. Another application was in the synthesis of aniline **36**, a monomer used for the synthesis of self-repairing and stimuli-responsive polymers (Scheme 5b).[73] Aryl chloride **34** was combined with functionalized primary amine **35** using an **L5**-based catalyst.

High molecular weight primary alkylamines, such as **37**, have also been successfully N-arylated (Scheme 6). Chow and co-workers performed this reaction to form aliphatic hydrocarbon-based generation 1−3 dendrimers that behave as solvatochromic chromophores (third generation shown).[74] After an unsuccessful approach to **38** via the N-alkylation of the corresponding dendritic alkyl bromide, *p*-nitrobromobenzene and primary amine **37** were linked via C−N coupling using an **L8**-supported palladium catalyst.

Diaminoanthraquinones are common structural units in organic materials that are often generated via Pd-catalyzed double C−N bond-forming reactions (Scheme 7). For example, Arslanov, Bessmertnykh-Lemeune, and their co-workers designed a new colorimetric molecular sensor for Hg^{2+} based on this building block (**40**, Scheme 7a).[75] The combination of 1,8-anthraquinone **39** and ethylendiamine using an **L6**-based catalyst yielded the N-arylated product in 39% yield. Subsequent N-alkylation to introduce phosphonic acid esters rendered the sensor water-soluble and strongly chelating. Similarly, Averin, Beletskaya, and their co-worker conducted the asymmetric cross-coupling between 1,5-dichloroanthraquinone **41** and various di- and trioxadiamines to investigate macrocycles with different cavity sizes (**42**, Scheme 7b).[76] The resulting chiral products are potentially applicable as asymmetric catalysts or in compounds for molecular recognition studies. A catalyst based on Josiphos ligand **L25** induced the desired planar chirality from achiral starting materials in 60% ee and 31% yield. Subsequent recrystallization provided the desired product **42** in 19% yield and 99% ee.

2.1.5. Applications of the Coupling of Primary Alkylamines in the Synthesis of Ligands. Pd-catalyzed methods for cross-coupling alkylamines have enabled the rapid generation of NHC ligands with novel structures and catalytic properties. For instance, Peris and co-workers performed a 6-fold N-arylation reaction on triphenyl core **43** to generate a (tris)NHC for Suzuki−Miyaura, α-arylation, and hydroamination reactions (**44**, Scheme 8a).[77] *tert*-Butylamine reacted six times in the presence of an **L24** [1,3-bis(2,6-diisopropylphenyl)imidazolylidene]-based catalyst in excellent yield (98%). With the reverse multiple C−N cross-coupling approach, Grubbs and colleagues obtained intermediate **46** to prepare rigid NHC precursor **47** (Scheme 8b).[78] Diamine **45** successfully reacted with two *o*-bromostyrene units furnishing the doubly N-arylated product **46** in 79% yield. The sequential monoarylation of diamines is also feasible, as Hoveyda and co-workers demonstrated in the synthesis of bidentate chiral NHC precursor **52** (Scheme 8c).[79] First, C−N coupling occurred

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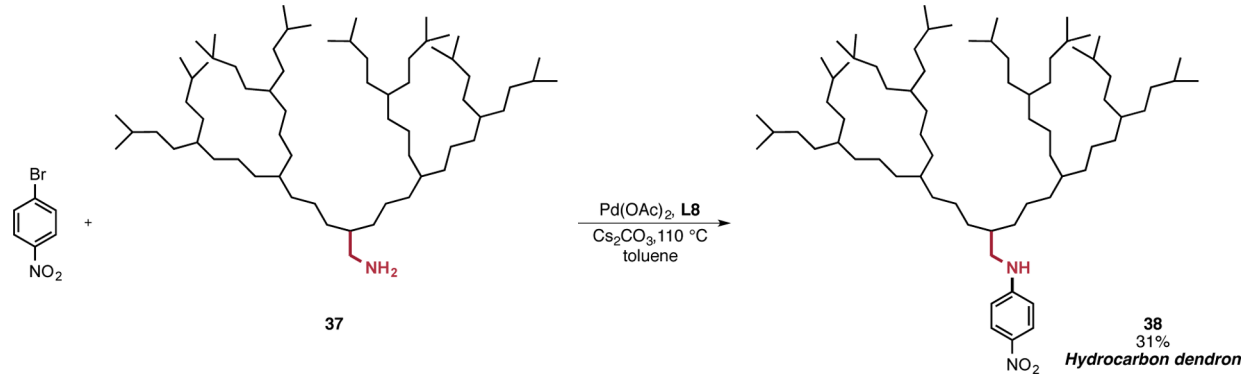
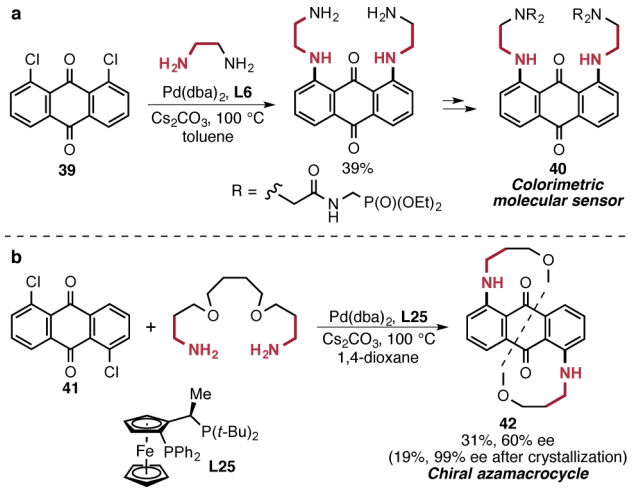
Scheme 6. Synthesis of a Hydrocarbon Dendron via the Coupling of a Primary Alkylamine



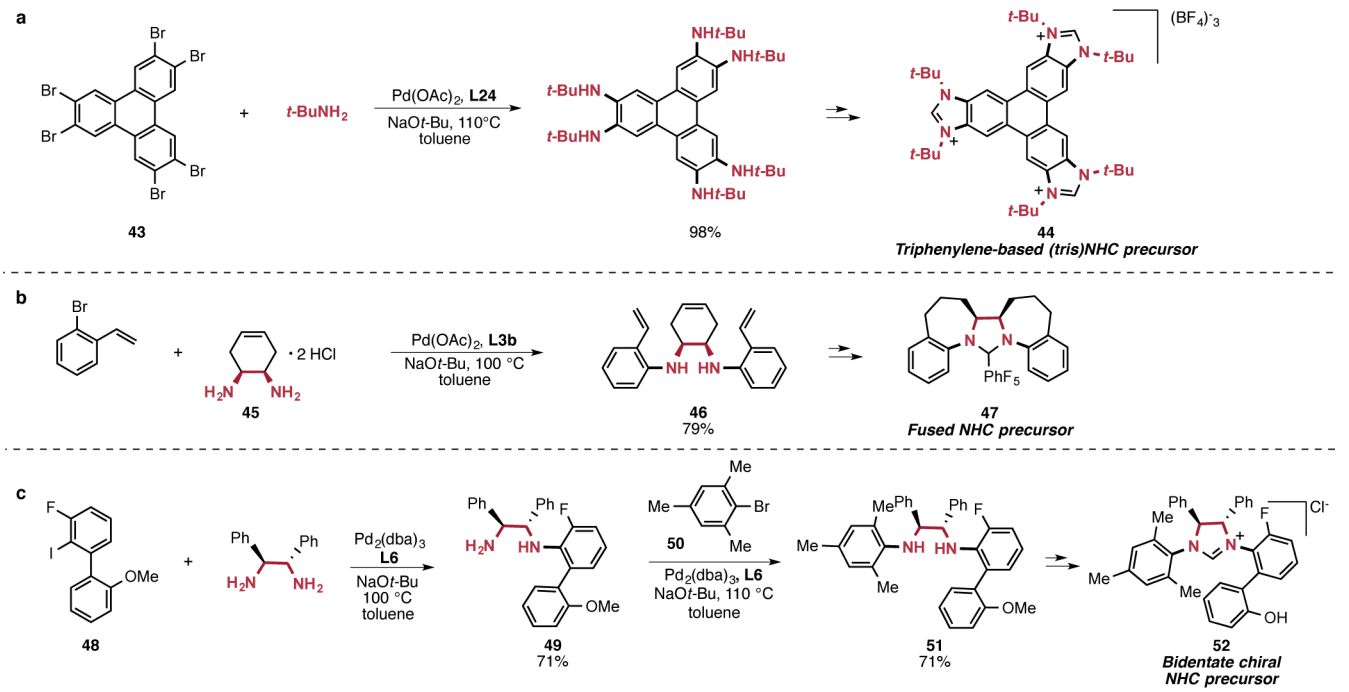
Scheme 7. Synthesis of Diaminoanthraquinones via the Coupling of Alkyl Primary Amines



exclusively between one amino group and biaryl iodide **48** to produce intermediate **49**. The second aryl halide (**50**) was then added to the reaction mixture and a second amination gave compound **51** (71%). Even though both aryl halides were quite hindered, the desired product (**51**) was formed in overall 50% yield in two steps.

Another application of alkyl C−N coupling was described by Johnston and co-workers, who employed primary amine **53** as a chiral auxiliary to synthesize enantiomerically enriched β-diketimine ligand **56** (Scheme 9).[80] The axially chiral species containing isoquinoline and 2-aminonaphthalene units is known as the IAN amine and it is an important building block for several asymmetric catalysts. (*S*)-α-Methylbenzylamine (**53**) was combined with naphthol triflate to provide intermediate **54** in 52% yield. Afterward, the reaction with 1-chloroisoquinoline afforded a 1:1 mixture of diastereoisomers **55a** and **55b**, which were readily separable by fractional recrystallization. Lastly, removal of the resolving agent furnished the desired ligand in 63% yield and 96% ee.

Scheme 8. Synthesis of NHCs via the Coupling of Primary Alkylamines



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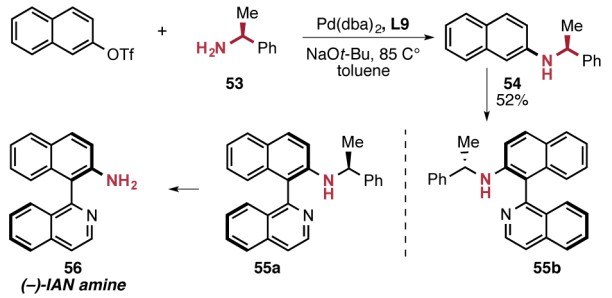
Scheme 9. Synthesis of Chiral Ligand via the Coupling of an Alkyl Primary Amine



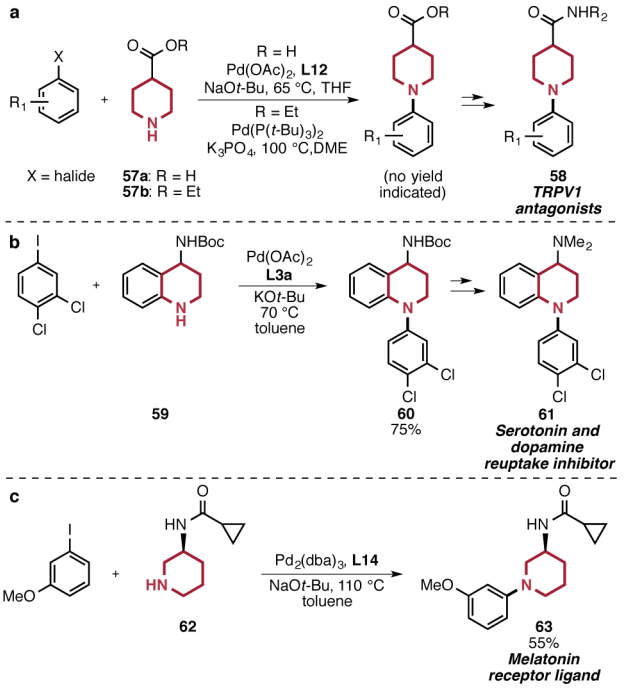
2.2. Secondary Alkylamines

The coupling of secondary alkylamines, particularly cyclic amines, is of great relevance in medicinal chemistry settings.[40] To date, only a few specific methods describe the coupling of secondary alkylamines compared to other nucleophiles.[25,81] For instance, Buchwald and colleagues reported that the use of **L15** as a supporting ligand enabled the N-arylation of numerous acyclic and cyclic secondary amines with very low catalyst loadings.[54] A typical challenge of this transformation is the use of amines that can easily undergo β-hydride elimination side reactions. Advances in ligand design have led to protocols that largely overcome this issue by facilitating the rapid reductive elimination of the intermediate palladium amido complex (in preference to β-hydride elimination), to generate the desired tertiary amine. The applications of Pd-catalyzed C−N coupling with secondary aliphatic amines most frequently utilize catalysts based on **L6**, **L7**, or a dialkylbiarylphosphine.

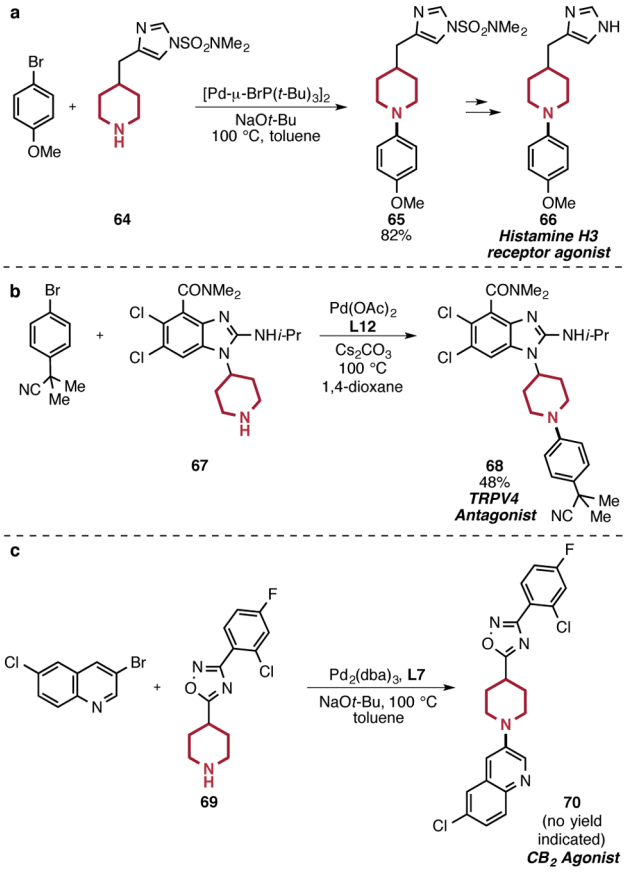
2.2.1. Applications of the Coupling of Secondary Alkylamines in Medicinal Chemistry. *2.2.1.1. Piperidine, Pyrrolidine, and Related Cyclic Secondary Amines.* Piperidine is ranked as the most frequent nitrogen heterocycle in U.S. FDA approved drugs.[40] Substituents on this heterocycle are often found at the N1- and C4-positions; thus, the N-arylation of C4-functionalized piperidines is a widely employed transformation. Examples of the N-arylation of piperidines bearing carboxylic acid derivatives are shown in Scheme 10. Player and co-workers (Johnson & Johnson) synthesized an array of piperidine carboxamides **58** as candidates for pain management (Scheme 10a).[82] Two sets of conditions were employed to couple piperidine acid **57a** and the ester analogue **57b**. While the reaction with **57a** was carried out in the presence of NaO-*t*-Bu, a weak base was preferred with compound **57b**, presumably to prevent a side reaction of the ester group. Shao and co-workers (Sunovion) employed *N*-Boc-protected piperidine **59** in order to prepare tetrahydroquinoline **61**, a compound with potent antidepressant activity (Scheme 10b).[83] The secondary amine selectively reacted with the aryl iodide to provide intermediate **60** in good yield (75%). Li and co-workers successfully coupled another amide-substituted piperidine (**62**) to access melatonin receptor ligand **63**, employed in a study of sleep disorders (Scheme 10c).[84]

Heterocycle-containing piperidines are among the frequent derivatives encountered in drug candidates (Scheme 11). Ishikawa and co-workers combined 4-bromoanisole and piperidine **64**, bearing an imidazole group, on route to H3 receptor agonist **66**, which showed activity against inflammation, migraine, and anxiety disorders (Scheme 11a).[85] The reaction was performed using [Pd-μ-BrP(*t*-Bu)$_3$]$_2$ as catalyst, giving rise to intermediate **65** in 82% yield. The imidazole was

Scheme 10. Applications of Substituted Piperidines in Drug Discovery



Scheme 11. Examples of Heterocyclic-Containing Piperidines in Medicinal Chemistry



protected, presumably to prevent potential coordination of the free NH to the palladium center and subsequent catalyst deactivation. Piperidines directly attached to heterocycles

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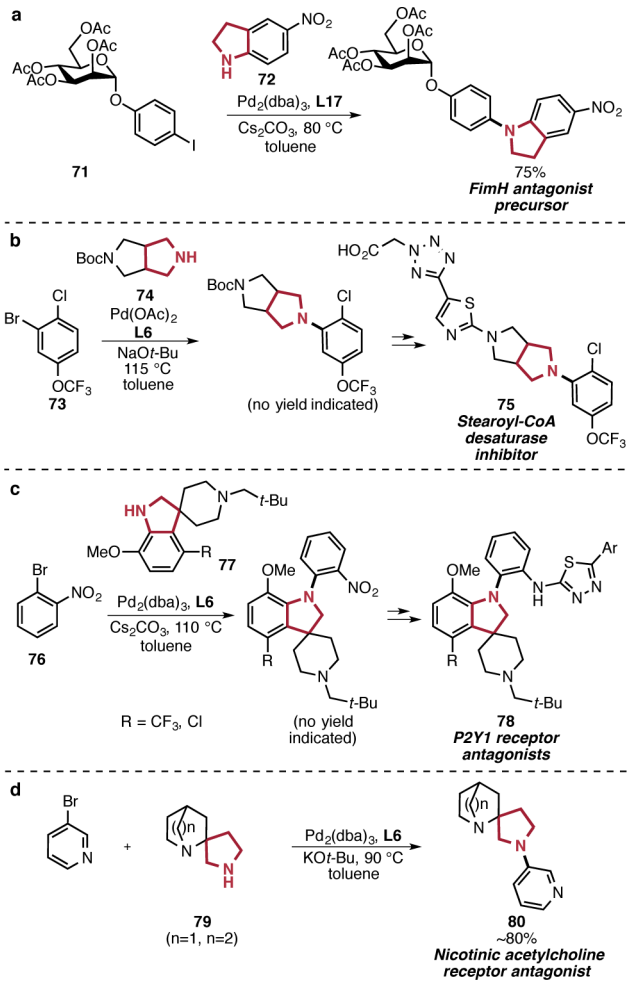
readily underwent Pd-catalyzed C−N coupling (Scheme 11b,c). Hilfiker and co-workers (GSK) coupled benzimidazole-based piperidine **67** in the last step toward TRPV4 antagonist **68**, a candidate to treat acute lung injuries (Scheme 11b).[86] Similarly, piperidine **69**, bearing an oxadiazole ring, selectively reacted at the C−Br position of 6-chloro-3-bromoquinoline in the synthesis of CB_2 agonist **70**, of interest for pain management, as reported by DiMauro and co-workers (Amgen) (Scheme 11c).[87]

Pyrrolidine is the fifth most abundant nitrogen heterocycle and the most common five-membered nonaromatic cyclic amine in pharmaceuticals.[40] In search of drug candidates for urinary track infections, Ernst and co-workers carried out the N-arylation of nitro-group-containing indoline **72** with protected aryl mannoside **71** (Scheme 12a).[88] A catalyst

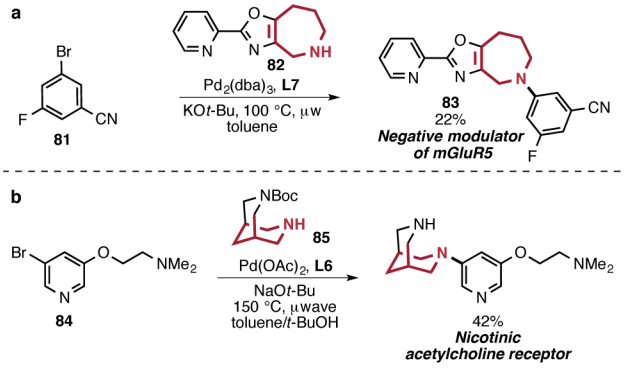
Scheme 12. Use of Pyrrolidines in the Synthesis of Drug Candidates



based on **L17** provided the title compound in 75% using a weak base. Lachance and co-workers (Merck) prepared stearoyl-CoA desaturase (SCD) inhibitor **75** containing a bispyrrolidine linker as a candidate to treat obesity or type II diabetes (Scheme 12b).[89] Protection of one of the amino groups in **74** guaranteed a selective C−N bond-forming reaction with aryl bromide **73**. Removal of the Boc group and further functionalization via S_NAr afforded the biologically active compound **75**. Scheme 12c,d shows the syntheses of spirocyclic pyrrolidine-based drug candidates. Spiro-indoline **77** was employed by Hu and co-workers (Bristol-Myers-Squibb) in the synthesis of P2Y1 receptor **78** as a compound to improve symptoms from thrombosis.[90] The cross-coupling reaction between **76** and **77** was induced by an **L6**-based catalyst. In addition, spiro-pyrrolidines **79** readily underwent N-arylation with 3-bromopyridine in the route to nicotinic acetylcholine receptor agonists **80**, candidates for the treatment of schizophrenia and neurodegenerative diseases developed by Strachan and co-workers (Targacept).[91]

The coupling of azepane **82** in the synthesis of compound **83**, a negative modulator of metabotropic glutamate receptors studied to treat peripheral and CNS disorders, proved challenging (Scheme 13a).[92] Burdi and co-workers (Sepracor)

Scheme 13. Examples of the Coupling of Secondary Cyclic Amines in the Pharmaceutical Industry



combined the seven-membered amine and activated aryl bromide **81** with an **L7**-based catalyst to furnish the target *N*-arylated product in 22% yield. Tomassoli and Gündisch were able to couple 3-bromopyridine **84** and (di)aza(bi)cyclic species **85** in the presence of an **L6**-based catalyst (Scheme 13b).[93] A solvent mixture composed of toluene and *t*-BuOH was required to promote solubility of the coupling partners, and microwave heating enhanced C−N bond formation. Prior protection of one nitrogen atom in **85** was necessary to prevent diarylation.

2.2.1.2. Piperazine and Related Cyclic Secondary Amines. Piperazine is listed as the third most frequent nitrogen-containing heterocycle in FDA-approved drugs after piperidine and pyridine.[40] Regarding substitution patterns, 83% of piperazine rings in pharmaceuticals have the heterocycle functionalized at both the N1- and N4-positions. In most Pd-catalyzed C−N coupling reactions, piperazine is used in its protected or substituted form, whereas only a few examples involve the direct coupling of piperazine (Scheme 14a,b). Scott and co-workers (AstraZeneca) generated intermediate **87** in the synthesis of oncology target **88** by reacting ortho-substituted aryl bromide **86** and piperazine (Scheme 14a).[94] The reaction occurred in the presence of an **L6**-based catalyst and at high temperature using a polar aprotic solvent (dimethylacetamide). Park and co-workers (SK Chemicals) were able to selectively functionalize unprotected piperazine **90** at the less-hindered nitrogen of the nucleophile (Scheme 14b).[95] In the synthesis of a potential agent for treating type II diabetes, agent **92**, a C−N bond was first established between aryl bromide **89** and **90** to provide intermediate **91**. Then, a second N-arylation took place at the 2-substituted piperazine amine to afford the title compound. Notably different ligands, **L6** and **L7**, respectively, were utilized for each step. In contrast, Carroll and co-workers

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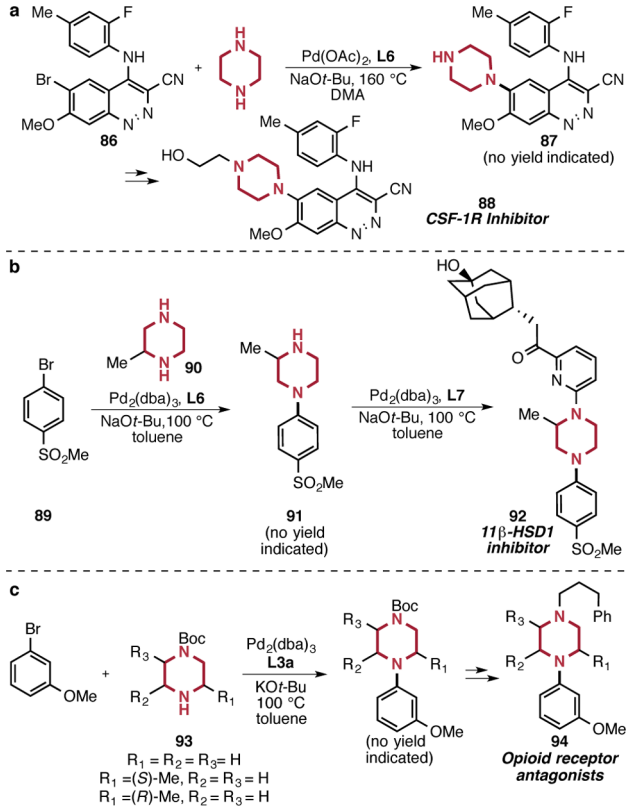
Scheme 14. Applications of Piperazine in Medicinal Chemistry

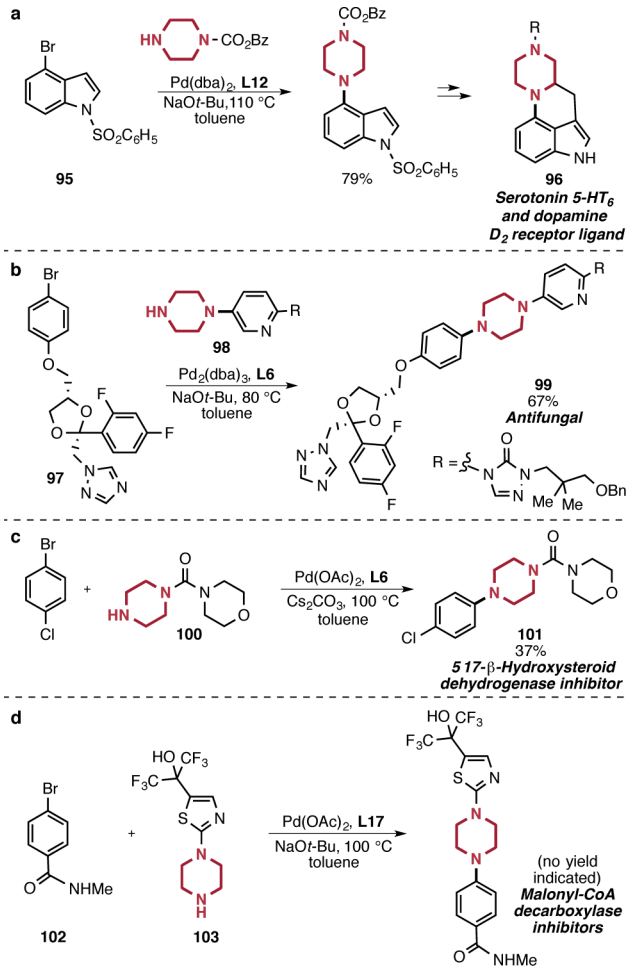


protected piperazine **93** to guarantee its coupling with 3-bromoanisole at the more hindered nitrogen atom (Scheme 14c).[96] The reaction was carried out with **L3a** as a supporting ligand, and it was followed by Boc removal and subsequent N-alkylation to yield opioid receptor antagonist **94**.

Scheme 15 shows several N-arylation reactions of N4-substituted piperazines. Kehler and colleagues combined N-protected 4-bromoindole **95** with *N*-carbamatepiperazine in the presence of an **L12**-based catalyst to access drug candidate **96**, which shows promise against several neurological diseases, including schizophrenia and Parkinson's disease (Scheme 15a).[97] Similarly, Yang and co-workers prepared antifungal **99**, which showed improved solubility and bioavailability in comparison to other triazole-based agents, by reacting aryl bromide **97** with heterocyclic-containing piperazine **98** (Scheme 15b).[98] In addition, urea-containing piperazine **100** also underwent N-arylation as part of the synthesis of antileukemia agent **101** (Scheme 15c).[99] In this transformation, Denny and co-workers employed an **L6**-based catalyst and a weak base to arrive at the target compound in modest yield (37%). Finally, Tang and co-workers (Merck) developed a series of thiazole-substituted piperazines as malonyl-CoA decarboxylase (MCD) inhibitors for the potential treatment of type II diabetes.[100] In the presence of a $Pd(OAc)_2$/**L17** combination, 4-bromobenzamide **102** was successfully coupled with functionalized piperazine **103**.

Various modifications on the piperazine core are also common in pharmaceutical agents due to the new chemical and structural properties that these changes introduce into the drug backbone. For instance, Batey and colleagues reacted 2,5-diazabicyclo[4.1.0]heptane **104**, consisting of a piperazine fused to a cyclopropane ring, to access fluoroquinolone antibacterial

Scheme 15. N-Arylation of 4-Substituted Piperazines



105, an analogue of ciprofloxacin (Scheme 16a).[101] The cross-coupling reaction occurred most efficiently with **L6** as a supporting ligand and Cs_2CO_3 as the base in DMF. Similarly, Wang and co-workers (Wyeth) employed the C−N coupling of aryl bromide **106** with diazabicycle **107** to generate oncology candidate B-Raf inhibitor **108** using an **L6**-based catalyst (Scheme 16b).[102] Carter and co-workers (Roche) found that the N-arylation of piperazinone **110** with protected indole **109** proceeded in good yield (74%) in the presence of an **L3a**-based catalyst.[103] Subsequent steps led to triple reuptake inhibitor **111**, of interest for the treatment of depression (Scheme 16c). In addition, Tafesse and co-workers (Purdue Pharma) prepared a promising neuropathic painkiller (**113**) in excellent yield (90%) by coupling 1,4-dibenzodiazepane **112** with 4-iodobenzotrifluoride (Scheme 16d).[104] The enhanced acidity of the secondary aniline relative to the secondary alkylamine in **112** allowed this transformation to occur selectively without the need for protecting groups.

Morpholine is the 17th most common *N*-heterocycle encountered in commercial pharmaceuticals[40] and C−N cross-coupling is often used for its functionalization. In order to overcome multidrug resistance in cancer treatment, Hajós and colleagues developed a new class of morpholine-containing thiazine-based compounds (Scheme 17a).[105] Chlorothiazine **114** was transformed into intermediate amine **115** in excellent yield (92%) through the use of a $Pd_2(dba)_3$/**L17** catalyst. Similarly, Pan and co-workers (Novartis) prepared a series of

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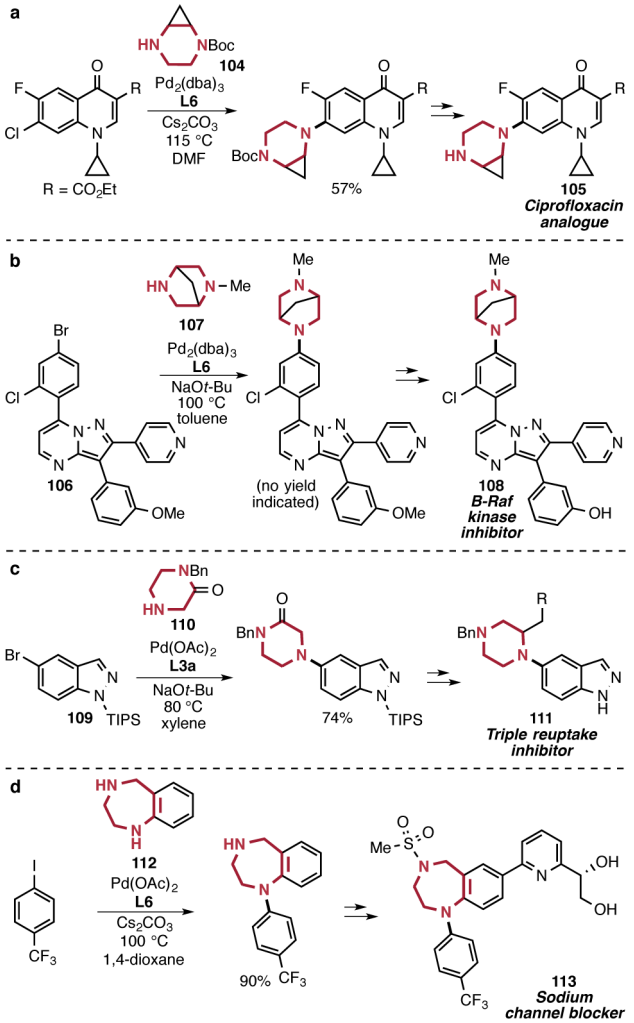
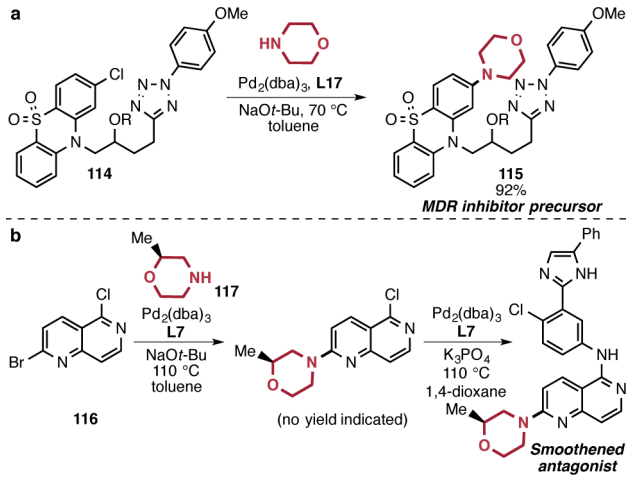
Scheme 16. Piperazine Derivatives in C−N Cross-Coupling Reactions



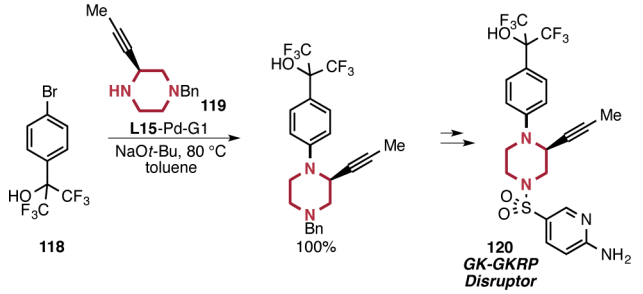
Scheme 17. Examples of Morpholine Coupling in the Synthesis of Pharmaceutically Interesting Compounds



smoothened antagonists in search for a treatment of medulloblastoma and basal cell carcinoma by employing the Pd-catalyzed cross-coupling of morpholine **117** (Scheme 17b).[106] The reaction selectively took place at the aryl bromide of heterocyclic electrophile **116** in the presence of an **L7**-based catalyst. A second C−N coupling with an aniline substrate provided the final product.

2.2.2. Applications of the Coupling of Secondary Alkylamines in Process Chemistry. After the discovery of diabetes pharmaceutical candidate GK-GKRP disruptor **120**, Bourbeau and co-workers (a medicinal chemistry group at Amgen) developed an improved nonracemic synthesis featuring fewer steps, higher yield, and a better safety profile on a 100-g scale (Scheme 18).[107] Given the efficacy of the Pd-catalyzed

Scheme 18. C−N Cross-Coupling of Ortho-Substituted Piperazine 119 Using an L15-Based Catalyst



coupling of aryl bromide **118** with piperazine **119** in the medicinal chemistry route, the same strategy and reaction conditions were repeated in the large-scale operation. In the presence of an **L15** first-generation palladium precatalyst, hindered 2-alkynyl piperazine **119** reacted quantitatively with the para-substituted arene at 80 °C with NaO-*t*-Bu used as the base.

2.2.3. Application of the Coupling of Secondary Alkylamines in the Synthesis of Natural Products. Baran and co-workers demonstrated an impressive example of a C−N coupling reaction in the synthesis of (+)-psychotetramine (**123**), a unique dimeric alkaloid connected through an uncommon C7−N1 bond (Scheme 19).[108] The formation of this bond represented a very challenging N-arylation between two complex and highly hindered fragments: ortho-substituted aryl bromide **121** and indoline **122**. Moreover, two additional NH groups were left unprotected. After thorough optimization of the reaction conditions, an **L15**-based catalyst provided the best yield of the N-arylated product (41%). Attempts to improve the result by employing an excess of the nucleophile, slow addition of the catalyst, or generating the active catalyst via a water activation protocol reported by Buchwald were unsuccessful. Only the use of an excess of aryl bromide was beneficial to the yield.

2.2.4. Applications of the Coupling of Secondary Alkylamines in Materials Chemistry and Chemical Biology. Acyclic secondary aliphatic amines are common units in organic materials. For example, a fluorescent probe for proton-coupled DNA folding, **125**, developed by Mata and Luedtke, was constructed by fusing deoxycytidine **124** and dimethylaniline units using **L12** as the supporting ligand (82%, Scheme 20a).[109] Dialkylamines are also frequently used to prepare fluorescent materials, such as pyrenes. Given the multiple applications of this class of molecules, Edkins, Marder and their co-workers reported a general strategy to selectively functionalize the 2- and 7-positions of pyrene with two different nucleophiles (Scheme 20b).[110] As an example, 2-cyano-7-(*N*,*N*-diethylamino)pyrene **126** was prepared by sequential Ir-catalyzed borylation and cyanation reactions followed by Pd-

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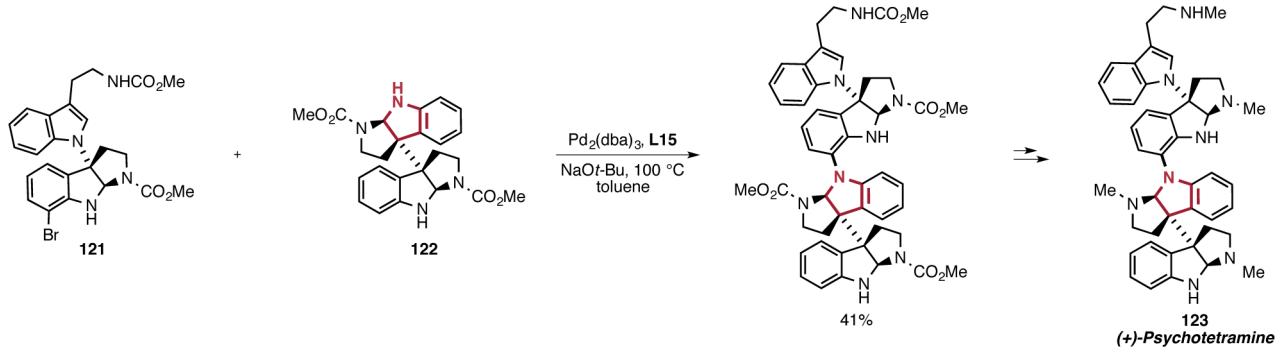
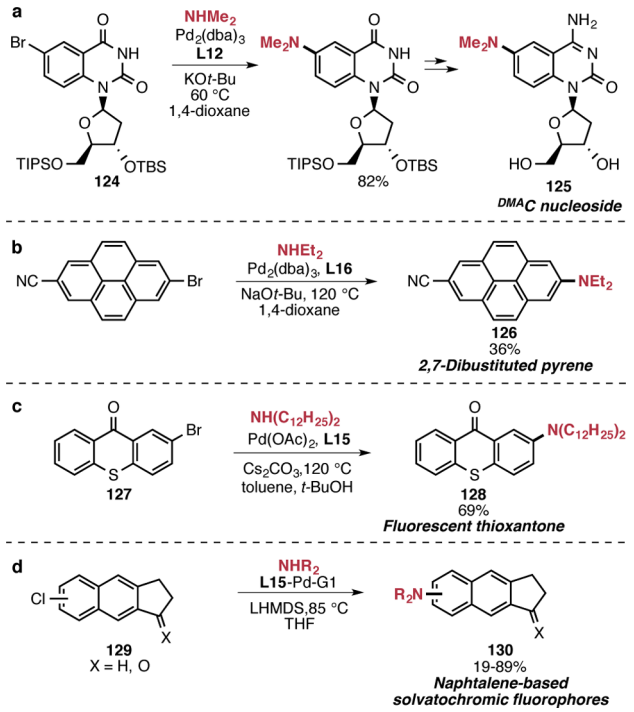
Scheme 19. Use of Secondary Amine N-Arylation in Total Synthesis



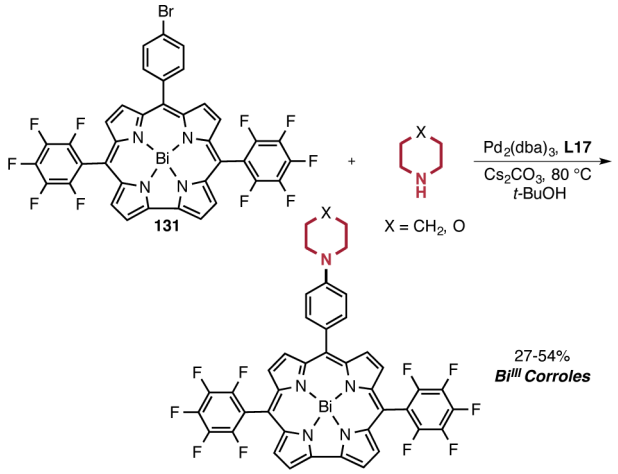
Scheme 20. Applications of Linear Dialkylamines in the Synthesis of Organic Materials



catalyzed N-arylation. Unsuccessful attempts to form the C−N bond using a stoichiometric quantity of CuI led to the use of Pd-catalyzed coupling of dimethyl amine with **L16** as the supporting ligand, which afforded **126** in modest yield (36%). This strategy allowed for the introduction of an acceptor and a donor group on opposite sides of the planar conjugated compound, giving rise to potential optoelectronic materials. Nazir et al. also introduced dialkylamines as strongly electron-donating substituents onto thioxanthone derivative **127** to increase the quantum yield of the final fluorescent molecule **128** (Scheme 20c).[111] In particular, long chain secondary amines were successfully coupled, using an **L15**-based catalyst, conferring excellent solubility properties to the final materials. In a similar manner, Brummond and co-workers reported the first systematic synthesis of a naphthalene-based family of fluorescent markers for biological applications (Scheme 20d).[112] As is common in many fluorophores, compound **130** was composed of a conjugated framework containing both an electron-withdrawing and an electron-donating group. A number of linear dialkylamines and cyclic amines (e.g., pyrrolidine, piperidine, morpholine) were installed at various positions of the benzene ring using Pd-catalyzed C−N coupling. The reactions were carried out with an **L15** first-generation palladium precatalyst and LHMDS as the base with a range of aryl chlorides **129**.

In Scheme 21 is depicted an example of a cross-coupling reaction between secondary cyclic amines and corrole **131**,

Scheme 21. Corrole Functionalization via Piperazine and Morpholine Coupling



which contains a Bi(III) atom to stabilize the macrocycle during its functionalization. Among the reaction conditions explored by Schoefberger and co-workers, the use of **L17** as a supporting ligand in the presence of a weak base, at 80 °C, prevented decomposition or demetalation of the macromolecule as well as potential competing S_NAr reactions of the pentafluoroaryl substituents present in the molecule.[113]

3. ANILINES

3.1. Primary Anilines

Given the modest nucleophilicity of primary anilines, C−N coupling has emerged as a powerful alternative to traditional S_NAr reactions. Primary anilines are considered one of the more straightforward coupling partners for palladium-catalyzed N-arylation because of the lack of potentially competing β-hydride elimination and increased acidity compared to primary aliphatic amines.[4] Therefore, the number of examples of applications of primary aniline coupling reactions in different fields is very large. Specifically, diarylamines are highly common structural units in organic materials and are among the top 20 most frequent functional groups in biologically active molecules.[42]

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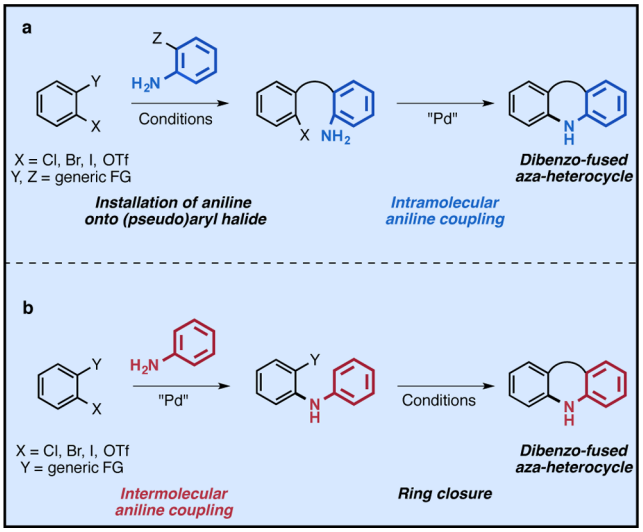
Thanks to advances in ligand design, the coupling of primary anilines has become a versatile process that encompasses a broad scope of aryl halides[52,54,114] and sulfonates[53,115,116] and is selective for the formation of the monoarylation product. Catalyst systems based on **L6**, **L7**, diarylbiarylphosphines (**L17** and **L18**),[4,53,54] **L10**,[52,116,117] and P−N ligands[24,114] are used in numerous primary aniline coupling processes, although **L6**, **L7**, PR_3 (PCy_3, P-*t*-Bu_3, PPh_3), and dialkylbiarylphosphines are the most frequently employed in practice.

3.1.1. Applications of the Coupling of Primary Anilines in the Synthesis of Heterocycles. The palladium-catalyzed arylation of anilines is a versatile strategy to construct nitrogen-based dibenzo-fused heterocycles (Scheme 22). Typically, tandem processes involving the intramolecular

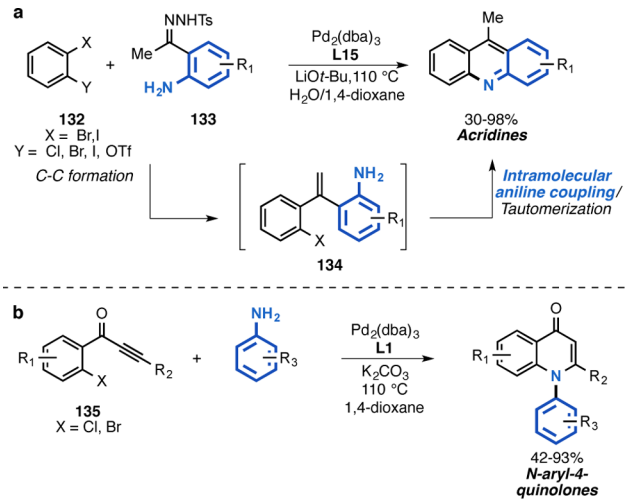
Scheme 22. General Strategies for the Synthesis of Heterocycles via the Coupling of Primary Anilines



or intermolecular N-arylation of an aniline efficiently give rise to tricyclic aza-heterocycles in a one-pot process. As shown in Scheme 22a, ortho-functionalized anilines can be first attached to a (pseudo)aryl halide. Subsequent intramolecular C−N coupling then affords the desired heterocycle. Alternatively, sequential intermolecular aniline coupling/cyclization steps can be carried out to obtain the same products (Scheme 22b).

Following the approach displayed in Scheme 22a, Wang and colleagues prepared a series of acridines through a Pd-catalyzed two-step sequence: C−C bond formation and subsequent intramolecular N-arylation (Scheme 23a).[118] From 1,2-dihaloarenes (**132**, X = Cl, Br, I, OTf) and *N*-tosylhydrazones (**133**), a large number of substituted acridines were prepared in the presence of an **L15**-based catalyst and LiO-*t*-Bu as the base. Addition of water to the reaction mixture was found to increase the yield of product (30−94%), so a mixture of H_2O/1,4-dioxane was used as solvent. The reaction with unsymmetrical 1,2-dihaloarenes proceeded in a highly regioselective manner, with the weaker C−X bond reacting first. Additionally, the in situ preparation of *N*-tosylhydrazones (**133**) was demonstrated from the corresponding ketones and tosyl hydrazine, allowing for a one-pot protocol from readily available starting materials. Mechanistic studies suggested that carbene migratory insertion followed by *β*-hydride elimination leads to intermediate **134**, which then undergoes intramolecular N-arylation facilitated by the same Pd species to yield the target heterocycle. In addition,

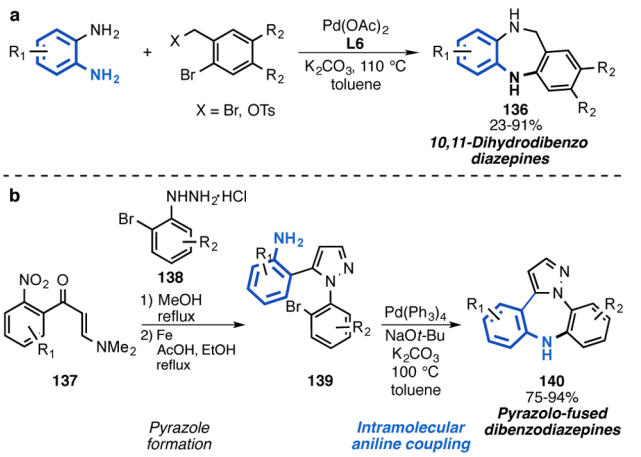
Scheme 23. Synthesis of Acridines and *N*-Aryl-4-quinolones via the Coupling of Primary Anilines



Xu disclosed a tandem process to access *N*-aryl-4-quinolones where two C−N bonds were established between *o*-haloaryl propargyl ketones **135** and primary anilines with a single catalyst [$Pd_2(dba)_3$/**L1**] (Scheme 23b).[119]

The Pd-catalyzed intramolecular coupling of anilines has also been used to prepare dibenzodiazepines, which are important pharmaceutical targets (Scheme 24). As a practical alternative

Scheme 24. Synthesis of Dibenzodiazepines via the Intramolecular Coupling of Primary Anilines



to dibenzodiazepinone reduction, Laha and co-workers developed a Pd/**L6**-catalyzed tandem process for the synthesis of 10,11-dihydro-dibenzodiazepines (**136**) (Scheme 24a).[120] Presumably, intermolecular Pd-catalyzed N-benzylation of 1,2-diaminoarenes with 2-bromobenzyl bromides occurs first, followed by intramolecular N-arylation to furnish the seven-membered-ring-containing heterocycles in 23−91% yield.[121] Additionally, Domínguez and co-workers prepared a series of (pyrazolo)dibenzodiazepines (**140**) in an effort to enhance the drug-like properties of the final compounds (Scheme 24b).[122] The substrates (**139**) were obtained by pyrazole formation from previously prepared nitroenaminones (**137**) and *o*-bromophenylhydrazines (**138**), followed by reduction of the nitro group. Although attempts to perform the desired intramolecular N-arylation with intermediate **139** using a Cu-

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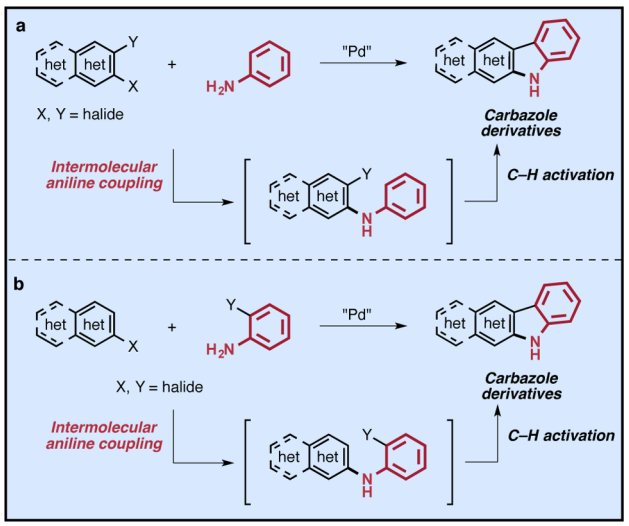
catalyzed approach or in the presence of a Pd/bidentate phosphine catalyst were unsuccessful, the reaction proceeded in excellent yield (75−94%) using Pd(**L1**)$_4$ and a mixture of K_2CO_3/NaO*t*-Bu as the base.

The palladium-catalyzed intermolecular coupling of anilines has been widely used to access carbazole derivatives. Intermolecular C−N coupling, followed by intramolecular C−C bond formation, is the most common strategy to assemble these heterocycles, which are ubiquitous in bioactive compounds and organic materials.[123,124] Scheme 25 displays

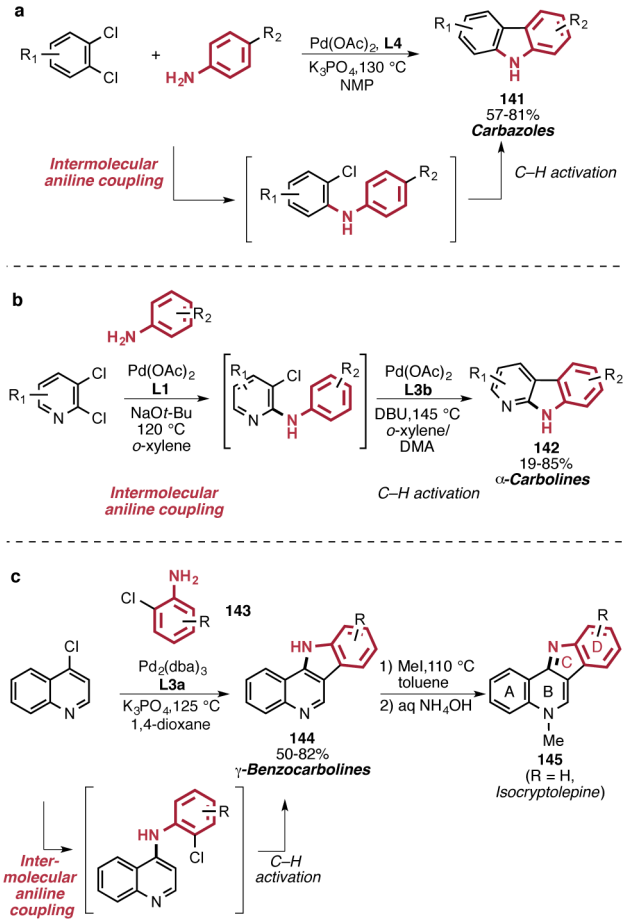
Scheme 25. General Strategies for the Synthesis of Carbazole Derivatives via the Coupling of Primary Anilines



possible coupling partners to carry out the tandem process: 1,2-dihaloarenes (X = Y or X ≠ Y) can react with anilines (Scheme 25a), or an aryl halide and an *o*-haloaniline can be combined (Scheme 25b) to arrive at a similar intermediate. A subsequent ring-closing C−H activation reaction leads to the formation of the desired carbazole systems. The use of heteroaryl halides and their benzo-fused derivatives expands the reaction scope. Most frequently, a single catalyst, often based on a trialkylphosphine ligand, is able to induce both the N-arylation and C−H activation steps in a convenient one-pot process.

In a recent report by Ackermann, the tandem N-arylation/C−H activation reaction involving aryl chlorides in both steps was shown for the first time (Scheme 26a).[125] With a catalyst based on **L4**, a variety of free NH carbazoles (**141**) were directly accessed from 1,2-dichloroarenes and primary anilines, avoiding the need for protecting groups. In addition, examples of N-substituted carbolines (pyrido[2,3-*b*]indoles) and indole derivatives were also prepared in this manner (not shown). The groups of Maes[126] and Cuny[127] contemporaneously reported methods for the synthesis of *α*-carbolines (**142**) from anilines and 2,3-dichloropyridines (Cuny's method is shown in Scheme 26b). Cuny developed a one-pot, two-step protocol involving a change in catalyst, whereas Maes's method required two separate reactions. Both research groups found that the use of DBU as the base at elevated temperatures was optimal to prevent competing hydrodehalogenation during the C−H activation step. Additionally, Maes developed another process to access benzocarbolines (**144**) in a one-pot procedure (Scheme 26c).[128] The resulting tetracyclic heterocycles were then methylated to provide the final products (**145**), derivatives

Scheme 26. Synthesis of Carbazole-Based Heterocycles via the Sequential Intermolecular Coupling of Primary Anilines/C−H Activation Reactions



of the antiplasmodial natural product isocryptolepine. A variety of D-ring-substituted analogues were prepared in this manner to explore their bioactivity. In this protocol, *o*-chloroanilines (**143**) were reacted with 4-chloroquinoline to afford the benzocarbolines. Both steps were facilitated by Pd$_2$(dba)$_3$/**L3a** to provide **144** in 50−82% yield. The Pd-catalyzed intramolecular arylation of electron-deficient pyridines, which proved more challenging than that of other (hetero)arenes,[129] could be achieved under the reported conditions.

An alternative approach to prepare N-substituted carbazoles and related dibenzo-fused aza-heterocycles is by the double N-arylation of primary amines (aryl or alkyl) with 2,2′-dihalodiiaryl precursors (Scheme 27). In one-pot procedures, consecutive intermolecular and intramolecular C−N bond forming events give rise to the *N*-aryl heterocycles. After the first reports of this carbazole synthesis by the groups of Nozaki[130,131] and Chida,[132] Zhou and Verkade developed conditions requiring lower catalyst loading and shorter reaction times through the use of proazaphosphatrane ligands (Scheme 28).[133] In the presence of **L26**, a variety of primary anilines and several alkylamines were successfully coupled with 2,2′-dihalobiphenyls to provide the desired N-substituted carbazoles (**145**) in 34−99% yield. More recently, Dang, Langer, and their co-workers reported a multistep route to biscarbazoles **148a** and **148b** (Scheme 29, next page) involving three Pd-catalyzed coupling reactions of anilines.[134] First, inter- and intramolecular N-arylation of *p*-anisidines (top) or *m*-anisidines (bottom) with

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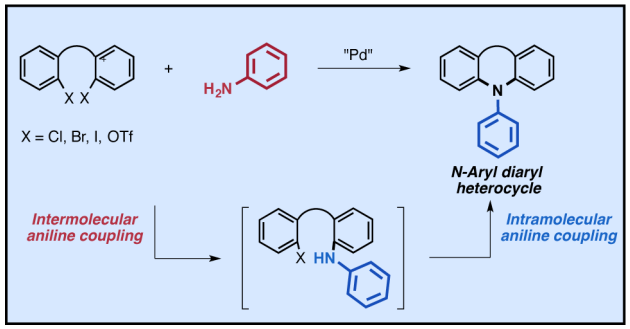
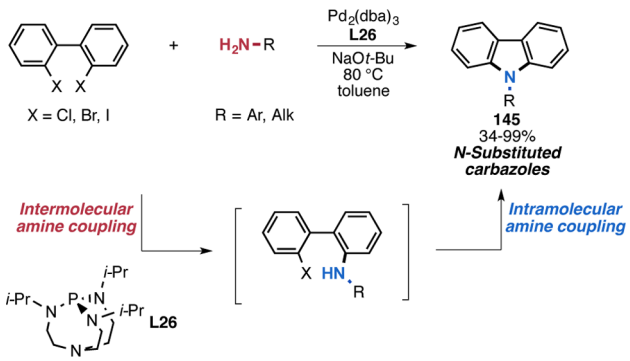
Scheme 27. Synthesis of Carbazoles via the Double N-Arylation of Primary Anilines



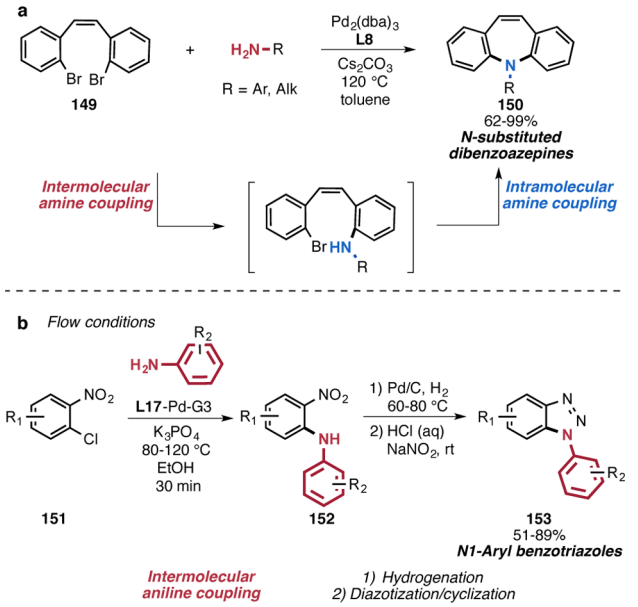
Scheme 28. Synthesis of Heterocycles via the Double N-Arylation of Primary Anilines



bistriflate **146** furnished carbazoles **147a** and **147b**. Subsequent conversion of the methoxy groups into triflates, followed by an N-arylation/C−H activation sequence, successfully introduced a second carbazole into the structure, yielding 3,9′- and 2,9′-biscarbazoles (**148a** and **148b**). Different ligands were used for different N-arylation steps: **L7** for the first two and **L17** for the third.

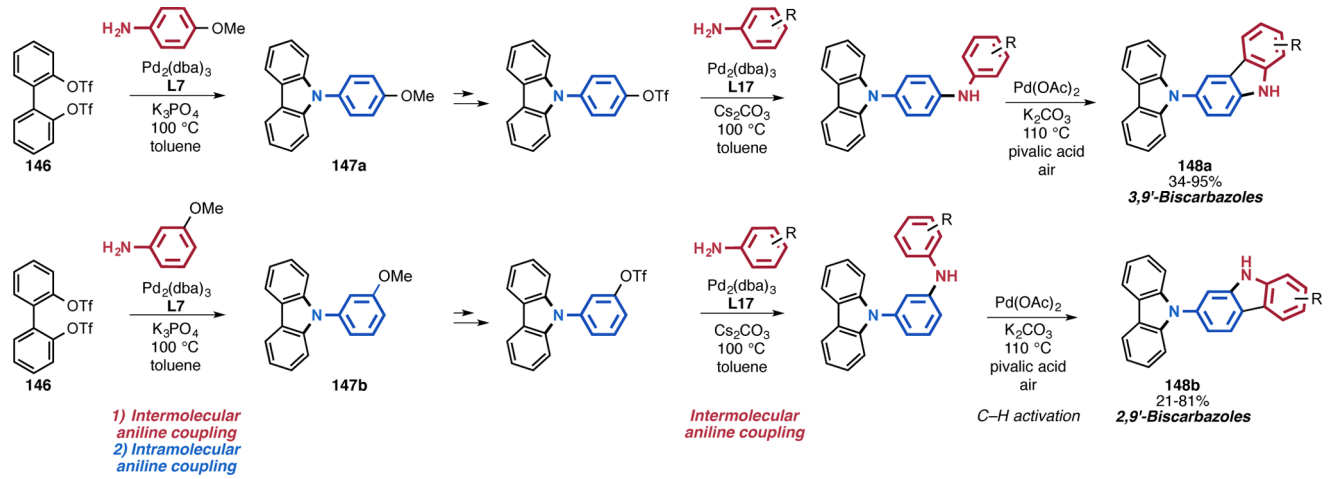
Another example of the use of the double N-arylation was reported in the synthesis of dibenzoazepines (**150**) from dibromo arenes (**149**) and primary anilines and amines by Liang and co-workers (Scheme 30a).[135] In the presence of a catalyst based on **L8**, (*Z*)-1,2-bis(2-bromophenyl)ethene (**149**) reacted with a variety of amines to afford the desired tricyclic

Scheme 30. Synthesis of N-Substituted Dibenzoazepines and Benzotriazoles via the Intermolecular Coupling of Primary Anilines



compounds in good yield (62−99%). Buchwald employed Pd-catalyzed aniline coupling to build *N1*-aryl benzotriazoles in continuous flow (**153**) (Scheme 30b).[136] The aza-heterocycles were obtained in a three-step process involving C−N bond formation, hydrogenation, and diazotization/cyclization. First, on the basis of the electronic nature of the starting reagent (**151**), either S_NAr or Pd-catalyzed N-arylation reactions gave rise to intermediate **152**. Electron-rich and fluorine-substituted chloronitrobenzenes were successfully coupled with anilines in the presence of **L17**−Pd-G3 precatalyst and K_3PO_4 in a EtOH/H_2O solution. The use of a Pd-based catalyst allowed for a reduction in the reaction temperature from 160−180 °C (required for the S_NAr reaction) to 80−120 °C. After the formation of the C−N bond, sequential hydrogenation and diazotization/cyclization steps afforded the desired products (**153**) in good yield (51−89%). This method serves as an alternative to postfunctionalization of benzotriazoles, which typically results in mixtures of regioisomeric products.

Scheme 29. Synthesis of Biscarbazoles via the Coupling of Primary Anilines



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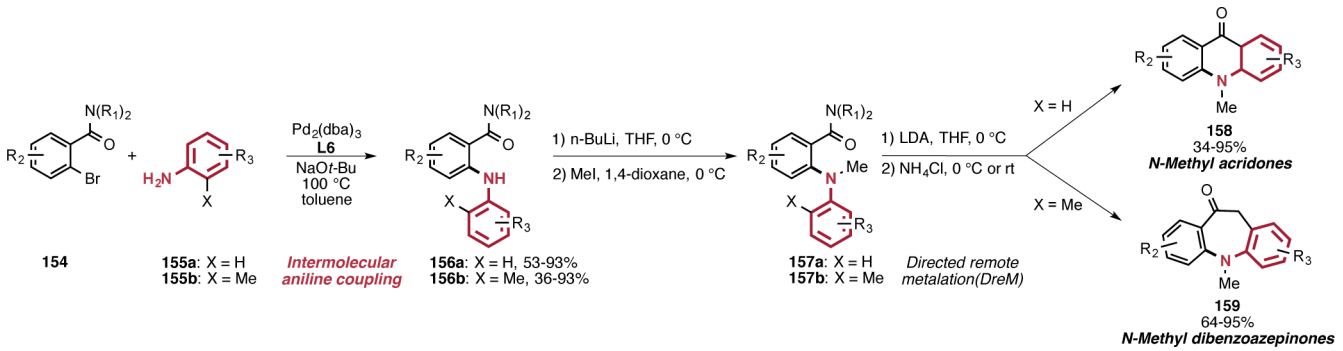
Scheme 31. Synthesis of *N*-Methylacridones and Dibenzoazepinones via the Coupling of Primary Anilines

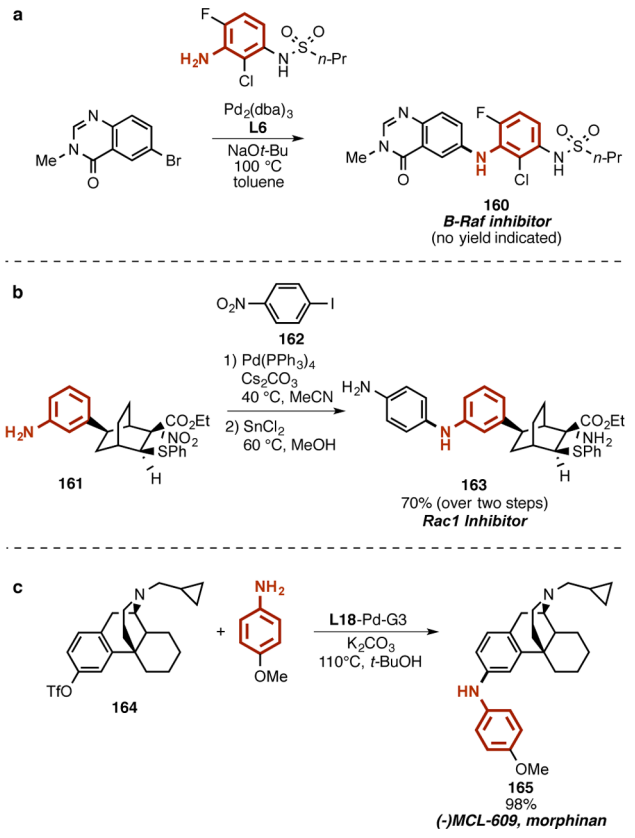


Snieckus and colleagues prepared a variety of *N*-methylacridones (**158**) by sequential aniline coupling and LDA-mediated cyclization (Scheme 31).[137] First, anilines (**155a**) underwent N-arylation with *o*-bromobenzamides (**154**) using an **L6**-based catalyst to form intermediate **156a**. Although it was observed that the N-methylated precursor **157a** gave better results in the final ring-closure step, the direct coupling of *N*-methylaniline and compound **154** provided low yield. Thus, the N-methylation of **156a** with *n*-BuLi and MeI was preferred to generate intermediate **157a**. Then, the reaction of **157a** with LDA afforded the desired *N*-methylacridones (**158**) in 55−95% yield. Alternatively, when the methyl group was replaced with a MOM group, the free NH acridones could ultimately be obtained (not shown). While investigating the reaction scope, Snieckus reported that diarylamine **157b**, bearing a methyl group ortho to the amine, was transformed into the dibenzoazepinone analogue (**159**) instead, under identical reaction conditions. Given the high applicability of dibenzoazepinones in the field of medicinal chemistry, the new pathway was further optimized and a series of dibenzoazepinones (**159**) were chemoselectively obtained in 64−95% yield (along with minor amounts of the acridone).

3.1.2. Applications of the Coupling of Primary Anilines in Medicinal Chemistry. *3.1.2.1. Preparation of Drug Candidates Containing Diarylamines.* Diarylamines are prevalent substructures in drug candidates and are frequently generated by the Pd-catalyzed coupling of anilines due to the high versatility and broad scope of this method. Medicinal chemists have employed a variety of phosphine ligands for this transformation, with **L6** and dialkylbiarylphosphines being the most common.

The groups of Ren (Array BioPharma) and Rudolph (Genentech) prepared a series of B-Raf^{V600E} inhibitors displaying good selectivity profiles toward cancer targets (**160**, Scheme 32a).[138] A variety of sulfonamide-containing anilines were coupled to the quinazolinone precursor to give the drug candidates, among which compound **160**, synthesized by Pd-catalyzed C−N cross-coupling using **L6**, was identified as the most potent. Similarly, Ferri, Contini, and their co-workers described the synthesis of norbornene-containing Rac1 inhibitors (**163**), in which cycloaddition and Pd-catalyzed aniline coupling reactions were the key steps (Scheme 32b).[139] Activated *p*-nitroiodobenzene (**162**) was coupled with several stereoisomers of aniline **161** using $Pd(PPh)_4$. The reaction proceeded at low temperature (40 °C) in the presence of a weak base, which was necessarily used due to the presence of nitro groups in both reaction partners. Among the different stereoisomers, compound **163** was identified as most active and

Scheme 32. Synthesis of Bioactive Compounds Containing Diarylamines via the Coupling of Primary Anilines



was produced on a 1-g scale. While searching for new treatments for drug abuse, Neumeyer prepared a series of enantiomerically pure opioids (Scheme 32c).[140] *p*-Anisidine was separately reacted with aryl triflate **164** and its enantiomer in order to investigate the stereoisomer-dependent properties of the products (**165**, only one enantiomer shown). The active catalyst was generated using the third-generation palladium precatalyst of **L18**, allowing the coupling to occur in excellent yields (98% for **165** and 89% for the corresponding enantiomer). These were greatly improved results compared to previous examples in which catalysts based on $Pd(OAc)_2$/**L6** and $Pd(OAc)_2$/**L9** were used (9−26% yield).[141]

McKinnel and co-workers (Theravance) investigated a new generation of long-lasting β_2-agonists (**168**) for the treatment of respiratory disorders (Scheme 33a).[142] The target compounds were generated in a highly convergent synthetic route in which aryl bromide **166** and highly functionalized

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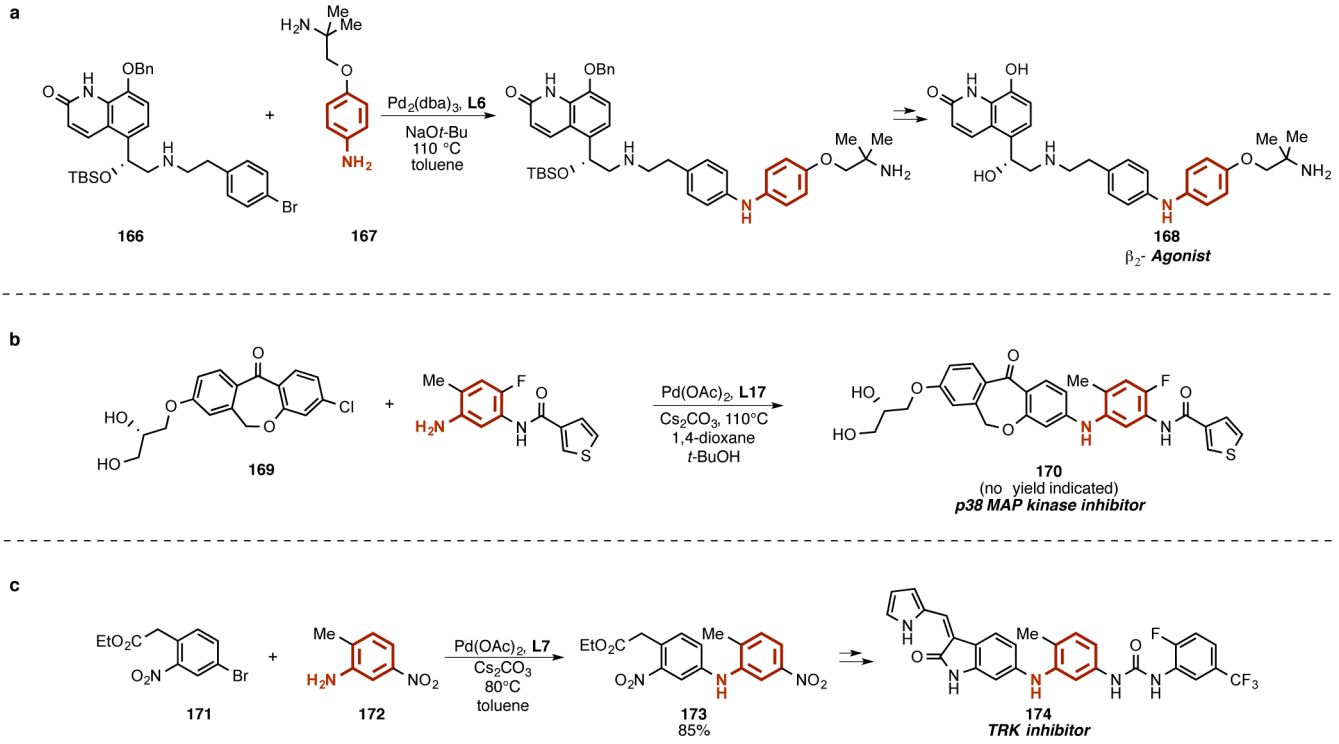
Scheme 33. Synthesis of Biologically Active Diarylamines



aniline **167** were coupled near the end of the sequence. Additionally, Laufer prepared a series of metabolically stable dibenzoxepinones containing diarylamines to potentially treat inflammatory diseases (Scheme 33b).[143] A number of anilines were coupled to a tricyclic core (**169**), arriving at **170** as the lead compound. A weak base was used due to the presence of unprotected primary and secondary alkyl alcohols and a secondary heterocyclic amide in the starting materials. Molteni and co-workers (Novartis) also employed the coupling of anilines to access TRK inhibitor **174**, which proved to be efficient in restricting tumor growth (Scheme 33c).[144] At the early stages of the synthetic process, Pd-catalyzed coupling of nitro-containing coupling partners **171** and **172** furnished intermediate **173** (85%) in the presence of an **L7**-based catalyst with Cs_2CO_3 as the base.

Given the widespread presence of heteroanilines in biologically active compounds, the coupling of primary anilines and (hetero)aryl halides is frequently employed in the synthesis of drug candidates. This method is an alternative to the N-arylation of heteroarylamines with aryl halides when the former are unavailable or the coupling reactions proceed in low yield. Examples of cross-coupling reactions between primary anilines and halopyrimidines are shown in Scheme 34. Beria and co-workers (Nerviano Medical Sciences) conducted a high-throughput screen in search of anticancer polo-like kinase 1 inhibitors (Scheme 34a).[145] A series of anilines were successfully combined with tricyclic core **175**, with compound **177** showing the highest antitumor activity. An **L6**-based catalyst facilitated the reaction between 2-iodopyrimidine **175** and ortho-substituted aniline **176**. 4-Halopyrimidines are also effective coupling partners with anilines, as demonstrated by García-Domínguez et al. in their improved synthesis of the antileukemia DNMT inhibitor **181** (Scheme 34b, top).[146] The patented synthesis of compound **181**[147] followed the same multistep route, but the C–N bonds were formed via S_NAr reactions, with low yields reported for both steps (51% for compound **179** and 4% for compound **181**). Thus, a Pd-catalyzed approach was explored as an alternative. The coupling of *p*-nitroaniline and heteroaryl chloride **178** proceeded in 85% yield under previously reported conditions for water-promoted catalyst activation. No competing N-arylation of the 2-aminopyrimidine present in the aryl chloride was observed under the reaction conditions. Attempts to carry out the reaction between intermediate **180** and 4-chloroquinoline under identical conditions resulted in 70% of undesired bis-N-arylated product from reaction at both the primary and secondary anilines present in **180**. Switching to a solvent mixture of 50:50 *t*-BuOH/DMF increased the solubility of the nucleophile, leading to observation of the desired monoarylated product **181** in 73% yield, as deduced by ^{1}H NMR. However, due to significant difficulties with product purification, the route was redesigned. The requisite C–N bond was formed between 4-chloroquinoline and ethyl 4-aminobenzoate, giving rise to fragment **182**, which was further elaborated to deliver compound **181** (Scheme 34b, bottom). The latter synthetic route resulted in a more convergent process with a higher overall yield and lack of formation of side products.

Pd-catalyzed reactions between anilines and halopyrazines to access pharmaceutical targets are displayed in Scheme 35. Springer and colleagues arrived at BRAF inhibitor **183** after several modifications of the 1,4-pyrazine core of the drug candidate (Scheme 35a).[148] A catalyst based on **L6** was suitable for the coupling of 3,4,5-trimethoxyaniline and 1,2-dichloropyrazine (no yield was indicated). Additionally, Wurz and co-workers (Amgen) was able to couple pyridazine **184** with ortho-substituted aniline **185** in the last step of the synthesis of p38α MAPK inhibitors (**186**), which are active against inflammatory diseases (Scheme 35b).[149] A large number of analogues could be prepared by using this route.

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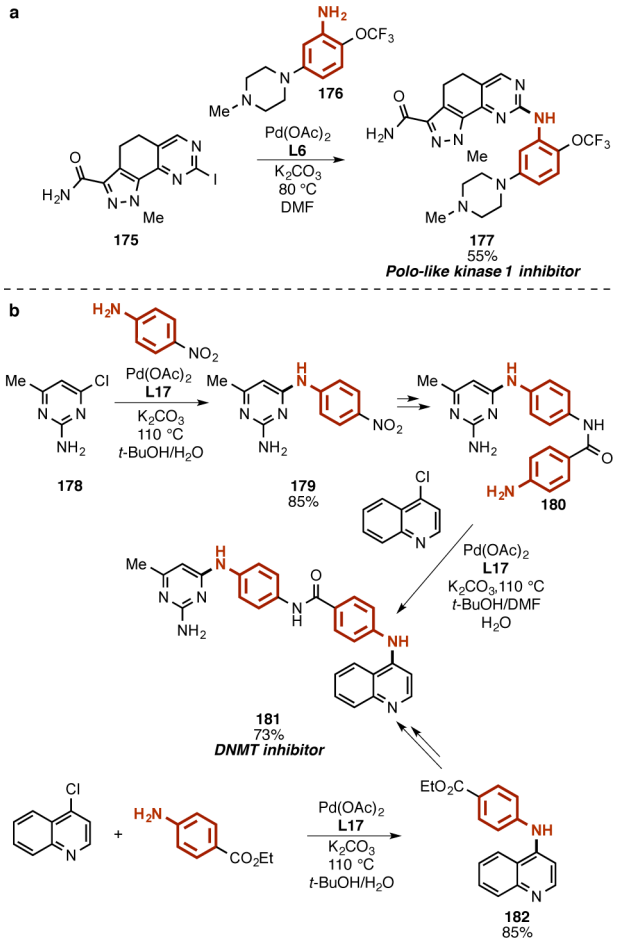
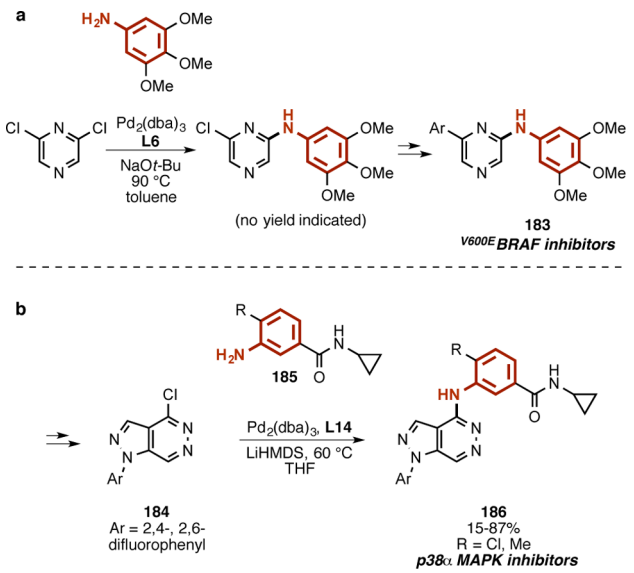
Scheme 34. Synthesis of Bioactive Compounds Containing Pyrimidine(aryl)amines via the Coupling of Primary Anilines

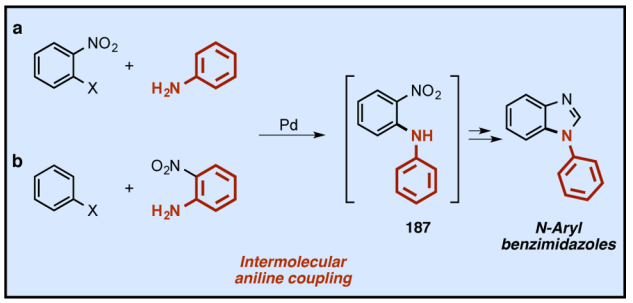


Scheme 35. Synthesis of Biologically Active Compounds Containing Pyrazine(aryl)amines via the Coupling of Primary Anilines



3.1.2.2. Preparation of Drug Candidates Containing Benzimidazoles and Related Azoles. In addition to the preparation of diarylamines, the coupling of anilines is frequently employed to assemble N-arylated benzo-fused azoles, common heterocyclic substructures of drug candidates. Scheme 36 shows two general strategies commonly used to

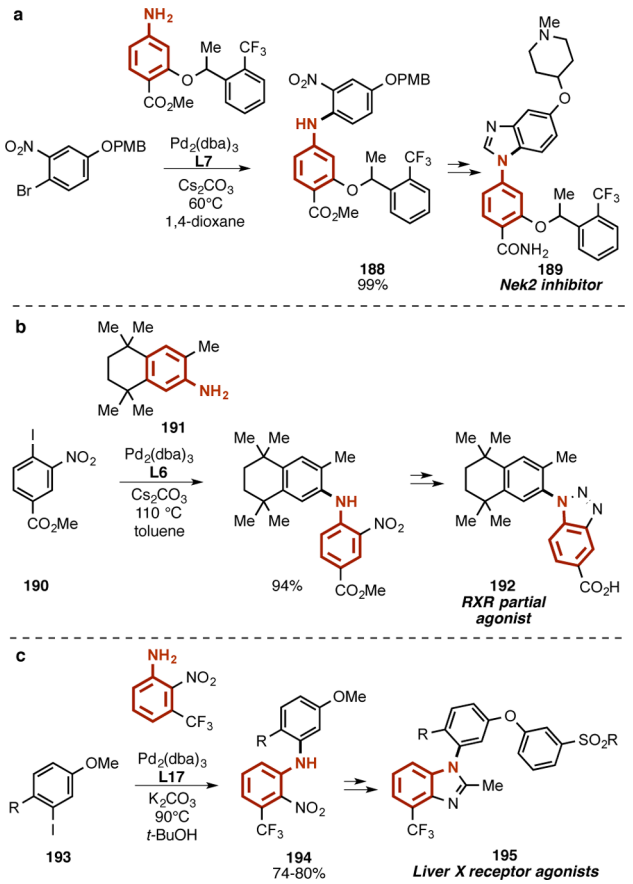
Scheme 36. General Strategies for the Synthesis of *N*-Arylbenzimidazoles via the Coupling of Primary Anilines



synthesize benzimidazoles via aniline coupling processes. In Scheme 36a, an aniline is combined with an *o*-nitroaryl halide to form intermediate **187**. In Scheme 36b, an *o*-nitroaniline is coupled to an aryl halide. In both cases, subsequent reduction of the nitro group in **187** provides a diamine intermediate in route to *N*-arylbenzimidazoles.

Bayliss, Hoelder, and their co-workers followed the first approach to synthesize Nek2 inhibitor **189** (Scheme 37a).[150] They obtained intermediate **188** in quantitative yield from a Pd-catalyzed C−N cross-coupling reaction in the presence of

Scheme 37. Synthesis of Bioactive Compounds Containing Benzo-Fused Azoles via the Coupling of Primary Anilines



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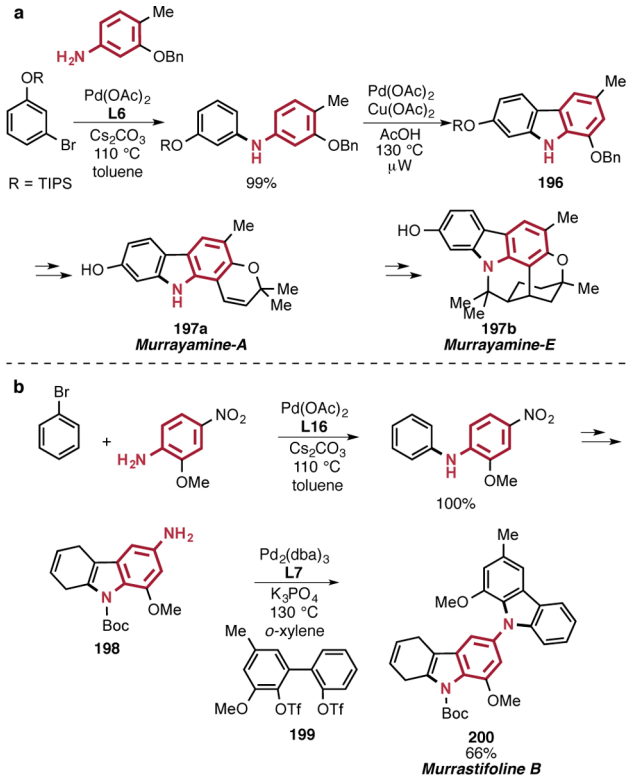
L7. Kakuta and co-workers adopted the same strategy to access RXR partial agonist **192**, a new type of target for the treatment of diabetes (Scheme 37b).[151] Keeping the common structure of RXR agonists, the flexibility of the molecule was reduced by introducing a triazole ring, which conferred RXR partial agonist activity. To form the five-membered ring, *o*-nitroaryl iodide **190** was reacted with ortho-substituted aniline **191** in excellent yield (94%). Following the strategy in Scheme 36b, Bernotas and co-workers (Wyeth Pharmaceuticals) coupled aryl halide **193** and an *o*-nitroaniline using **L17** as the supporting ligand to generate intermediate **194** en route to liver X receptor agonists **195** (Scheme 37c).[152]

3.1.3. Applications of the Coupling of Primary Anilines in the Synthesis of Natural Products. Carbazole alkaloids are a broad class of natural products typically found in terrestrial plants. Their structural complexity and therapeutic potential (antimicrobial activity) have attracted the attention of numerous synthetic research groups.[153] Notably, C−N/C−C bond-forming sequences to build carbazole units have been extensively employed in their preparation.[154−157] A diverse array of Pd/ligand catalyst systems have proved efficient for the assembly of carbazoles. Recently, Knölker and colleagues described the preparation of pyranocarbazole alkaloids **197a** and **197b** through carbazole formation and pyran ring annulations (Scheme 38a).[158] $Pd(OAc)_2$/**L6**-catalyzed N-

Scheme 38. Synthesis of Carbazole Alkaloids via the Coupling of Primary Anilines



arylation followed by a $Pd(OAc)_2$/$Cu(OAc)_2$-catalyzed oxidative C−C bond formation resulted in common intermediate **196**, which led to seven different natural products, such as murrayamines A (**197a**) and E (**197b**). Knölker also reported the first total synthesis of biscarbazole alkaloid murrastifoline B (**200**) (Scheme 38b).[159] The carbazole unit **198** was first constructed as before. Subsequent double N-arylation with bistriflate **199** following Nozaki and co-worker's protocol[130] furnished the target natural product in 66% yield. Thomson and co-workers disclosed the first enantioselective total synthesis of axially chiral dimeric carbazole bismurrayaquinone A (**203**, Scheme 39a).[160] The 2-fold arylation of dibromoarene **201** in the presence of $Pd(OAc)_2$/**L3b** gave rise to intermediate **202** in excellent yield (89%). The final product was successfully obtained in 99% ee. Jia's group prepared two other members of the carbazole alkaloid family, dictyodendrins B (**207**, Scheme 39b) and E.[161,162] This class of alkaloids, which are potential candidates for cancer chemotherapy, are distinguished by the presence of a pyrrolocarbazole core and sulfate groups in their outer aryl groups. Three Pd-catalyzed transformations, a Larock indole synthesis, and the sequential aniline coupling/C−H activation steps to form the carbazole were the key steps of a highly convergent approach to compound **207**. After several attempts to couple bromoindole **204** and aniline **205** resulted in significant amounts of debrominated side product, a one-pot tandem reaction was carried out using $Pd(OAc)_2$/**L3b** and NaO-*t*-Bu in DMSO at 160 °C. Intermediate **206** was obtained in 71% yield, and further steps led to the two natural products (only one shown) in 9 and 11 steps overall, the shortest routes to these molecules described to date.

3.1.4. Applications of the Coupling of Primary Anilines in Materials Chemistry and Chemical Biology. Given the widespread occurrence of diarylamines in small molecules and macromolecules present in organic materials, there are numerous examples of the Pd-catalyzed cross-coupling of anilines carried out in this field. Scheme 40 summarizes the common types of C−N coupling reactions performed to access advanced materials. Cyclic compounds can be accessed either by intramolecular N-arylation (Scheme 40a) or by a 2-fold coupling between a bisaryl halide and bisaniline (Scheme 40b). Conventional diarylamines are obtained by the intermolecular coupling of an aniline and an aryl halide (Scheme 40c), which occasionally is followed by a second N-arylation reaction to furnish the corresponding triarylamine (Scheme 40d). Additionally, several cross-coupling reactions can take place with arenes containing multiple halides or amines (Scheme 40e) to produce compounds with potentially interesting properties.

3.1.4.1. Synthesis of Materials via the Intramolecular Cyclization of Primary Anilines. As shown in Scheme 40a, an intramolecular Pd-catalyzed C−N cross-coupling was the key step in the synthesis of *p-tert*-butylphenol-based azacalix[*n*]-arenes **209a** and **209b** (Scheme 41a).[163] Diazacalix[8]arene (**209a**) and triazacalix[12]arene (**209b**) were obtained from tetramer **208** via intramolecular N-arylation in 10% and 6% yield, respectively. While catalysts based on $Pd_2(dba)_3$ and phosphine ligands **L3a**, **L6**, **L4**, and **L12**, among others, exclusively resulted in polymerization and reduction reactions, an **L17**-based catalyst provided a mixture of the 8- and 12-arene-unit macrocycles. Although the transformations proceeded in low yield, they allowed for the regioselective introduction of unprotected amines into these macrocycles for the first time. Chou, Wong, and their co-workers also employed the intramolecular coupling of primary anilines to assemble the indole and carbazole core units of compound **212**, a photosensitizer for organic dyes used in dye-sensitized solar cells (DSSCs) (Scheme 41b).[164] Although several indolocarbazole (ICZ) derivatives have been investigated to develop DSSC and organic photovoltaic (OPV) dyes, the 5,7-dihydroindolo-[2,3-*b*]carbazole isomer (**212**) remained unexplored due to its

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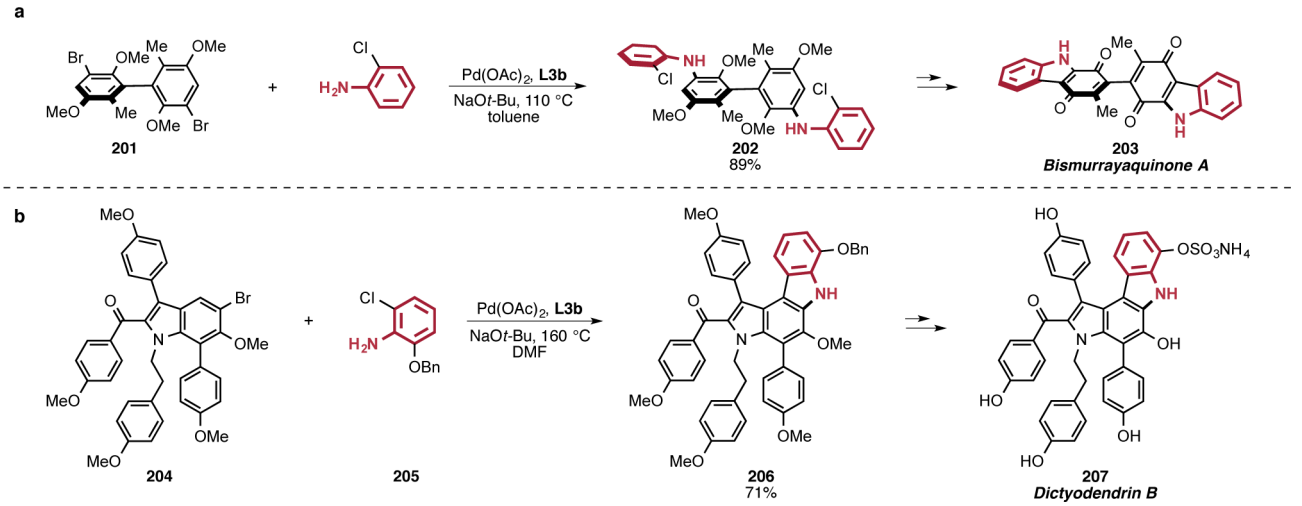
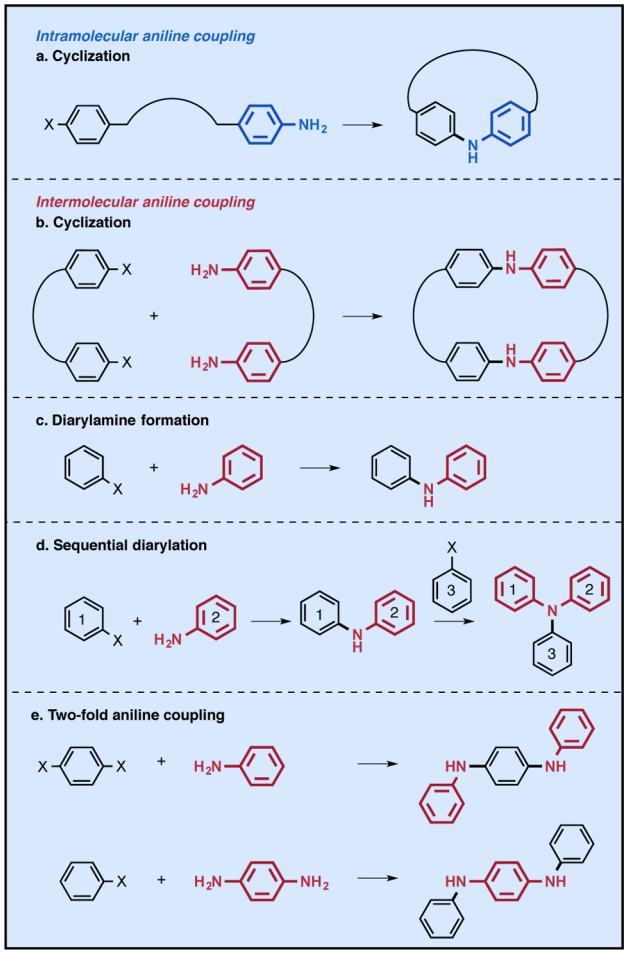
Scheme 39. Synthesis of Carbazole Alkaloids via a C−N/C−H Bond-Forming Sequence



Scheme 40. General Strategies for the Synthesis of Materials via the Coupling of Primary Anilines



difficult preparation. Chou and Wong's approach consisted of the double intramolecular N-arylation of compound **210** in the presence of a $Pd(OAc)_2$/**L3b** catalyst to provide the rigid heterocyclic core (**211**) in 90% yield. Subsequent steps furnished the novel C-shaped dye (**212**), which displayed excellent optical properties.

3.1.4.2. Synthesis of Materials via the Intermolecular Cyclization of Primary Anilines. Net annulation reactions can also be achieved by two intermolecular C−N bond-forming events between a bisaryl halide and bisaniline (Scheme 40b). Bunz and colleagues followed this approach to prepare the first stable diazaheptacene (**216**, Scheme 42a).[165] Azaacenes are commonly employed as structural core units in numerous organic field-effect transistor (OFET) and organic light-emitting diode (OLED) materials. However, diazaheptacene derivatives are highly prone to dimerization via Diels−Alder processes, which prevents their successful preparation. To overcome this issue, Bunz introduced silylethynyl protecting groups into coupling partners **213** and **214** and then carried out a Pd-catalyzed C−N coupling in the presence of **L15**-based palladium precatalyst (**L15**−Pd-G1) under microwave-heating conditions. Compound **215** and a series of silyl-containing [$Si(i\text{-}Pr)_3$ and $Si(Cy)_3$] analogues were obtained in 18−83% yield. Afterward, oxidation of *N,N′*-dihydrodiazaheptacene **215** led to the final compound **216**, which was stable enough to be fully characterized. In a similar manner, Yoshizawa and co-workers prepared fluorescent macrocycle **218** via two consecutive C−N bond-forming reactions (Scheme 42b).[166] They linked four anthracene fluorophores through diarylamine and alkoxylated aryl spacers to favor their interaction. A catalyst based on Pd/C and **L9** facilitated the N-arylation of bisaniline **217** to provide the target compound in 40% yield. The introduction of sp^3-hybridized nitrogen atoms into the backbone of the macrocycle brought the fluorophores closer together, resulting in improved solvato-fluorochromic behavior compared to the separate units.

3.1.4.3. Synthesis of Materials via the Intermolecular Coupling of Primary Anilines. Moore, Kennis, and their co-workers disclosed an example of the coupling of anilines with complex reacting partners **219** and **220** in their investigation on artificial antennas (**221**, Scheme 43).[167] A series of dyads, constituting a porphyrin core and a carotenoid linked by an aniline, were prepared to study the ability of the chromophore to quench the singlet excited states of the macrocycle. In a challenging Pd-catalyzed N-arylation reaction, different aniline-containing carotenoids (**220**) were attached to the iodoporphyrin (**219**) using **L6** as the supporting ligand.

Employing Pd-catalyzed C−N coupling, Mehl, Petersson, and their co-workers designed an efficient route toward

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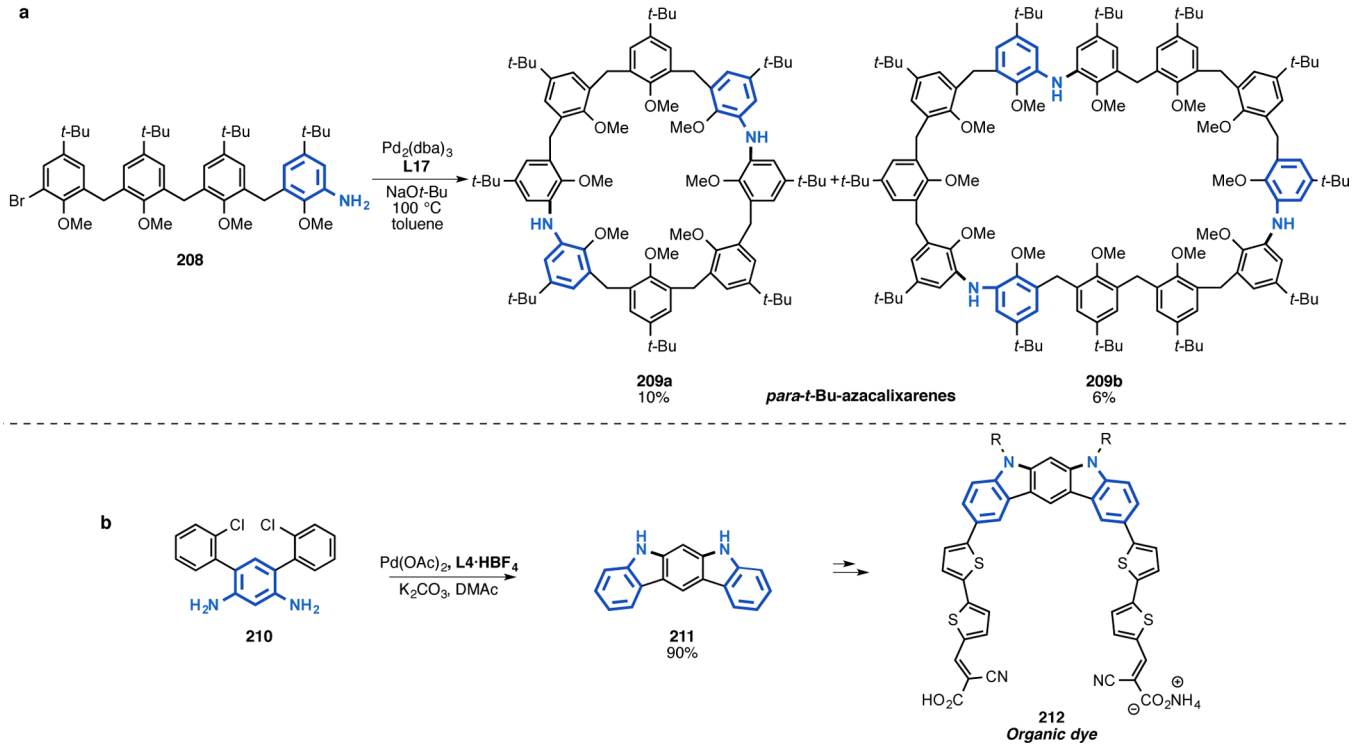
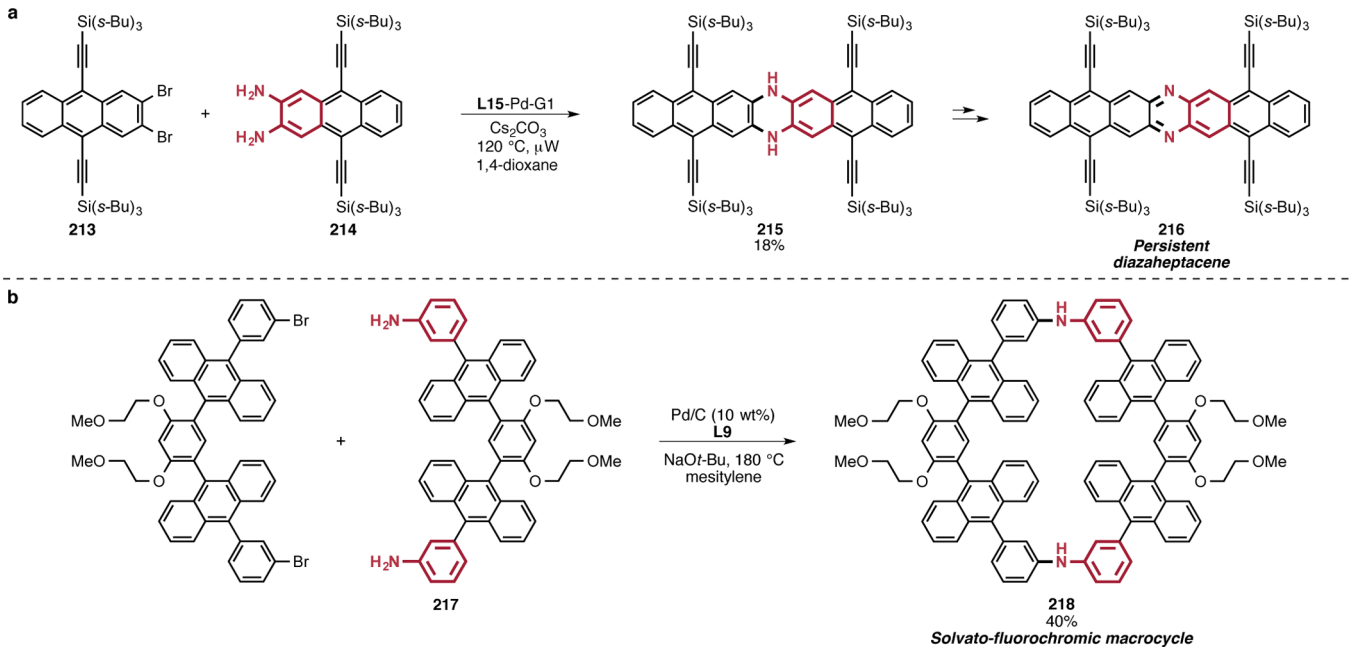
Scheme 41. Synthesis of Materials via the Intramolecular Cyclization of Primary Anilines



Scheme 42. Synthesis of Materials via the Intermolecular Cyclization of Primary Anilines



acridon-2-ylalanine **223** (Scheme 44a), a fluorescent unnatural amino acid that can serve as a probe to detect conformational changes in a protein.[168] In order to generate large amounts of the amino acid for in vivo experiments, they optimized the previous synthesis by Szymańska and co-workers[169] to achieve a more cost-effective process. Whereas the original route started from *p*-nitrophenylalanine and involved an Ullmann-type coupling, the new sequence began from the natural amino acid tyrosine and used a Pd-based catalyst instead. In the presence of $Pd(OAc)_2$, **L6**, and Cs_2CO_3, intermediate **222** was obtained in excellent yield (92%) on a 3-g scale. Yang and co-workers employed very similar cross-coupling conditions in the synthesis of HKGreen-4 (**225**, Scheme 44b), a fluorescent probe for peroxynitrite ($ONOO^-$) detection.[170] Through a C–N reaction, rhodol-based intermediate **224** was prepared in 82% yield. Similarly, Chalmers et al. prepared a new class of nucleic acid probes (**227**, Scheme 44c) through the N-arylation of primary amine **226**.[171] The reaction was employed to connect the two fragments of the probe: the long-lived radical tetramethylisoindolinoxyl (TMIO) and the pyrido[1,2-*a*]-

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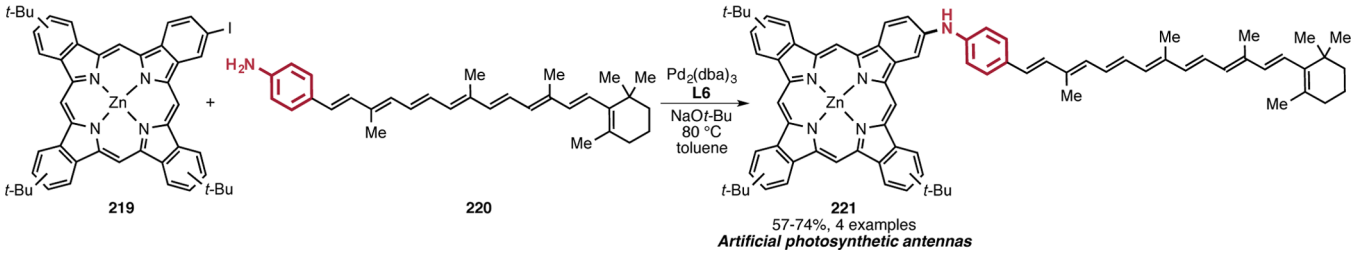
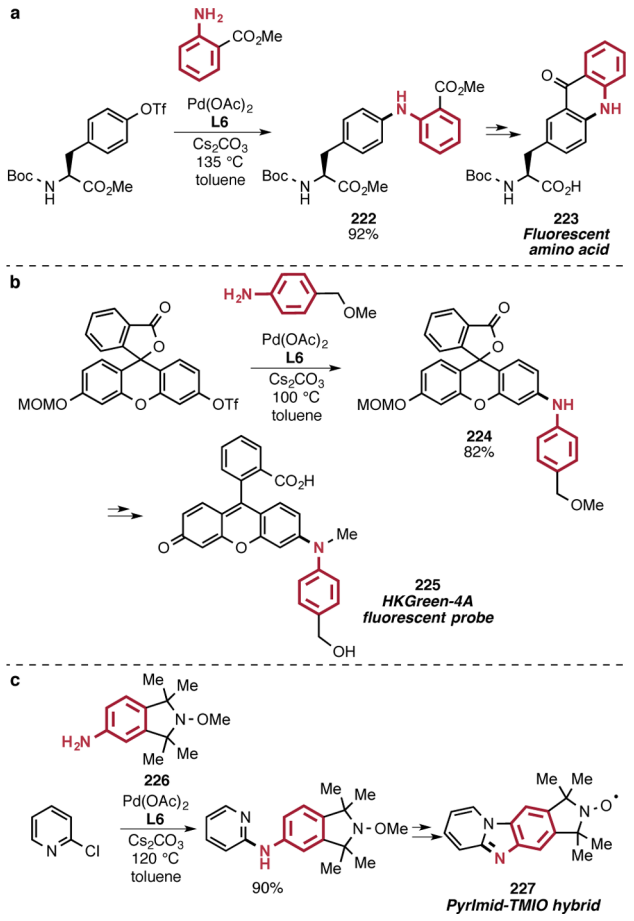
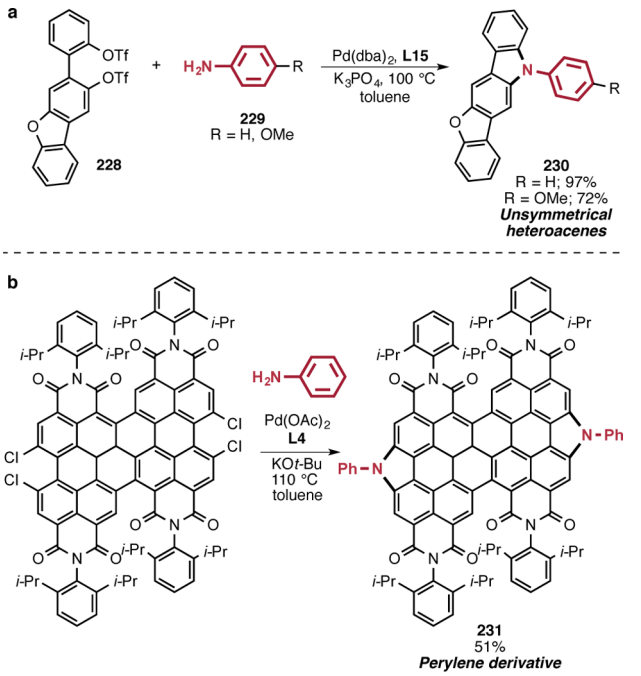
Scheme 43. Synthesis of Materials via the Intermolecular Coupling of Primary Anilines



Scheme 44. Synthesis of Materials via the Intermolecular Coupling of Primary Anilines



Scheme 45. Synthesis of Materials via the Sequential Intermolecular/Intramolecular Coupling of Anilines



benzimidazole (PyrImid) unit, which acts as a fluorescent nucleic acid binding site. In the presence of an **L6**-based catalyst, aniline **226** was successfully coupled with 2-chloropyridine in excellent yield (90%). However, when using 2-chloroquinoline, no product was observed. Alternatively, the reaction with opposite reacting partners, 2-aminoquinoline and the corresponding aryl chloride, provided the desired product, albeit in only 16% yield (not shown).

3.1.4.4. Synthesis of Materials via the Sequential Coupling of Anilines. Nozaki and co-workers applied a double N-arylation protocol to assemble the carbazole unit of unsymmetrical heteroacenes **230** (Scheme 45a).[172] These compounds, containing benzofuran and *N*-arylcarbazole units, behave as hole-transporting materials that can be potentially used in OFETs. The inter- and intramolecular coupling between bisaryl triflate **228** and anilines **229** in the presence of an **L15**-based catalyst and K_3PO_4 furnished the desired products in excellent yields (97% and 72%). With the same strategy, Negri, Wang, and their co-workers synthesized annulated di(perylene bisimide) **231** (Scheme 45b), a polycyclic aromatic hydrocarbon (PAH) with a strain-induced curved structure.[173] Other perylenes have been used as n-type materials, dyes, and pigments, but this uncommon "molecular bowl" and its potential applications in materials science remained unexplored. By using a 2-fold intermolecular N-arylation and subsequent ring-closing aniline coupling, the desired product was formed in 51% using a $Pd(OAc)_2$/**L4** catalyst.

Liang, Xue, and their co-workers prepared a series of unsymmetrical triarylamine-based organic dyes (**232**, Scheme 46a) with potential applications in DSSCs.[174] The core was built by sequential installation of the aryl groups, which was controlled by the correct choice of the supporting ligand. First, a catalyst based on **L3a** allowed for exclusive formation of monoarylated product in 84% yield. Then, the use of **L17** enabled the N-arylation of the secondary aniline in 60% yield. Additionally, Wong, Chou, and their co-workers demonstrated the Pd-catalyzed N-arylation of a very high molecular weight aniline in their synthesis of donor−acceptor dendrimers **233a** and **233b** (Scheme 46b).[175] The dipolar macromolecules contained phenylcarbazole donor (D) and 1,3,4-oxadiazole acceptor (A) units that conferred photoinduced electron

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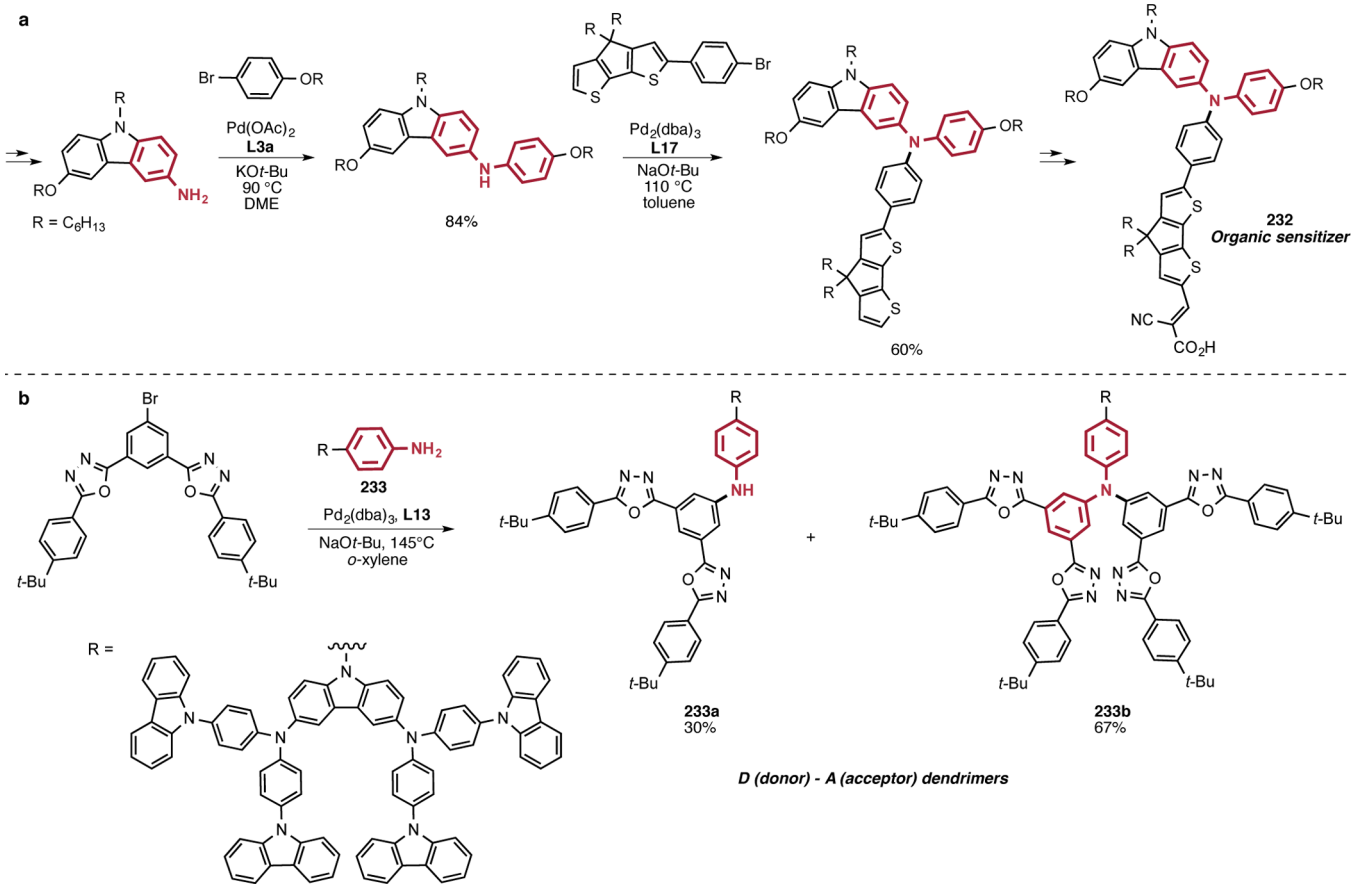
Scheme 46. Synthesis of Materials via the Sequential Intermolecular Couplings of Anilines

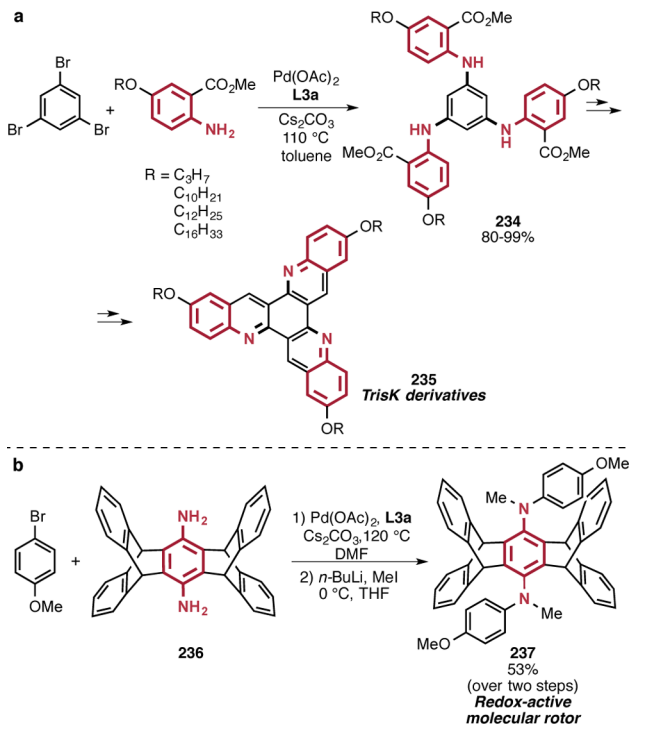


transfer (PET) properties to the material. The aniline linker was coupled to the D fragments via a C−N coupling reaction facilitated by a $Pd_2(dba)_3$/**L13** catalyst, giving rise to dendrimers **233a** and **233b** in 30% and 67% yield, respectively.

3.1.4.5. Synthesis of Materials via the Intermolecular Multiple Coupling of Primary Anilines. To explore the electronic properties and 2D self-assembly ability of π-conjugated systems with trigonal symmetry, Fichou and colleagues prepared a series of 5,11,17-triazatrinaphthylene (TrisK) derivatives (**235**, Scheme 47a).[176] Starting from 1,3,5-tribromobenzene, a triple C−N cross-coupling reaction with ortho-substituted anilines furnished intermediate **234**. In contrast to previously reported syntheses,[177] anilines bearing an *o*-ester group were used in place of those substituted with carboxylic acid groups. After optimization of the reaction conditions,[178] **L3a** was chosen as the ancillary ligand, resulting in an increase of yield from the 36% obtained in previous syntheses to 80−99%. Using bisaniline **236**, Yang et al. synthesized a redox-controlled molecular rotor (**237**) by combining an H-shaped pentiptycene framework with a redox-active *p*-phenylenediamine (PPD) group (Scheme 47b).[179] The two fragments were connected by a 2-fold Pd-induced N-arylation in the presence of an **L3a**-based catalyst (63% yield), and subsequent methylation afforded the desired product in 84% yield.

3.1.5. Applications of the Coupling of Primary Anilines in the Synthesis of Ligands. Fontaine and co-workers (Dow Chemical) designed a Hf-based catalyst that incorporated bidentate ligand **239** for olefin polymerization (Scheme 48a top).[180] The new catalyst proved to be stable and

Scheme 47. Synthesis of Materials via Multiple N-Arylation Reactions



efficiently provided high molecular weight ethylene/1-octene copolymers at temperatures of 120 °C. Initially, the

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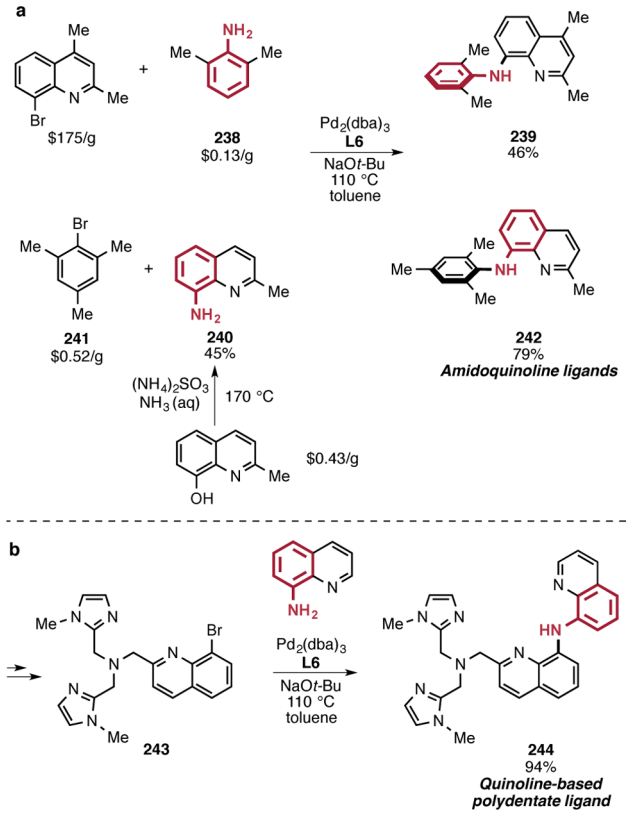
Scheme 48. Examples of Ligand Synthesis via the Coupling of Primary Anilines

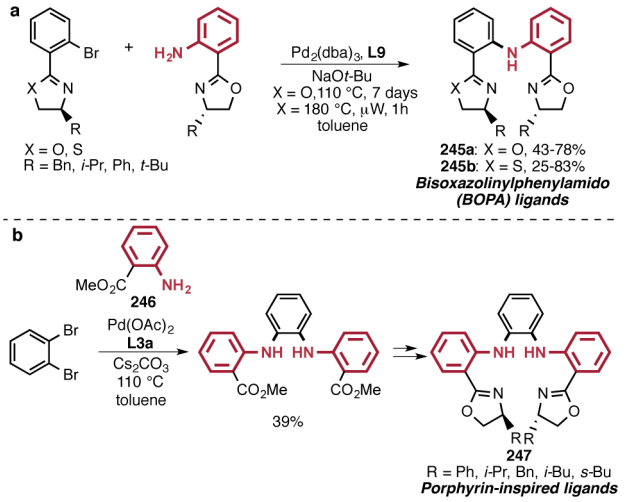


amidoquinoline ligand was synthesized in a single Pd-catalyzed cross-coupling step from 8-bromo-2,4-dimethylquinoline and hindered aniline **238**. However, the high cost of the starting materials and relatively low yield of the transformation made it unrealistic on scale. Alternatively, a related ligand (**242**), prepared through a more cost-effective synthetic route (Scheme 48a bottom), was developed by the same group. First, 8-hydroxyquinaldine was transformed into aniline **240** following a literature procedure. Under identical cross-coupling conditions, intermediate **240** was coupled to aryl bromide **241**, furnishing the final ligand in 79% yield. Although the new ligand was slightly modified from **239**, the key structural components were maintained, resulting in comparable catalytic activity.

Given the interesting properties of polymetallic complexes, Suess and Peters synthesized four polydentate ligands of type **244** (Scheme 48b), which proved able to accommodate multiple metals.[181] The quinoline-based ligands were assembled by combining 8-aminoquinoline and a series of 8-bromoquinolines (**243**) bearing alkyl amino imidazole, pyridine, or alkoxy groups, using an **L6**-based catalyst. Despite the potential ability of both coupling partners to coordinate to the palladium center and poison the catalyst, the cross-coupling reactions proceeded in excellent yield (88−94%).

Since the first report of chiral tridentate bis(oxazolinylphenyl)amine (BOPA) ligands by McManus and Guiry, several variations on their structure have been disclosed.[182] Pd-catalyzed C−N cross-coupling has been a key reaction in the synthesis of BOPA ligands, allowing for the connection of two hindered oxazoline-containing fragments in a highly convergent approach (**245a**, Scheme 49a).[183] More importantly, this strategy has enabled the preparation of unsymmetrical BOPA ligands using fragments with different

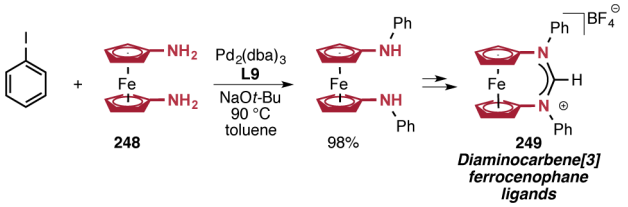
Scheme 49. Examples of the Synthesis of BOPA-type Ligands via the Coupling of Primary Anilines



substitution patterns. For instance, in a recent publication, Guiry and co-workers prepared a series of BOPA analogues containing thiazole and oxazole rings, resulting in a novel non-C_2-symmetric ligand (**245b**, Scheme 49a).[184] Related porphyrin-inspired ligands have also been shown by Gao and co-workers to combine the chiral activity of BOPA ligands with the features of porphyrins (i.e., extended conjugation and the presence of several coordinating nitrogen atoms) (**247**, Scheme 49b).[185] The synthesis of the porphyrin surrogate began with the 2-fold coupling of aniline **246** and 1,2-dibromobenzene using **L3a** as the ligand in moderate yield (40%). Subsequent formation of the five-membered heterocycle led to the final ligand, whose manganese complexes enabled asymmetric epoxidation reactions in the presence of H_2O_2.

Employing the Pd-catalyzed coupling of **248**, Bielawski and co-workers developed a new class of carbene-type ligands bearing a 1,1′-disubstituted ferrocene backbone (**249**, Scheme 50).[186] Diaminoferrocene was coupled with iodobenzene in the

Scheme 50. Ferrocene-type Ligand Synthesis via the Coupling of Primary Anilines



presence of a Pd/**L9** catalyst to yield the desired intermediate in quantitative yield. The final ligands were able to form redox-active complexes with transition metals.

3.2. Secondary Anilines

Due to the larger size of secondary anilines, they are generally considered more difficult coupling partners than primary anilines for N-arylation reactions. With the exception of *N*-methylaniline, *N*-alkylanilines are more challenging compared to diarylamines, presumably due to reduced acidity and the possibility of β-hydride elimination as a side reaction.[4,54] There are a number of applications of the coupling of secondary anilines, with the synthesis of organic materials being the most

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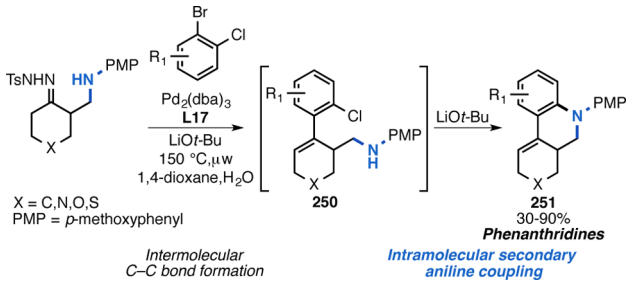
prominent. Catalysts based on **L10**,[52] **L15**,[54] and *N*-arylpyrrole-based monophosphines, among others, have been described for this transformation. However, the most frequently encountered catalyst systems for the coupling of secondary anilines are based on **L3a**[16,187] and dialkylbiarylphosphines, such as **L15** and **L16**.

3.2.1. Applications of the Coupling of Secondary Anilines in the Synthesis of Heterocycles. Barluenga, Valdés, and their co-workers employed the intramolecular N-arylation of secondary anilines in their cascade synthesis of phenanthridines (**251**, Scheme 51).[188] The C−C bond-forming

Scheme 51. Synthesis of Phenanthridines via the Intramolecular Coupling of Secondary Anilines

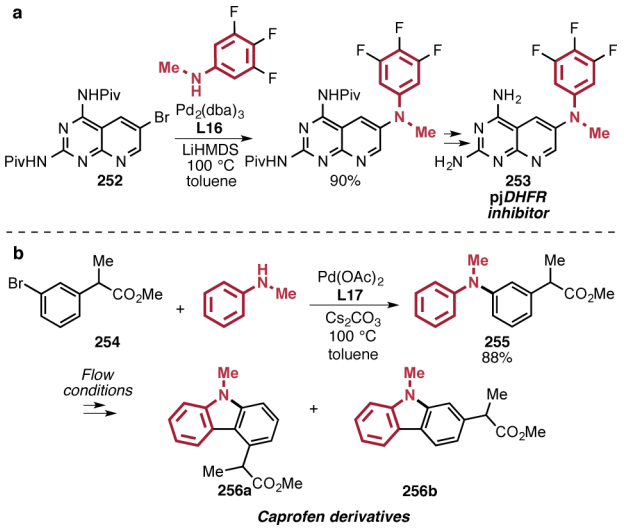


reaction between 1,2-dihaloarenes and tosylhydrazones (obtained from the corresponding *β*-amino ketones) afforded intermediate **250**, and subsequent coupling of the secondary amine yielded the desired tricyclic structures in 30−90% yield. Mixing the hydrazone and the aryl halide with a Pd/**L17** catalyst and LiO-*t*-Bu in a H_2O/1,4-dioxane mixture under microwave heating allowed the process to be performed in a single-flask operation. In addition, the formation of the hydrazone in situ from the corresponding carbonyl and tosylhydrazone was demonstrated, affording the final products in comparable yields. The use of the enantiomerically enriched Mannich adducts provided the corresponding chiral phenanthridines in 92−99% ee.

3.2.2. Applications of the Coupling of Secondary Anilines in Medicinal Chemistry. Gangjee and co-workers utilized Pd-catalyzed C−N coupling in a SAR study of *pj*DHFR inhibitors, promising candidates to treat infections in immunodeficient patients (Scheme 52a).[189] Initially, heteroaryl bromide **252** was successfully combined with primary anilines by employing $Pd_2(dba)_3$/**L17** (not shown). However, the use of *N*-methylanilines under identical conditions resulted in incomplete conversions, presumably due to the larger size of the nucleophile. Switching to a catalyst based on the smaller ligand, **L16** readily generated the coupling products of aryl bromide **252** and a variety of electron-poor, electron-rich, and ortho-substituted *N*-methylanilines in good yields (55−96%). Notably, 3.2 equiv of the base (LHMDS) was required to achieve good results. The introduction of the *N*-methyl group significantly increased the lipophilicity of the final products, and compound **253** was the most potent analogue reported.

3.2.3. Applications of the Coupling of Secondary Anilines in Process Chemistry. Given the significant advantages of photochemical reactions in flow and the potential of continuous processes for large-scale synthesis, Collins and co-workers designed a UV light flow reactor to efficiently generate druglike compounds (Scheme 52b).[190] To demonstrate the utility of this technology, they prepared a series of carbazole-based analogues of caprofen (**256a** and **256b**), a nonsteroidal anti-inflammatory drug. First, Pd-catalyzed N-

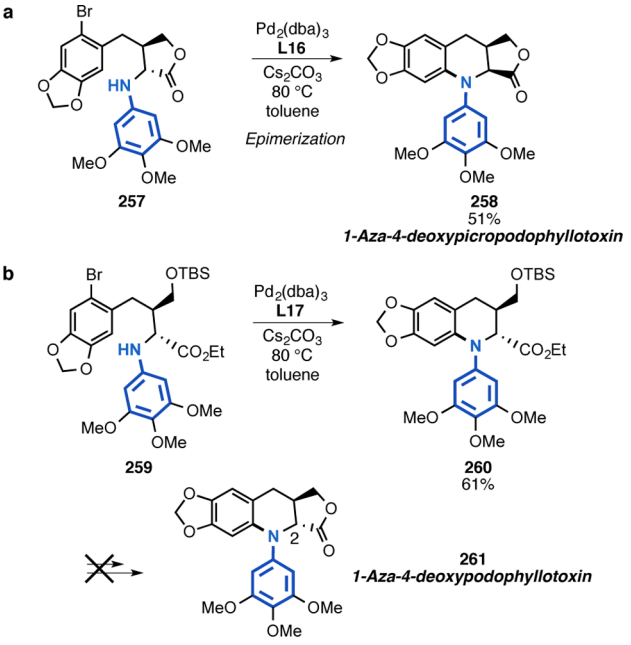
Scheme 52. Synthesis of Drug Candidates via the Intermolecular Coupling of Secondary Anilines



arylation of *N*-methylaniline and aryl bromide **254** afforded intermediate **255** in excellent yield (88%). Subsequent cyclization under photochemical flow conditions in the presence of an oxidant provided **256** as a mixture of isomers.

3.2.4. Applications of the Coupling of Secondary Anilines in the Synthesis of Natural Products. De Borggraeve and colleagues carried out an intramolecular Pd-catalyzed N-arylation in the synthesis of aza analogues of the 4-deoxypodophyllotoxin (DPT) family of bioactive natural products (Scheme 53).[191] In the last step of the synthetic route, compound **258** (1-aza-4-deoxypicropodophyllotoxin) was obtained by subjecting intermediate **257** to C−N coupling conditions using **L16** as the ancillary ligand.[192] Although the intramolecular C−N bond-forming step was successful, the reaction was accompanied by the undesirable epimerization of

Scheme 53. Synthesis of Natural Products via the Intramolecular Coupling of Secondary Anilines



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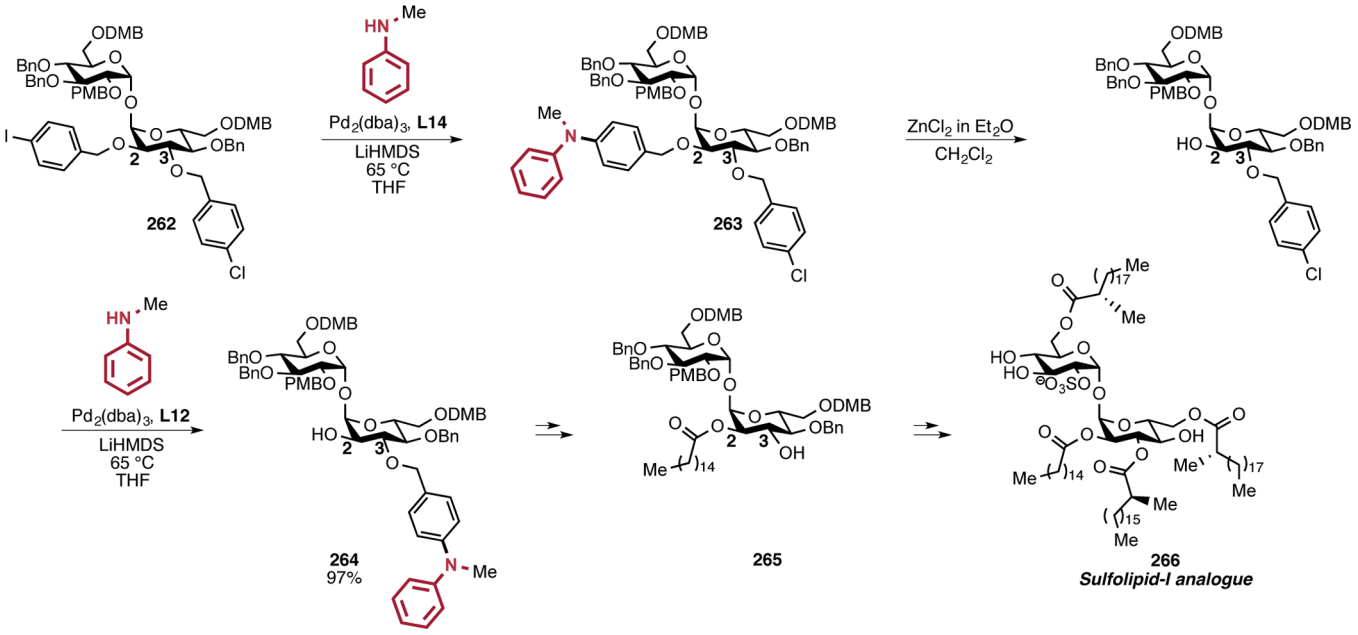
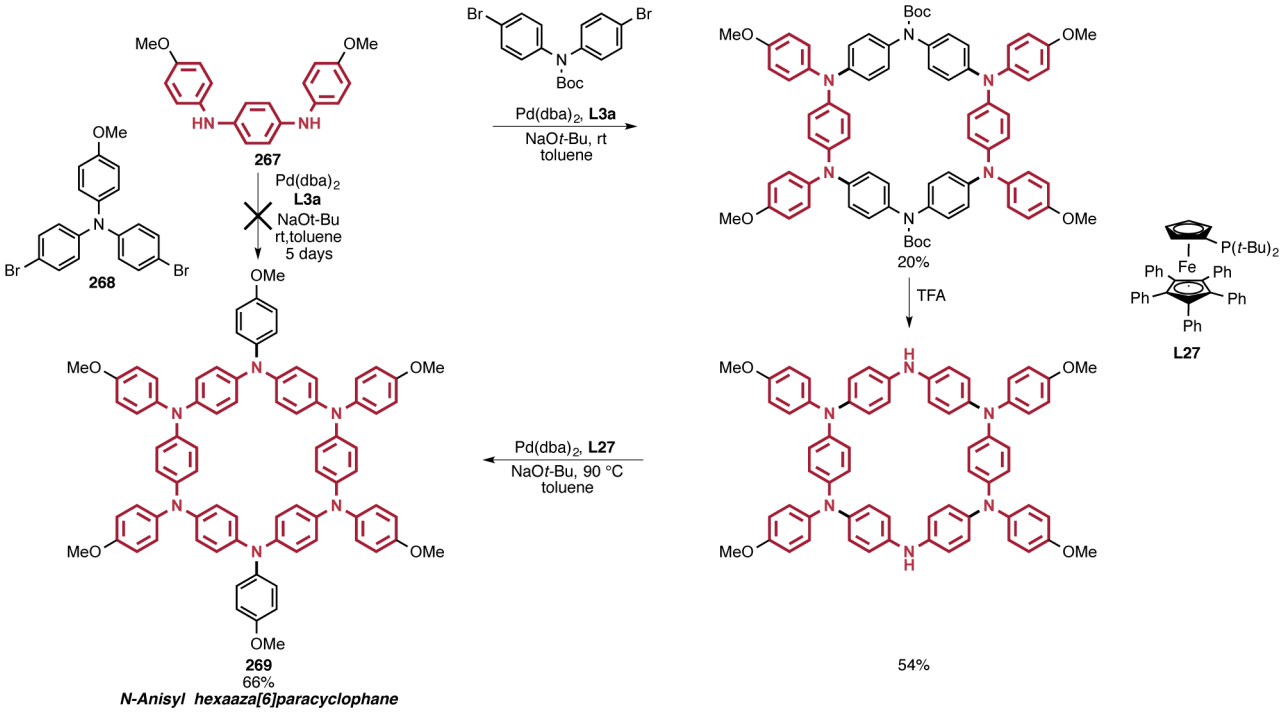
Scheme 54. Use of N-Arylation of Secondary Anilines To Remove Protecting Groups Selectively



Scheme 55. Synthesis of Materials via the Intermolecular Cyclization with Secondary Anilines



the C2 chiral center, presumably to relieve the strain at the trans-fused lactone. Therefore, the multistep sequence was redesigned to access compound **260**, the open lactone precursor of the desired product **261** (1-aza-4-deoxypodophyllotoxin). The intramolecular N-arylation of TBS-protected intermediate **259** was achieved with an **L17**-based catalyst. However, the final lactonization step failed to afford the cis-fused lactone, providing isomer **258** again.

Leigh and Bertozzi performed the intramolecular N-arylation of *N*-methylaniline twice in the synthesis of sulfolipid-I (SL-I) analog **266**, which is a participating metabolite in the pathogenesis of tuberculosis (Scheme 54).[193] Following the strategy for selective cleavage of protecting groups developed by Buchwald, Seeberger, and their co-worker,[194] two halobenzyl ethers, namely, *p*-iodobenzyl (PIB) and *p*-chlorobenzyl (PCB) groups, were first introduced to furnish intermediate **262**. Subsequent N-arylation at the more reactive aryl iodide occurred in the presence of an **L14**-based catalyst to afford species **263**. The amine-functionalized benzyl group was then exclusively removed with zinc chloride, giving rise to the free alcohol. This reaction represents an interesting case where a N-arylation reaction was used to activate a protecting group for subsequent removal. A second N-arylation was then carried out at the benzylic aryl chloride using **L12** as the ancillary ligand to

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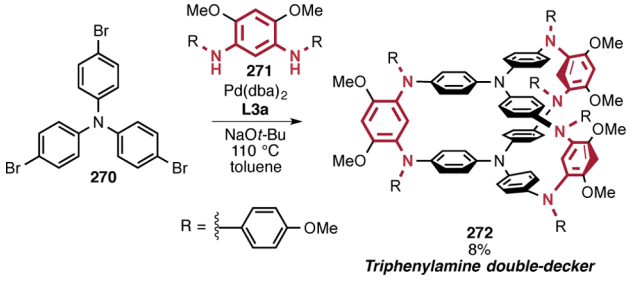
form compound **264** in excellent yield. Subsequent acylation of the C2-hydroxy group and deprotection of the C3 alcohol provided intermediate **265**, which was then transformed into desired product **266**. This synthetic route can potentially be expanded to access a variety of analogues, including the parent compound SL-I.

3.2.5. Applications of the Coupling of Secondary Anilines in Materials Chemistry and Chemical Biology. *3.2.5.1. Synthesis of Materials via the Intermolecular Cyclization of Secondary Anilines.* Palladium-catalyzed C−N coupling has been employed as a powerful synthetic tool to form macrocycles (Scheme 40, section 3.1.4). Ito, Tanaka, and their co-workers have frequently followed this strategy for the construction of organic materials, such as *N*-anisyl-substituted hexaaza[6]paracyclophane (**269**, Scheme 55).[195] As opposed to the intramolecular coupling approach for the synthesis of azacyclophanes **209a** and **209b** (Scheme 41, section 3.1.4.1), macrocycle **269** was obtained via intermolecular N-arylation. Initial attempts to generate **269** in a single step from bisaniline **267** and dibromoarene **268** failed to deliver the desired product. Instead, a three-step route, including two C−N coupling reactions, ultimately provided the macrocycle, which proved suitable to form charge-transfer complexes. Catalysts based on different ligands (**L3a** and **L27**, QPhos, respectively) were used in each C−N bond-forming step. More recently, Ito and co-workers assembled triphenylamine (TPA) double-decker **272** by C−N coupling in order to study the behavior and conformation of the corresponding diradical cation (Scheme 56).[196] TPA-based ammonium radical cations are

Scheme 56. Synthesis of Double-Decker 272 via the Intermolecular Cyclization of Secondary Anilines



typically stable redox reagents or catalysts for organic reactions, as well as spin sources in magnetic materials. However, three-dimensional TPA compounds, such as **272**, are less well studied compared to their two-dimensional analogues due to their challenging preparation. The two TPA planar units in compound **272** were linked via multiple N-arylation reactions at the para positions of the arenes with three bisaniline units. Tris(4-bromophenyl)amine (**270**, 2 equiv) and bisaniline **271** (3 equiv)[197] were reacted in the presence of $Pd(dba)_2$ and **L3a** using NaO-*t*-Bu as the base. Although the desired product was obtained in low yield (8%), this process offers a synthetic route to geometrically complex TPA frameworks that might be otherwise inaccessible

3.2.5.2. Synthesis of Materials via the Intermolecular Coupling of Secondary Anilines. As shown in this section, intermolecular C−N couplings of secondary anilines are robust processes for accessing relevant organic materials, including those with high molecular weights. Liaw and co-workers synthesized polynorbornene-based polymer **275** (Scheme 57a), potentially applicable in optical communications and biomedicine, by Pd-catalyzed N-arylation.[198] The electroactive pyrenyl and TPA components of the polymer were connected by coupling aryl bromide **273** with *N*-alkylarylamine **274** (74%).[199] The reaction was enabled by an **L3a**-based catalyst in the presence of NaO-*t*-Bu. Subsequent ring-opening metathesis polymerization (ROMP) and hydrogenation steps delivered the final polynorbornene, which displayed solvatochromic behavior as well as absorption in the near-infrared region. Under similar reaction conditions but using a weak base, Terazono et al. coupled large diarylamine **276** to prepare hexad-type compound **277** (Scheme 57b).[200] This species was able to reproduce the chemical process through which plants release excess harvested sunlight as heat, preventing any tissue damage or toxin generation. Diarylamine **276**, bearing five Zn−porphyrins attached to a hexaphenylbenzene core, was successfully coupled with rhodamine-type aryl bromide in 47% yield.

A common way to functionalize fluorenes, frequent building-blocks in fluorescent organic materials, is to introduce diarylamines and form the corresponding TPA units. Illustrative is the synthesis of monomer **279**, which was utilized as a genetically encoded tag for protein conjugation (Scheme 58a).[201] Kool and co-workers successfully reacted bromofluorene **278** with diphenylamine in the presence of $Pd(OAc)_2$/**L3a** (67% yield). By using a weak base, the reaction was compatible with a reactive formyl group.

3.2.5.3. Synthesis of Materials via Multiple Intermolecular Couplings of Secondary Anilines. The introduction of diarylamines into the skeleton of organic materials often improves their electronic properties. Palladium-catalyzed C−N coupling reactions with arenes bearing several halides allows for the addition of multiple diarylamines simultaneously (Scheme 40e, section 3.1.4). Scheme 58b,c displays examples of 2-fold cross-coupling reactions between diarylamines and bis-aryl bromides to generate optically active compounds. Shimizu and co-workers prepared a series of near-infrared-active fluorophores (**280**) through a Horner−Wadsworth−Emmons reaction and subsequent $Pd_2(dba)_3$/**L15**-catalyzed C−N coupling with diphenylamine.[202] In another report by Adachi and co-workers, a PEPPSI−**L24** catalyst promoted the N-arylation of secondary anilines with 2,6-dibromo-9,10-anthraquinone to effect the synthesis of red fluorescent molecules **281**.[203]

Additional examples of multiple C−N couplings are shown in Scheme 59. Lee, Seok, and their co-workers performed 4-fold N-arylation reactions of secondary anilines to tune the properties of Spiro-OMeTAD derivatives, units applicable to the fabrication of solar cells (Scheme 59a).[204] A family of *o*-, *m*-, and *p*-methoxydiarylamines were reacted with spiro-fluorene **282** using **L3a** as the ancillary ligand (40−45% yield), with compound **283** showing the highest energy conversion efficiency. Systematically changing the position of the methoxy group on the nucleophile resulted in a variety of materials with different optoelectronic properties. Additionally, Gryko, Blanchard-Desce, and their co-workers employed *p*-methoxydiarylamines to prepare π-expanded diketopyrrolopyrroles (**285**, Scheme 59b), promising fluorophores for bioimaging.[205] Fluorene-based bisaryl bromide **284** and bis(4-methoxyphenyl)amine were subjected to coupling conditions using a third-generation **L15** precatalyst (**L15**−Pd-G3), giving rise to the target compounds in moderate yields.

3.2.6. Applications of the Coupling of Secondary Anilines in the Synthesis of Ligands. The N-arylation of

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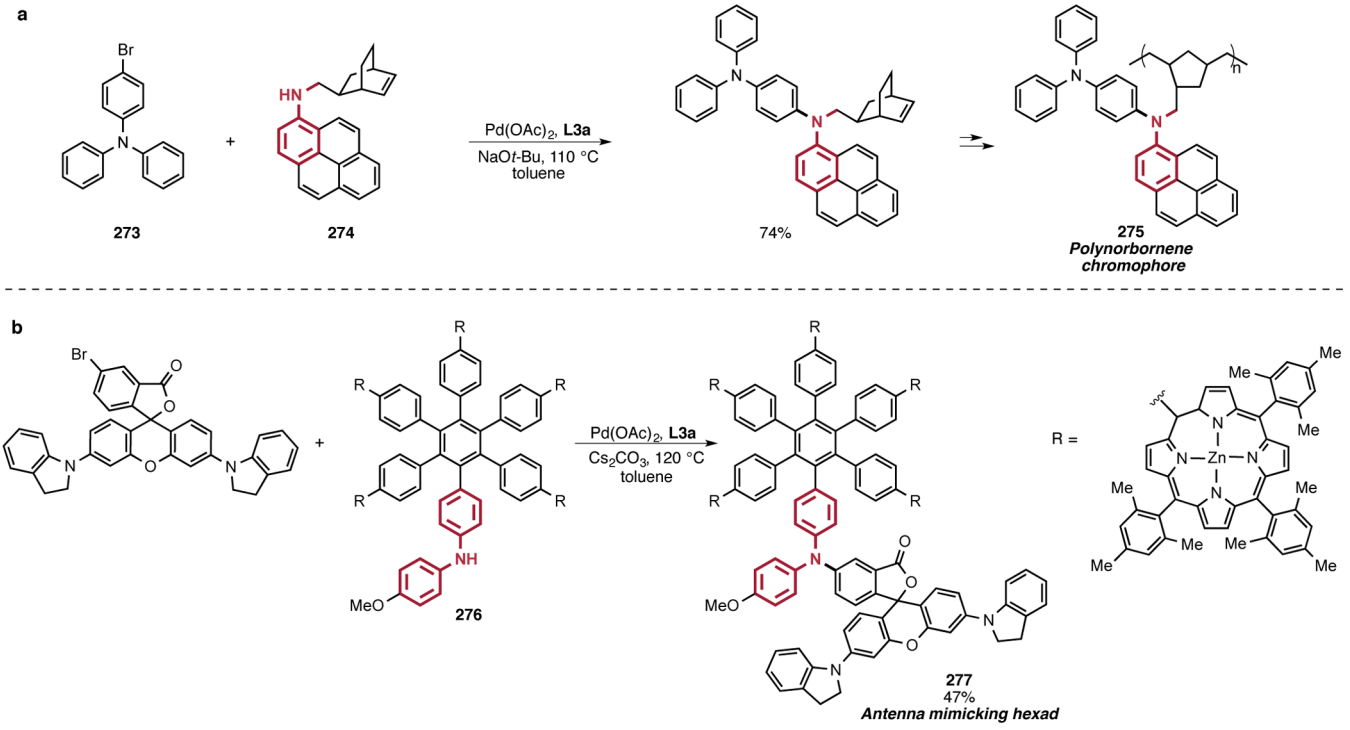
Scheme 57. Synthesis of Materials via the Coupling of Secondary Anilines



secondary anilines has also been utilized for the synthesis of metal-coordinating ligands. Examples of C−N coupling on ligand frameworks (Scheme 60a), as well as direct N-arylation of metal complexes (Scheme 60b), have been demonstrated. Zhong and co-workers prepared a series of structurally diverse mixed valence Ru complexes with optical and redox properties (**287**, Scheme 60a) by systematic variation of the substituents on each tridentate arm.[206] Although terpyridine units could potentially coordinate to the palladium center and impede the catalytic reaction, a series of *p*-methoxy, *p*-methyl, and *p*-chloroanilines were successfully coupled to aryl bromide **286**, giving rise to 12 different ruthenium complexes. Additionally, Meerholz and co-workers synthesized several Ir complexes by direct Pd-catalyzed C−N bond formation between metallacycle **288** and substituted diarylamine **289** (Scheme 60b).[207] A variety of cross-linkable green-emitting complexes (**290**) for the fabrication of OLED devices were successfully generated with this method. The properties of the final compounds were greatly improved by the addition of one, two, or three TPA groups bearing a cross-linkable oxetane fragment into the 2-phenylpyridine ligands.

4. HETEROANILINES

Given the large number and wide range of nitrogen-based heterocycles in biologically active compounds, Pd-catalyzed N-arylation of heteroanilines is a key reaction in the pharmaceutical industry. This transformation offers an alternative to the converse (cross-coupling of heteroaryl halides with anilines), when these substrates are not readily available or provide low reaction yield. Heteroanilines are typically more challenging coupling partners than standard anilines, due to the lower pK_a values and the corresponding decreased nucleophilicity of the amino group,[54] which varies to some degree with the position of the NH_2 on the heteroaryl ring. Often, the amino group is on a carbon adjacent to the heterocyclic nitrogen atom (e.g., 2-aminopyridine, 2- or 4-aminopyrimidine), which results in a structural unit with strong chelating ability, similar to an amidine.[208] However, a number of ligands are able to inhibit the κ^2-coordination of heteroanilines to the palladium center, preventing poisoning of the catalyst. Various methods for N-arylation of heteroanilines have been reported using bidentate ligands **L6** and **L7**.[209] More recently, examples with **L10**[52] and dialkylbiarylphosphines (**L18** and **L19**)[54,210] have also been disclosed. Due to the low solubility of certain heteroanilines in classic apolar C−N coupling-reaction solvents (e.g., toluene), more polar solvents such as *t*-BuOH are required in many cases.

4.1. Aminopyridines

Pyridine is the second most commonly encountered heterocycle in FDA-approved drugs.[40] Thus, there are a large number of applications of the coupling reactions of aminopyridines in medicinal or process chemistry. Despite being the least reactive isomer, the use of 2-aminopyridine as a substrate is most common among the examples of aminopyridine couplings found in the literature. To date, **L7** or **L17** have seen the most success as supporting ligands.

4.1.1. Applications of the Coupling of Aminopyridines in the Synthesis of Heterocycles. *4.1.1.1. Synthesis of Heterocycles via the Coupling of 2-Aminopyridines.* The tandem Pd-catalyzed aniline N-arylation/C−H activation sequence is a powerful synthetic strategy to build carbazoles and related structures (section 3.1.1). As previously shown in Scheme 26b, α-carbolines (pyrido[2,3-*b*]indoles) can be accessed by coupling anilines and 2,3-dichloropyridines. In a complementary approach, α-carbolines were also prepared from 3-bromo-2-aminopyridines and aryl iodides, first by Sakamoto and co-workers[211] and more recently by the group of Mineno and Mizufune (Takeda)[212] (Scheme 61a). Both α-carboline syntheses required different catalysts for each coupling step, as opposed to the one-pot protocols for carbazole preparation

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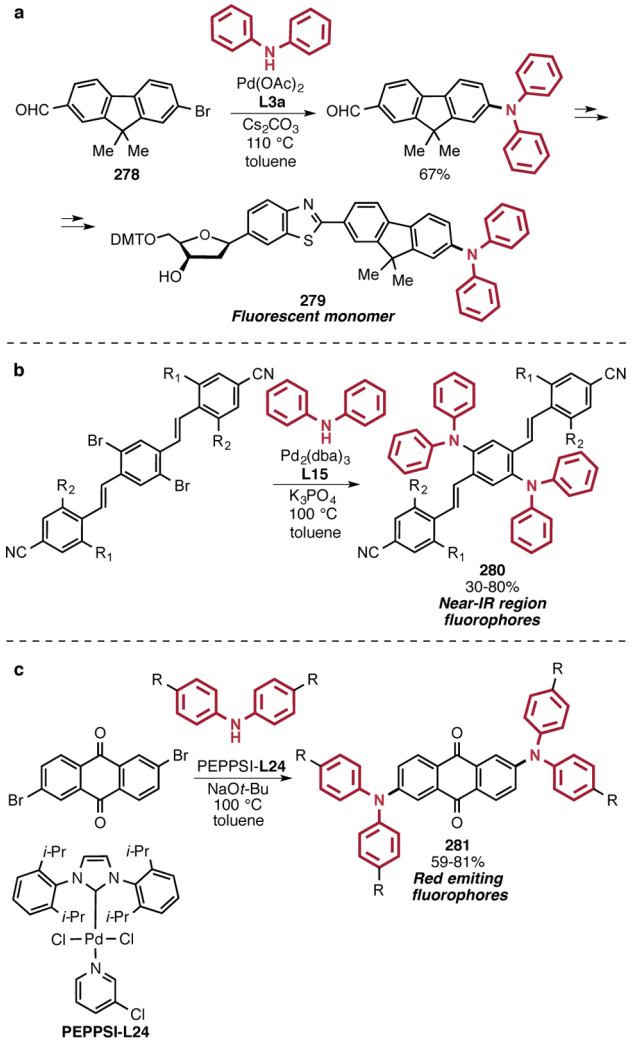
Scheme 58. Synthesis of Materials via Multiple Couplings of Secondary Anilines

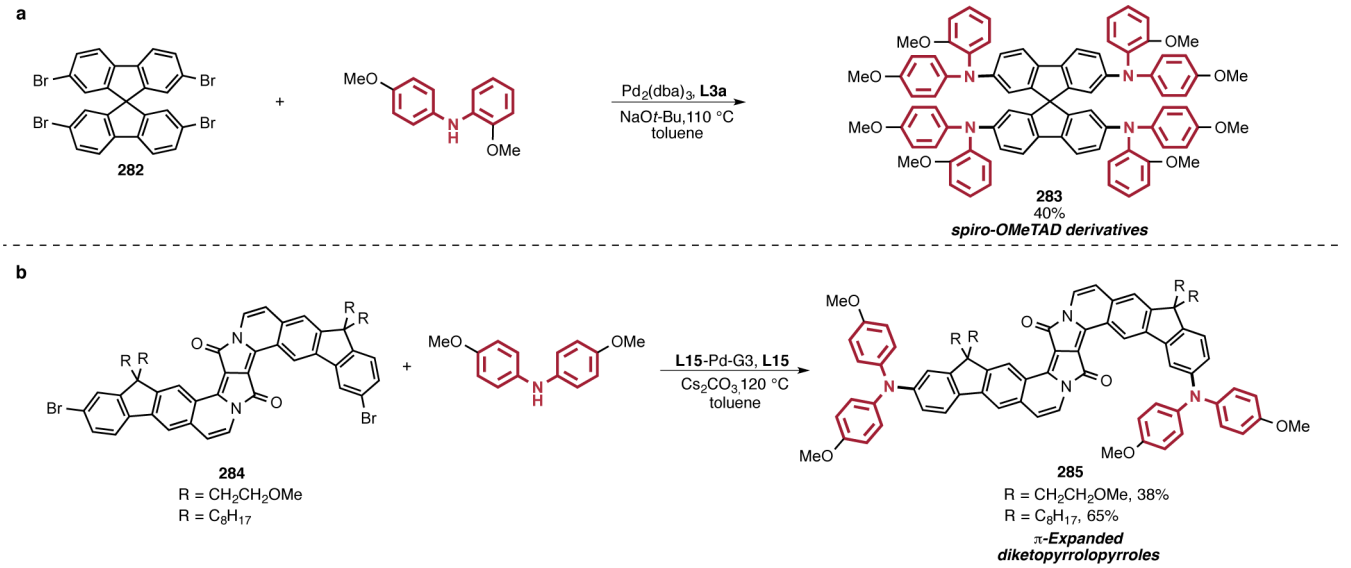


(Scheme 26, section 3.1.1). Selective N-arylation of 2-amino-3-bromopyridine with a variety of aryl iodides led to arylated intermediates of type **291**, which were isolated in 20−68% yield. Next, intramolecular arylation was carried out to yield the α-carbolines in 15−99% yield. Building upon the work by Maes's group,[213,214] Boganyi and Kámán synthesized more complex tetra- and pentacyclic systems (**292**, Scheme 61b).[215] A series of 2-aminopyridines and related nucleophiles (e.g., 2-aminoquinolines, 1-aminoisoquinolines) were successfully coupled to 4-chloro-3-iodoquinoline. The quinoline-fused heterocycles were obtained in 30−84% yield in a domino inter- and intramolecular C−N bond-forming process facilitated by a catalyst based on **L7**.

4.1.2. Applications of the Coupling of Aminopyridines in Medicinal Chemistry. *4.1.2.1. Synthesis of Drug Candidates via the Coupling of 2-Aminopyridines.* Scheme 62 shows several examples of the Pd-catalyzed combination of 2-aminopyridines with functionalized aryl iodides and bromides to generate biologically active targets. Kusakabe and co-workers (Shionogi Pharmaceuticals) arrived at lead compound **294** as a selective Mps1 inhibitor for studies on cancer treatment (Scheme 62a).[216] The reaction between 2,4-diaminopyridine **293** and methyl 4-iodobenzoate using **L7** as the ancillary ligand proceeded in 42% yield but with good chemoselectivity at the C2-position of the heteroaniline. Both nitrile and ester groups were tolerated in the presence of a weak base. Fukaya and co-workers (Dainippon Sumitomo Pharma) also employed **L7** to effect the reaction between polycyclic aryl bromide **295** and 2-aminopyridine (Scheme 62b).[217] The resulting compound **296**, obtained in 53% yield, was a selective TSPO ligand, potentially useful for the treatment of psychiatric disorders. Additionally, Gijsen and co-workers (Johnson & Johnson) synthesized γ-secretase modulator drug candidate **299** as a promising agent for treating Alzheimer's disease (Scheme 62c).[218] Ortho-substituted aryl bromide **297** was successfully coupled to pyridine **298** using **L17**, generating the final product in 63% yield.

4.1.2.2. Synthesis of Drug Candidates via the Coupling of 3-Aminopyridines. Trisubstituted amine **301** (Scheme 63) was one of the two candidates developed by Keenan, Charman, and

Scheme 59. Synthesis of Materials via Multiple Couplings of Secondary Anilines



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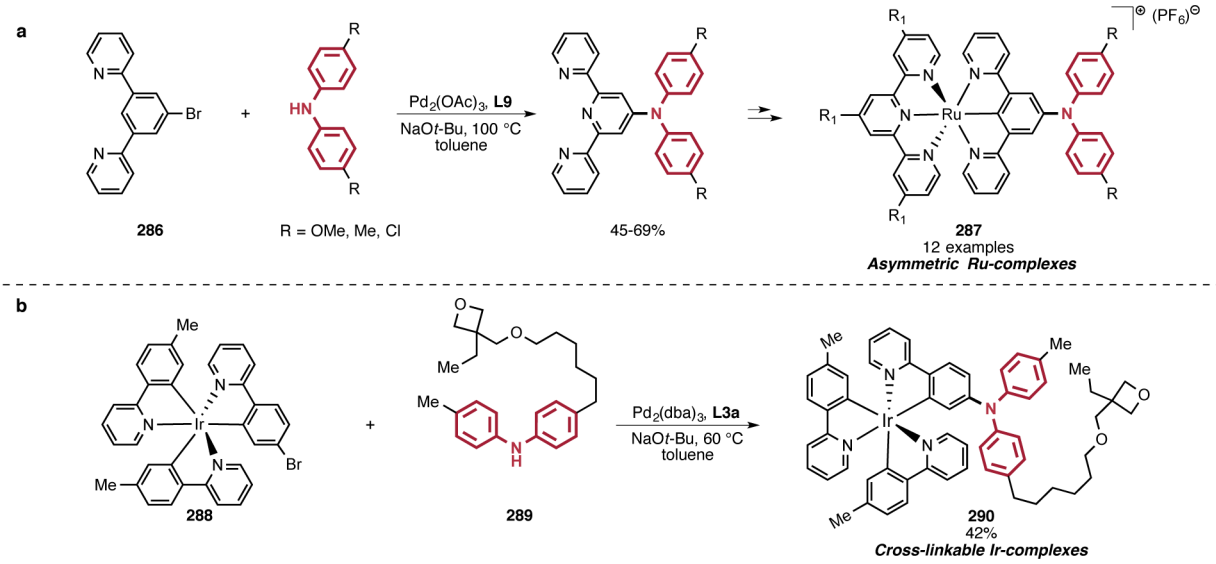
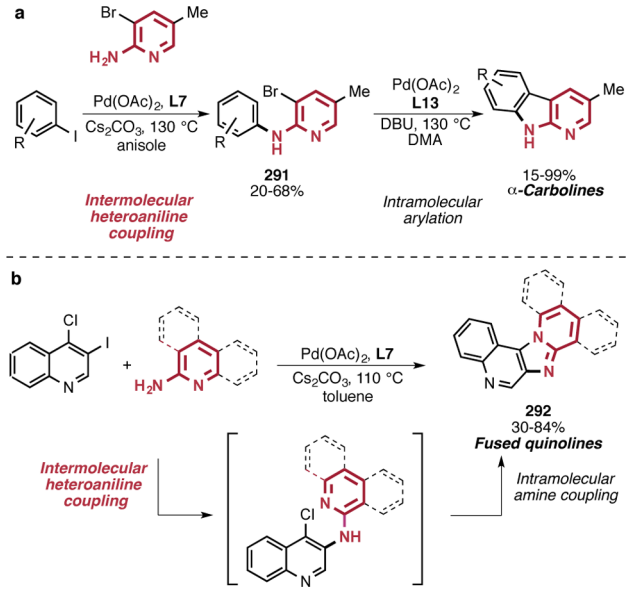
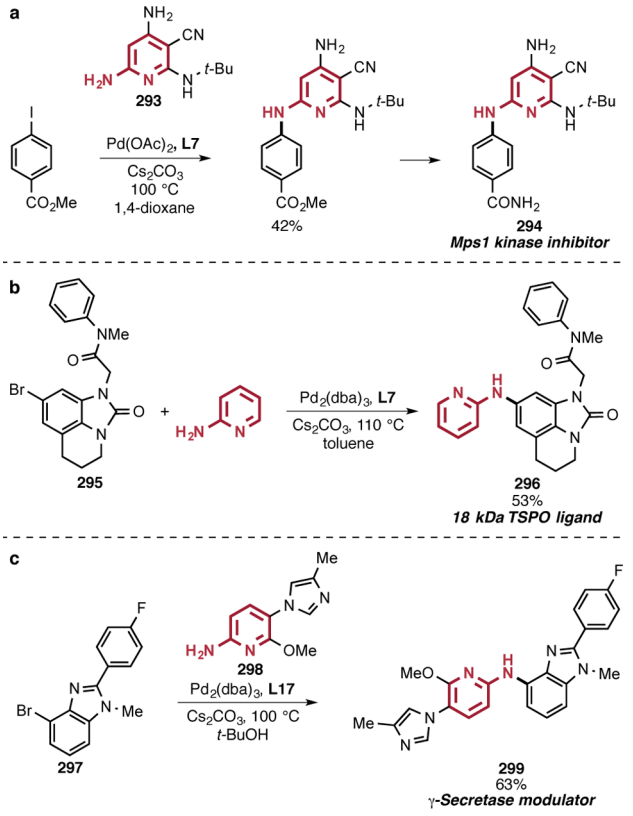
Scheme 60. Synthesis of Metal Complexes via the Coupling of Secondary Anilines



Scheme 61. Heterocycle Synthesis via Intermolecular 2-Aminopyridine Coupling



Scheme 62. Synthesis of Drug Candidates via 2-Aminopyridine Coupling



their co-workers while seeking alternative treatments for Chagas disease.[219] In a straightforward process, compound **301** was produced from commercially available starting materials on a multigram scale (nonoptimized process). Pd-catalyzed N-arylation of secondary 3-aminopyridine **300** with 4-bromobenzotrifluoride occurred in the presence of a catalyst based on $Pd(OAc)_2$/CombiPhos-Pd_6/**L7**[220] in modest yield (42%). The order of the steps in the sequence was crucial, as introduction of the *N*-Boc piperidine by reductive amination was only successful prior to the cross-coupling step.

4.1.3. Applications of the Coupling of Aminopyridines in Process Chemistry. *4.1.3.1. Scalable Synthesis of Drug Candidates via the Coupling of 2-Aminopyridines.* Mineno, Mizufune, and their co-workers (Takeda) applied their α-carboline synthesis protocol[212] to access aurora B kinase inhibitor **304**, a candidate for cancer therapy (Scheme 64).[221] The construction of the α-carboline core in the medicinal chemistry route was achieved via intermolecular Ullmann coupling, followed by intramolecular S_NAr. Although successful on a small scale, the Ullmann reaction presented several scalability issues, such as the use of expensive starting materials, very high reaction temperatures (190 °C), formation of homocoupling side products, and lack of reproducibility. Thus, the synthetic strategy was redesigned and a more efficient Pd-based approach was employed. The carboline unit was obtained by sequential C−N/C−C bond-forming steps from aryl iodide **302** and ortho-substituted 2-aminopyridine

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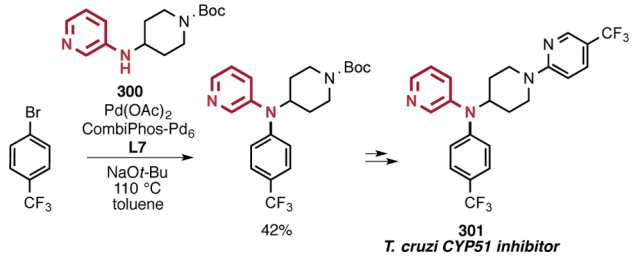
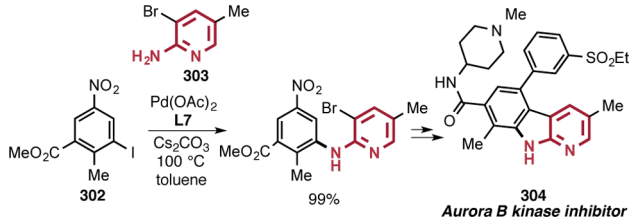
Scheme 63. Synthesis of Drug Candidate 301 via 3-Aminopyridine Coupling



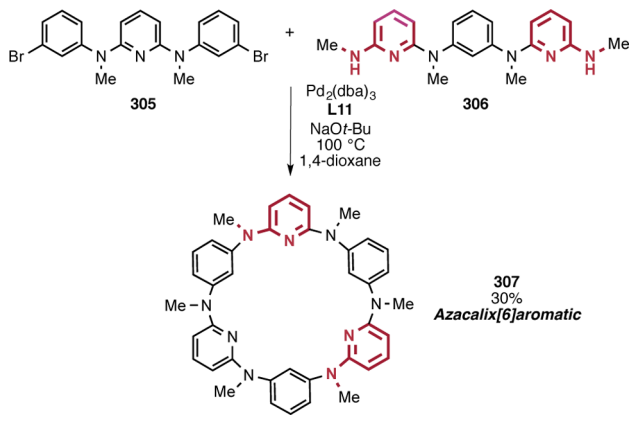
Scheme 64. Scalable Synthesis of Biologically Active Compound 304 via 2-Aminopyridine Coupling



303 under previously reported reaction conditions.[212] The process route resulted in a significant increase in overall yield compared to the medicinal chemistry route (from 11% to 48%).

4.1.4. Applications of the Coupling of Aminopyridines in Materials Chemistry. *4.1.4.1. Synthesis of Materials via the Coupling of 2-Aminopyridines.* Wang and co-workers prepared a series of new heterazacalix macrocycles in order to explore their supramolecular chemistry properties and ability to form host−guest complexes with fullerenes.[222] Specifically, they focused on the synthesis of N-substituted azacalix[6]aromatics based on various benzene, pyridine, and pyrimidine ring sequences (Scheme 65, pyridine-based

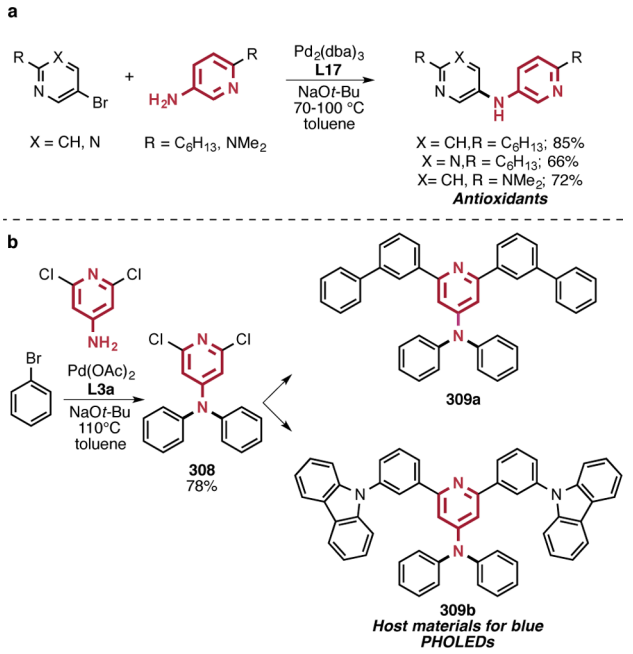
Scheme 65. Synthesis of N-Substituted Azacalix[6]aromatics via 2-Aminopyridine Coupling



azacalix[6]aromatic shown). Previously prepared linear trimers **305** and **306** were combined using a $Pd_2(dba)_3$/**L11** catalyst to provide macrocycle **307** in 30% yield. The yield when analogues of **305** and **306** were used ranged between 23% and 73%. Additionally, cyclizations involving three dimers undergoing head-to-tail C−N bond-forming reactions were feasible.

4.1.4.2. Synthesis of Materials via the Coupling of 3-Aminopyridines. Valgimigli, Pratt, and their co-worker employed the Pd-catalyzed coupling of (hetero)anilines (benzene-, pyridine-, and pyrimidine-based) and (hetero)aryl bromides to prepare a new family of radical-trapping antioxidants (Scheme 66a shows 3-aminopyridine coupling).[223]

Scheme 66. Synthesis of Interesting Materials via the Coupling of 3-Amino- or 4-Aminopyridines



The resulting heterocycles were found to be stable antioxidants that proved suitable as fossil fuel additives over a broad temperature range. The majority of the cross-coupling reactions were carried out in the presence of a $Pd_2(dba)_3$/**L17** catalyst.

4.1.4.3. Synthesis of Materials via the Coupling of 4-Aminopyridines. In search of highly efficient blue phosphorescent organic light-emitting diodes (PHOLEDs), Lee synthesized new chromophores **309a** and **309b** as core structures of the host materials (Scheme 66b).[224] The two phosphorescent compounds were successfully accessed from common intermediate **308**, which itself was prepared via a double Pd-catalyzed N-arylation reaction. On a 60 mmol scale, 4-amino-2,6-dichloropyridine was combined with bromobenzene in the presence of a $Pd(OAc)_2$/**L3a** catalyst, yielding **308** in excellent yield (80%).

4.1.5. Applications of the Coupling of Aminopyridines in the Synthesis of Ligands. *4.1.5.1. Synthesis of Ligands via the Coupling of 2-Aminopyridines.* While exploring NHC ligands, Chianese and co-workers developed a new series of pyridine-based bidentate structures with different steric environments.[225] Two of these ligands derived from benzimidazolium salt precursors **314a** and **314b** (Scheme 67a), which were obtained through a series of Pd-catalyzed N-arylation reactions between hindered substrates. First, Pd-catalyzed coupling of ortho,ortho-disubstituted aniline **310** with 1-bromo-2-iodobenzene using **L8** as the supporting ligand afforded intermediate **311** in 64% yield. Subsequent coupling of **311** with 2-aminopyridines **312a** and **312b** furnished compounds **313a** and **313b** in high yield. Different ligands were employed for each nucleophilic coupling partner. The corresponding NHC-pyridine ligands successfully formed Pd

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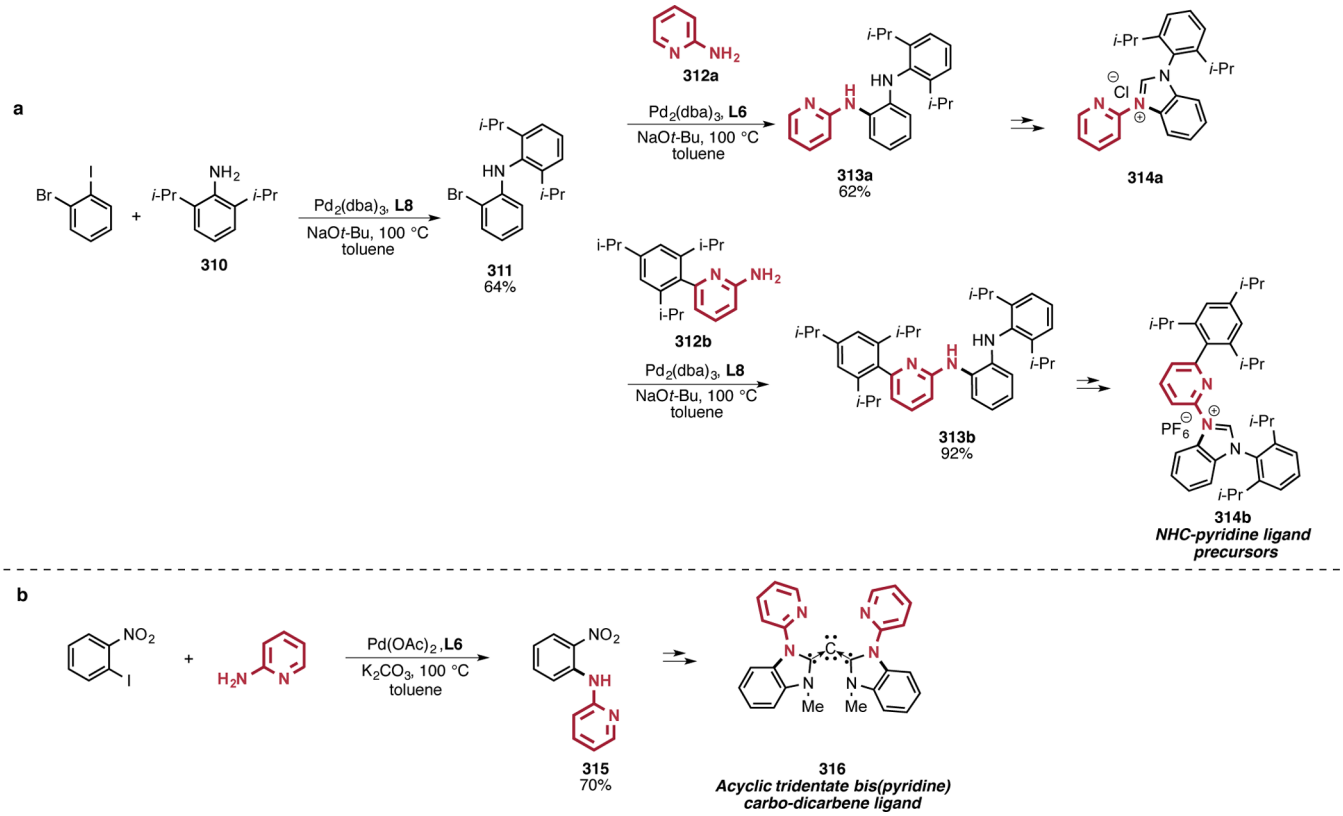
Scheme 67. Synthesis of Ligands via 2-Aminopyridine Coupling



complexes that facilitated the alkylation and amination of allylic carbonates.

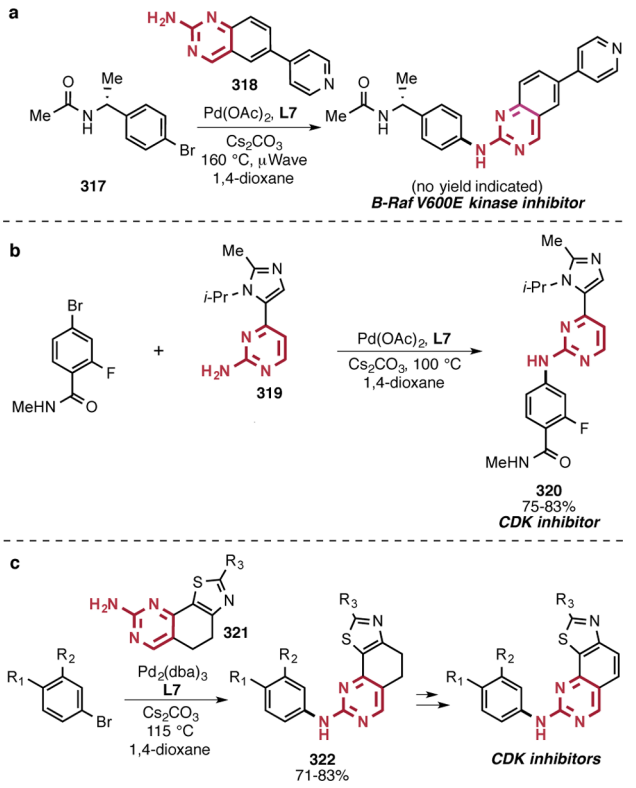
Aiming to explore new carbodicarbene ligands, Hsu, Ong, and their co-workers synthesized and characterized the first pincer-type carbodicarbene **316** (Scheme 67b).[226] The synthetic route toward the tridentate ligands began with the N-arylation of 2-aminopyridine with 2-iodonitrobenzene to afford nitroaniline **315**. The cross-coupling reaction occurred in the presence of a catalyst based on $Pd(OAc)_2$/**L6**, providing the desired intermediate in 70% yield. The use of weak base was required due to the presence of a base-sensitive nitro group. Investigation of the new ligand revealed it possessed predominantly allene character, and the Pd complex derived from it proved to be an effective catalyst for Heck−Mizoroki and Suzuki−Miyaura coupling reactions.

4.2. Aminopyrimidines

Pyrimidine is the 10th most common nitrogen heterocycle in FDA-approved pharmaceuticals.[40] Moreover, 88% of pyrimidine-containing drugs possess an amino group on the arene ring, with 2-aminopyrimidines (38%) and 2,4-diaminopyrimidines (38%) being most prevalent. Despite the low basicity of 2-aminopyrimidines (pK_a = 3.54), the corresponding N-arylation reactions have been successfully accomplished, providing an alternative to *N*-arylguanidine condensation to access the desired (heteroaryl)aryl amines.

4.2.1. Applications of the Coupling of Aminopyrimidines in Medicinal Chemistry. *4.2.1.1. Synthesis of Drug Candidates via the Coupling of 2-Aminopyrimidines.* Examples of drug synthesis in which functionalized 2-aminopyrimidines react with aryl bromides are shown in Scheme 68. In all cases, a catalyst based on **L7** with Cs_2CO_3 as base was used to facilitate the reaction at temperatures over 100 °C. Vasbinder and co-workers (AstraZeneca) identified a new class of B-Raf inhibitors for the potential treatment of

Scheme 68. Synthesis of Drug Candidates via 2-Aminopyrimidine Coupling Reactions



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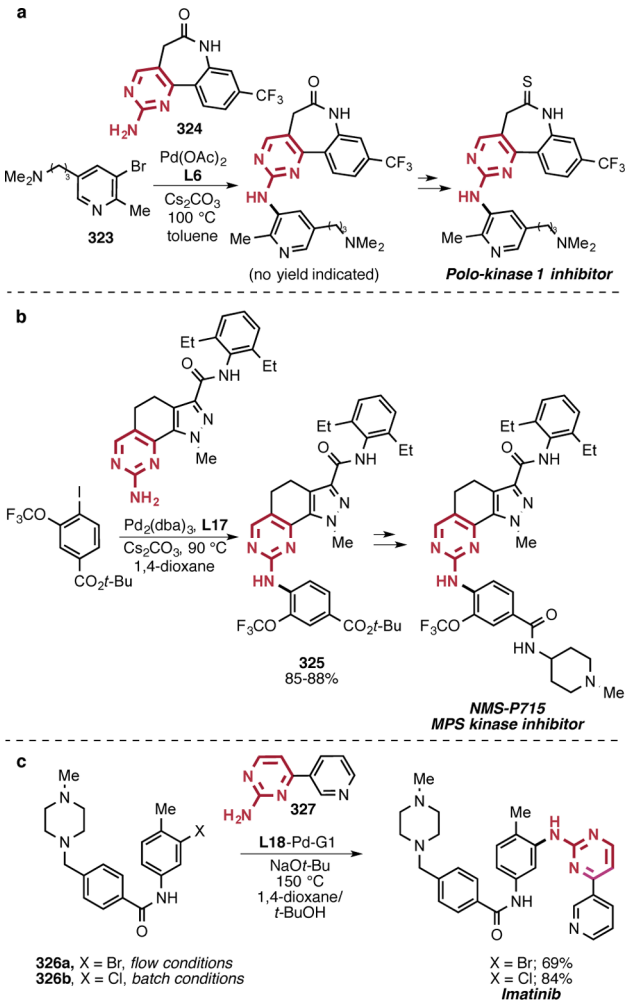
melanoma (Scheme 68a).[227] In the last step of the synthetic route, enantiomerically pure aryl bromide **317** was successfully coupled to 2-aminopyrimidine **318** under microwave-heating conditions. Also at AstraZeneca, Jones and co-workers developed a family of imidazole/pyrimidine-based CDK inhibitors as promising anticancer drugs (Scheme 68b).[228] Previously prepared aminopyrimidine **319** was reacted with a series of activated aryl bromides to afford the N-arylated products, among which compound **320** was found to be most active. Notably, attempts to perform the cross-coupling step with primary amide-containing aryl bromides resulted in bis-arylation side products due to a lack of chemoselectivity. Alternatively, the use of a *p*-cyanoaryl bromide and subsequent hydrolysis of the coupling product provided the desired primary amide. McIntyre et al. prepared another type of CDK inhibitor based on pyrimidine and thiazole units (Scheme 68c).[229] In several cases, *N*-aryl-2-aminopyrimidine intermediates **322** were accessed via enaminone and arylguanidine condensation. When this strategy failed, Pd-catalyzed coupling of primary aminopyridines **321** and aryl bromides was used instead, adapting conditions previously reported by Yin and co-workers.[209] Although poor results were obtained with electron-rich and heteroaryl bromides, the reaction was efficient for electron-deficient and -neutral electrophiles, allowing for the large-scale synthesis of a series of analogues in good yield.

Additional applications of 2-aminopyrimidine cross-coupling for drug discovery are illustrated in Scheme 69. Duffey and co-workers (Millennium Pharmaceuticals) prepared a number of antitumor polo-like kinase 1 inhibitors with a pyrimidine-containing tricyclic core (Scheme 69a).[230] As in previous examples, the (aryl)aminopyrimidine group could be constructed by condensing enamines and arylguanidines (previously made from the corresponding anilines). However, when the required aniline was difficult to access, 2-aminopyrimidine **324** was prepared instead and coupled to aryl bromide **323** in the presence of **L6**.[231] Another class of compounds effective for inhibiting tumor growth was developed by Caldarelli and co-workers (Nerviano Medical Sciences) (Scheme 69b).[232] Pd-catalyzed cross-coupling was applied to access arylated 2-aminopyrimidine structures, such as **325**, using **L6** or **L17** as the supporting ligands. This strategy was also employed as an alternative to the classic guanidine condensation.

The coupling of heteroanilines has also been demonstrated in a flow setting. Ley and co-workers described a continuous synthesis of imatinib (Gleevec),[233] a myeloid leukemia drug developed by Novartis (Scheme 69c). The last step of the flow route involved the N-arylation of aryl bromide **326a** with 2-aminopyrimidine **327**, neither of which were soluble in toluene or xylenes, typical C−N coupling solvents. This issue was circumvented by switching to reaction conditions previously used to couple **327**[234] [$Pd_2(dba)_3$/**L7** in a 2:1 mixture of 1,4-dioxane/*t*-BuOH]. This system allowed for full solubilization of the reagents as well as the use of high reaction temperatures (150 °C). In order to dissolve the NaBr produced as a byproduct of the reaction, a water stream was incorporated at the end of the reaction. Under these conditions, the traditional $Pd_2(dba)_3$ catalyst source resulted in the formation of a significant amount of Pd black. However, switching to the **L18**-G1 precatalyst (10% mol) prevented catalyst decomposition and subsequent clogging. The desired product was formed along with small amounts of unreacted starting materials and the product of aryl bromide **326a** reduction, which required the use of column chromatography to collect the final product in

Scheme 69. Synthesis of Drug Candidates via 2-Aminopyrimidine Coupling



69% yield. Subsequently, Buchwald and colleagues disclosed a two-pot batch synthesis of imantib following this multistep route but with aryl chloride **326b** as the electrophile.[54] In this case, the catalyst loading was reduced to 2% to accomplish the C−N bond formation in 84% yield.

4.2.2. Applications of the Coupling of Aminopyrimidines in Materials Chemistry and Chemical Biology. *4.2.2.1. Synthesis of Materials via the Coupling of 2-Amino-4-pyrimidones.* As an extension of an earlier publication,[235] Gonzalez-Rodriguez and co-workers prepared two modified G-C dinucleoside monomers to study their self-assembly and supramolecular properties (Scheme 70).[236] In the new analogues, the G-N2 amino group was functionalized with two different electron-deficient arenes. The resulting rigid monomers were able to associate by strong hydrogen-bonding interactions, giving rise to highly stable tetrameric macrocycles. In the early stage of the synthesis, para-substituted aryl groups were successfully installed onto G-nucleobase **328** in moderate yield with exclusive selectivity for the aryl iodide.

4.3. Other Diazines

4.3.1. Applications of the Coupling of Aminobenzodiazines in the Synthesis of Heterocycles. Maes and co-workers reported the preparation of five tetraheterocyclic compounds by cross-coupling aminobenzodiazines and 2,3-dihalopyridines.[237] In one-pot processes, two consecutive C−N

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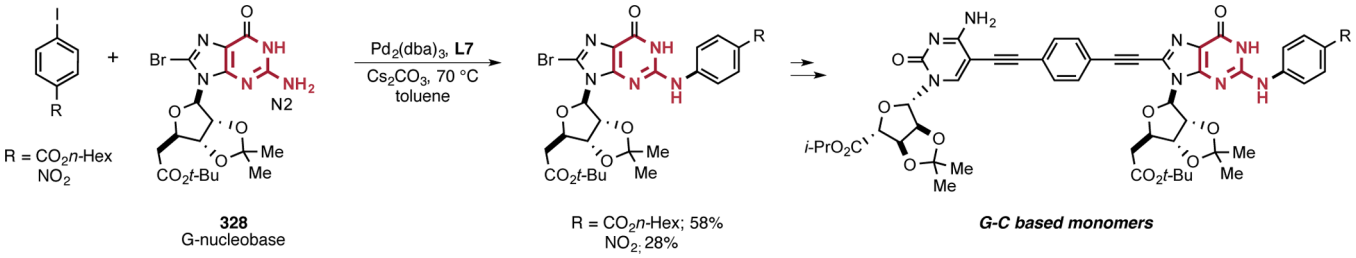
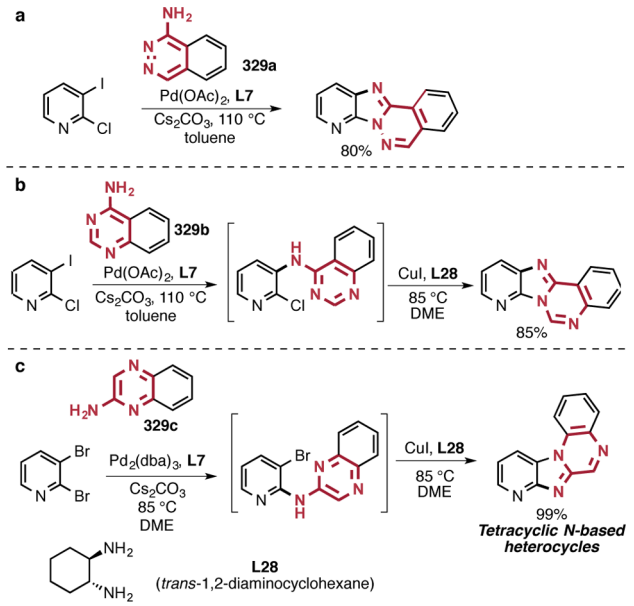
Scheme 70. Nucleobase Functionalization via 2-Amino-4-pyrimidone



bond-formation events occur in tandem (Scheme 71a) or in sequential operations (Scheme 71b,c). In all reactions, a Pd

Scheme 71. Heterocycle Synthesis via Aminodiazine Coupling



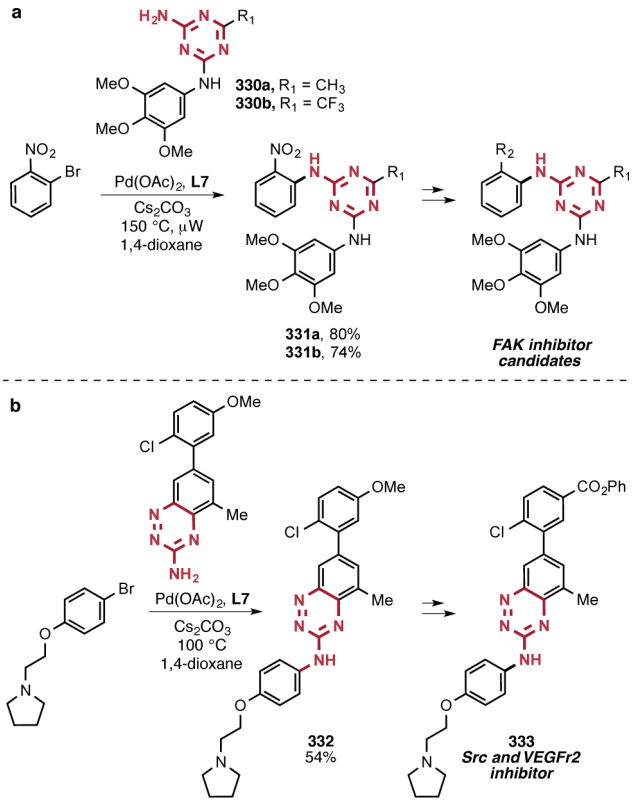
[a]DME = dimethoxyethane.

catalyst based on **L7** facilitated the first step in the presence of weak base and at high temperatures. In certain cases (Scheme 71b,c), a Cu catalyst supported by **L28** was required to achieve the ring-closing step at lower temperatures.[238] The coupling between both 2-chloro-3-iodopyridine and 2,3-dibromopyridine with the three previously prepared (hetero)anilines **329a−c** was successful in most cases.[239]

4.4. Aminotriazines

4.4.1. Applications of the Coupling of Aminotriazines in Medicinal Chemistry. *4.4.1.1. Synthesis of Drug Candidates via Coupling of 2-Amino-1,3,5-triazines.* Typically, the functionalization of the 1,3,5-triazine core is achieved by nucleophilic substitution on commercially available 2,4,6-trichloro-1,3,5-triazine.[240] However, Pd-catalyzed N-arylation of aminotriazines can be a practical alternative in cases where chloride displacement is difficult, such as when only one chloride is present. On the basis of a previous protocol to obtain trisubstituted 1,3,5-triazines through both methods,[240] Chen and co-workers prepared a series of potential FAK inhibitors with angiogenic activity (Scheme 72a).[241,242] Pd-catalyzed C−N bond formation between 1-bromo-2-nitrobenzene and heteroanilines **330a** and **330b** led to compounds

Scheme 72. Synthesis of Drug Candidates via Aminotriazine Coupling



331a and **331b** in excellent yield. The cross-coupling was performed under microwave-heating conditions, allowing for reaction times of 15−30 min.

4.4.1.2. Synthesis of Drug Candidates via Coupling of 3-Amino-1,2,4-triazines. Palanki and co-workers (TargeGen) identified prodrug candidate **333**, an inhibitor of Src kinase and VEGFr (Scheme 72b).[243] This compound was active against age-related macular degeneration, a main cause of vision loss. To obtain intermediate **332**, 4-(2-pyrrolidin-1-ylethoxy)-bromobenzene was combined with 3-amino-1,2,4-triazine in moderate yield.

5. AMINO FIVE-MEMBERED HETEROAROMATIC COMPOUNDS

Due to their frequent presence in biologically interesting compounds, five-membered amino-substituted heterocycles have become versatile building blocks in medicinal chemistry.[244] To date, attempts to employ C−N bond-formation reactions of many five-membered heteroaryl halides have proven challenging, often resulting in low yields of product, catalyst deactivation, or substrate decomposition.[245] As an

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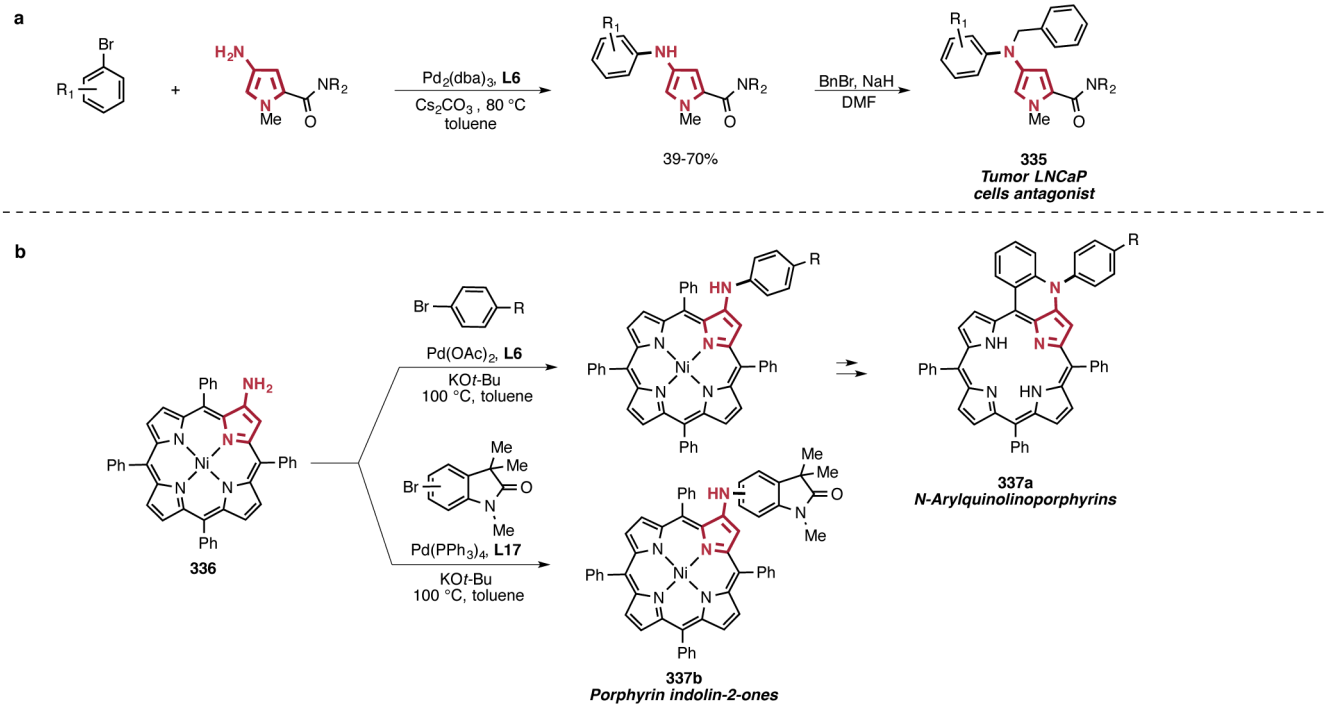
Scheme 73. Examples of Aminopyrrole Coupling



alternative, the N-arylation of the corresponding amino heterocycles has been reported by several research groups.[209,246,247] Thus, despite the sensitivity of five-membered heterocycles to strongly basic conditions, the palladium-catalyzed N-arylation of these compounds has been frequently exploited by medicinal chemists using ligands such as **L6**, **L7**, and **L17**.[208] Temperatures ranging from 60 to 150 °C are typically required to achieve satisfactory yields.

On the basis of their properties, we can distinguish between five-membered heterocycles incorporating one or two heteroatoms. The presence of an amino substituent in π-excessive heterocycles, such as pyrroles, thiophenes, and furans, further increases the electron density of the π-system, rendering them even more susceptible to decomposition. On the other hand, electron-deficient aminoheterocycles are less nucleophilic than typical arylamines. In the case of unprotected nitrogen-containing azoles, competitive N-arylation of the amino and heterocyclic N−H groups can lead to mixtures of products.

5.1. Aminopyrroles

5.1.1. Applications of the Coupling of Aminopyrroles in Medicinal and Materials Chemistry. Among one-heteroatom five-membered heterocycles, N-protected 3-aminopyrroles **334** were successfully arylated by Tanatani and co-workers to access tumor cell antagonists **335** (Scheme 73a).[248] The combination of $Pd_2(dba)_3$ and **L6** using Cs_2CO_3 as the base provided the desired products in moderate to good yields (39−70%). In a different setting, palladium-catalyzed C−N bond formation has proved efficient for the functionalization of complex structures such as porphyrins, valuable compounds for catalysis, as well as supramolecular and medicinal chemistry (Scheme 73b). Following the reduction of 2-nitroporphyrin to the corresponding amine (**336**), a variety of 2-arylamino porphyrins could be accessed using either **L6** or **L17** as supporting ligand. Under these conditions, porphyrins with intense UV−vis absorption bands (**337a**)[249] and containing biologically active fragments (**337b**)[250] were synthesized by Cavaleiro and co-workers.

5.2. Aminothiophenes

5.2.1. Applications of the Coupling of Aminothiophenes in Medicinal Chemistry. Sulfur-containing five-membered heterocycles are typically less challenging substrates for cross-coupling reactions due to their lack of sp^2-hybridized nitrogens and improved stability compared to that of other heterocycles.[251] Several methods have been reported using **L7** as the ancillary ligand for the N-arylation of aminothiophenes. Examples of this transformation using Cs_2CO_3 as base and employing relatively low temperatures (50−60 °C) are shown in Scheme 74. Under mild conditions, potent thiophene-based intermediates for the synthesis of PLK1 inhibitors have been prepared by Emmitte and co-workers (GlaxoSmithKline) in the presence of sensitive nitro and ester functional groups (**338**, Scheme 74a).[252,253] Moreover, this transformation exhibited selectivity for bromides over chlorides and proceeded smoothly with ortho-substituted aryl bromides. Scheme 74b shows the continuous synthesis of the antipsychotic olanzapine (Zyprexa), a drug prescribed for the treatment of bipolar disorders and schizophrenia, which was achieved in 83% overall yield.[254] Kirschning and colleagues replaced the originally reported nucleophilic aromatic substitution step between 2-fluoronitrobenzene and aminothiophene **339** with a Pd-catalyzed cross-coupling reaction, leading to the desired intermediate in high yield (91%) in either THF or EtOAc. The reaction was conducted in a flow reactor filled with steel beads and using high-frequency inductive heating (use of a magnetic field for rapid heating) at 50 °C (higher temperatures led to decomposition and lower ones to reduced yields). The presence of base-sensitive ortho-substituents in both coupling partners was not problematic under these reaction conditions.

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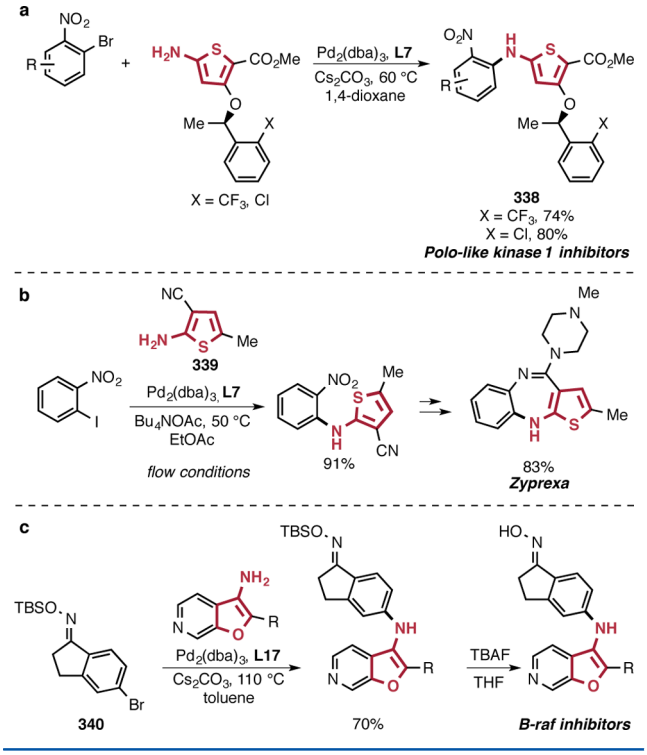
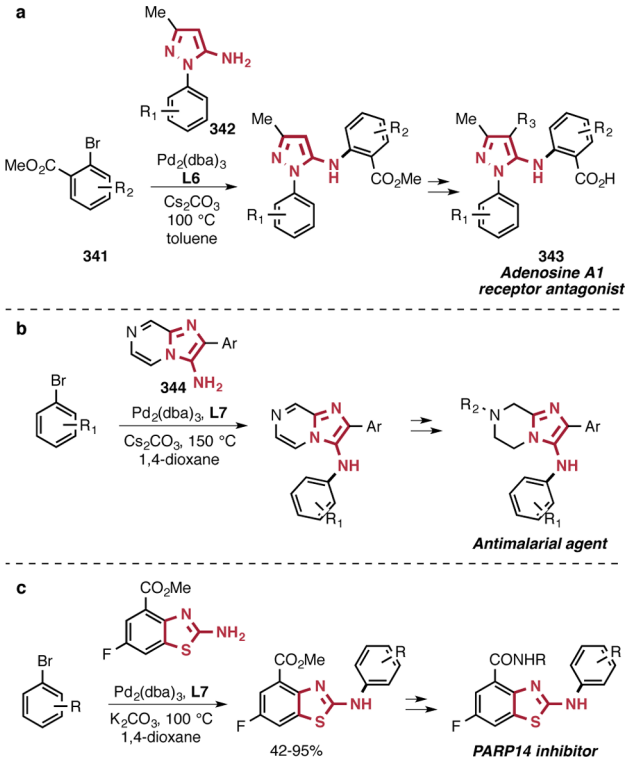
Scheme 74. Synthesis of Bioactive Compounds via Aminothiopehene and Aminofuran Coupling



Scheme 75. Synthesis of Drug Candidates via Aminopyrazole, Aminoimidazole, and Aminothiazole Coupling



5.3. Aminofurans

5.3.1. Applications of the Coupling of Aminofurans in Medicinal Chemistry. Although descriptions of amine-substituted oxygen-based heterocycles are rarely seen (no applications of Pd-catalyzed C−N cross-coupling reactions of aminooxazoles or aminoisoxazoles have been reported), the N-arylation of 3-aminofuropyridines with aryl bromide **340** was a practical means to access potent and selective B-Raf inhibitors (Scheme 74c).[255] Ren, Laird, and their co-workers (Array BioPharma) obtained the corresponding products in 70% yield using an **L17**-based catalyst system and Cs_2CO_3 at 110 °C.

5.4. Aminopyrazoles, Aminoimidazoles, and Aminothiazoles

5.4.1. Applications of the Coupling of Aminopyrazoles, Aminoimidazoles, and Aminothiazoles in Medicinal Chemistry. Five-membered ring arenes with two heteroatoms are ubiquitous structures in biologically active molecules. In particular, thiazole, imidazole, and benzimidazole are, respectively, the 6th, 7th, and 15th most common nitrogen heterocycles in FDA-approved pharmaceuticals.[40] N-Protected (i.e., the heteroaryl nitrogen atom is protected) aminopyrazoles and -imidazoles undergo N-arylation under similar conditions as aminopyrroles, although higher reaction temperatures are typically required. Griebenow and co-workers (Bayer) disclosed a synthetic route involving C−N bond formation between substituted aryl bromides **341** and 5-aminopyrazoles **342** to access a series of compounds to potentially improve renal function (**343**, Scheme 75a).[256] Using a weak base with **L6** as the supporting ligand, an ester group ortho to the reactive site was tolerated. For the coupling of 5-aminoimidazopyrazines **344** with aryl bromides in the synthesis of promising antimalarial agents, Chatterjee and co-workers (Novartis) found that **L7** gave the best results (Scheme 75b).[257] Very high reaction temperatures (150 °C) were required to form the desired products.

Five-membered heterocycles with a nitrogen and sulfur atom, such as 2-aminothiazoles and 2-(arylamino)thiazoles, are also common sulfur-based motifs found in pharmaceuticals. Although aminothiazoles, like amides, are weakly nucleophilic, there are several reports on the direct N-arylation of 2-amino(benzo)thiazoles using **L7**- or **L20**-based catalyst systems.[209,258] This transformation was employed by Wang et al. for the synthesis of PARP14 inhibitors with **L7** as the supporting ligand (Scheme 75c).[259] Utilizing K_2CO_3 as base prevented undesired reactions of the ester group, allowing the synthesis of 2-arylaminobenzothiazoles in good yield.

In the past several years, significant effort has been devoted to developing improved methods for the cross-coupling of amino-containing five-membered heterocycles, in order to employ milder reaction conditions and to expand the substrate scope. Of note is that several recently reported procedures allow the chemoselective C−N coupling of aminoazoles that possess multiple nitrogen atoms as potential sites of arylation. Methods for the N-arylation of unprotected amine-substituted N-heterocyclic compounds in a chemoselective fashion are displayed in Scheme 76. Shen, Hu and their co-workers showed that using Pd-catalyzed cross-coupling conditions, 3-amino-1*H*-pyrazoles (**345**) are arylated at the azole nitrogen atom (N1 or N2).[15] In contrast, nucleophilic aromatic substitution takes place solely at the amino group (N3) under acidic conditions (Scheme 76a).[260] Similarly, Ueda and Buchwald reported the catalyst-controlled chemoselective arylation of 2-aminobenzimidazoles shown in Scheme 76b.[261] The Pd-catalyzed arylation of 2-amino-1*H*-benzimidazoles (**346**) led to the formation of the N2-arylation product (**347**). However, when the coupling

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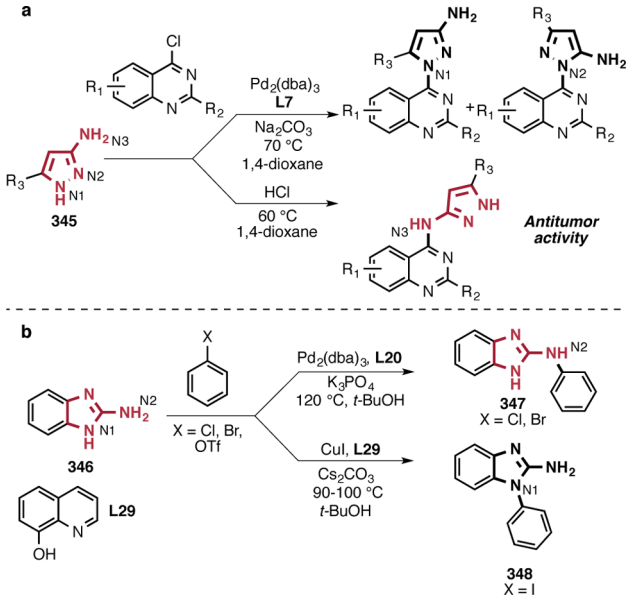
Scheme 76. Recent Methods for Selective Arylation of Unprotected Aminopyrazoles and Aminoimidazoles



was performed using Cu-catalyzed conditions, selective N1-coupling was observed to obtain compound **348**.

6. AMIDES AND AMIDE DERIVATIVES

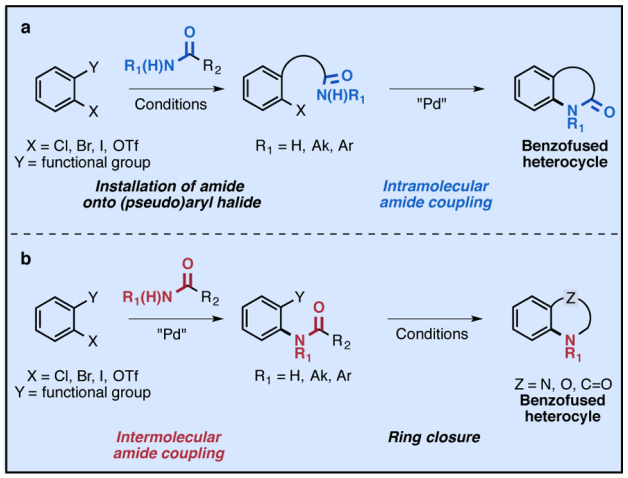
6.1. Primary Amides

The decreased nucleophilicity of amides compared to amines makes them challenging partners in Pd-catalyzed cross-coupling reactions. Moreover, κ^2-amidate complexes, in which both the nitrogen and oxygen atoms coordinate to the palladium center, can form during the reaction and inhibit the reductive elimination step.[262] Despite the inherent difficulties of these reactions, many catalysts have been developed to successfully combine primary amides with arenes over the past few years. Following the first report of intramolecular Pd-catalyzed primary amide coupling,[61] a protocol for the intermolecular version was soon developed for aryl bromides, iodides, and triflates.[18] This early catalyst system, based on **L7** as the supporting ligand and Cs_2CO_3 as the base, is still the most widely employed, presumably due to the availability of the ligand and excellent functional group tolerance. However, the necessity to expand the reaction scope to more accessible aryl chlorides and sulfonates led to the search for alternative ligands. Examples of primary amide N-arylation of aryl chlorides have been shown utilizing catalysts based on **L10**[51] and **L22**,[23] among others.[263,264] A major breakthrough was the use of dialkybiarylphosphines, which resulted in highly active catalysts able to promote the Pd-catalyzed amidation of unactivated (hetero)aryl chlorides[265,266] and sulfonates.[267,268]

6.1.1. Applications of the Coupling of Primary Amides in the Synthesis of Heterocycles. Palladium-catalyzed amide arylation is a practical tool for preparing benzo-fused nitrogen-containing heterocycles. Through the use of tandem or cascade reactions, these methods provide concise synthetic routes, which are often faster than traditional methods. **L7** and biarylphosphines are common ligands employed for amide coupling with reaction temperatures typically between 100 and 110 °C.

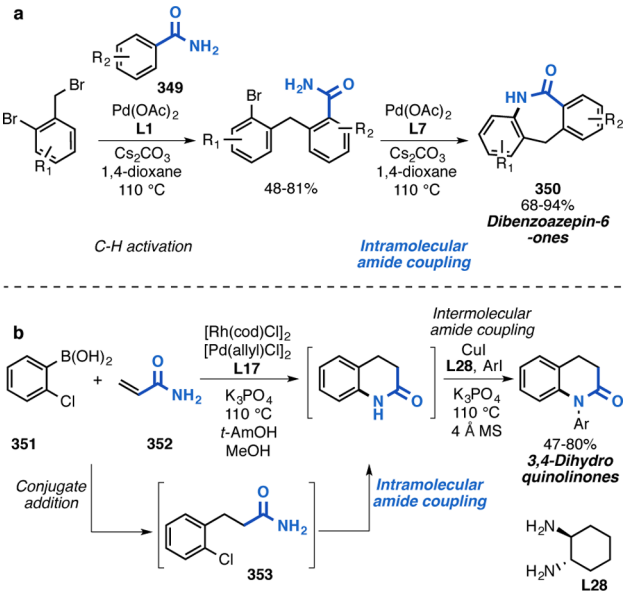
A typical approach for the rapid generation of heterocycles is to first attach an amide group as part of a substituent on an aryl halide and then carry out an intramolecular N-arylation, which gives rise to the desired heterocyclic ring (Scheme 77a).

Scheme 77. General Strategies for Heterocycle Synthesis via Amide Coupling



Following this strategy, Laha and co-workers developed a method to obtain pharmaceutically important dibenzoazepin-6-ones (**350**, Scheme 78a) involving two separate Pd-catalyzed

Scheme 78. Heterocycle Synthesis via Intramolecular Primary Amide Coupling



reactions: an intermolecular C−H activation followed by intramolecular amide coupling.[269] Given the different reactivity of alkyl and aryl bromides, chemoselective ortho-benzylation of primary amide **349** over N-arylation was observed in the presence of catalytic amounts of $Pd(OAc)_2$ and **L1**. Subsequent generation of the seven-membered ring was facilitated by a $Pd(OAc)_2$/**L7** catalyst system. A variety of dibenzo-fused azepinones (**350**) were readily formed in excellent yield. Likewise, Lautens and co-workers exploited Pd-catalyzed intramolecular amide coupling in a highly efficient, multi-

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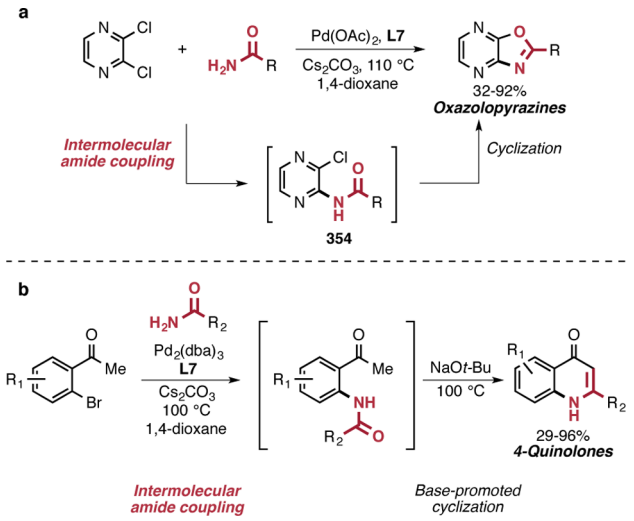
metal-catalyzed cascade process to generate 3,4-dihydroquinolinones (Scheme 78b).[270] The desired heterocycles were prepared through a one-pot protocol, which was performed in two operations. Rh-catalyzed conjugate addition of *o*-chloroarylboronic acid **351** onto acrylamide **352** followed by Pd-catalyzed N-arylation generated the desired 3,4-dihydroquinolone. The use of **L17** enabled amide coupling of unactivated aryl chloride **353**. Further functionalization of the newly formed heterocycle was possible by Cu-catalyzed N-arylation of the lactam with aryl iodides in a second operation (attempts to perform this step with Pd catalysis were unsuccessful). Notably, iodoanilines reacted exclusively with the δ-lactam and no side reactions from the aniline were observed, even in the presence of remaining Pd from the first steps of the sequence.

Other strategies have employed intermolecular amide coupling/cyclization sequences to access heterocycles (Scheme 77b). Bunch and co-workers disclosed a domino-type method to obtain 2-substituted oxazolopyrazines (Scheme 79a).[271]

Scheme 79. Heterocycle Synthesis via Intermolecular Primary Amide Coupling



These uncommon structures, which are closely related to benzoxazoles, possess attractive properties for drug candidates, such as high water solubility and additional hydrogen-bonding sites via the additional nitrogen atoms. The reaction sequence started with a Pd-catalyzed primary amide N-arylation with an activated aryl chloride, followed by Pd-assisted cyclization of intermediate **354**.[272] A related protocol catalyzed by CuI[273] was previously reported for dihaloarenes containing at least one Br or I atom, but the use of Pd catalysis expanded the process to 2,3-dichloropyrazine. A great number of oxazolopyrazines were obtained by employing **L7** as the supporting ligand at 110 °C in 4 h (in most cases). In a related process, Huang and co-workers (Amgen) developed an efficient system to obtain 2-substituted 4-quinolones using a two-operation, one-pot process (Scheme 79b).[274] This method entailed an intermolecular Pd-catalyzed amidation of 2′-bromoacetophenones followed by a base-induced, intramolecular aldol condensation, which afforded the desired heterocycles. The use of a catalyst based on **L7** and a weak base in the C−N bond-forming step prevented competing α-arylation of the ketone. The reaction proceeded smoothly with primary amides derived from alkyl, aryl, and heteroaryl carboxylic acids to provide 4-quinolones in good overall yield (29−96%).

The regioselective synthesis of N-substituted benzimidazoles constitutes a challenging task that has been addressed on multiple occasions. Typically, N-functionalization of benzimidazoles results in the formation of mixtures of regioisomers due to the similar chemical nature of the nitrogen atoms.[275] In 2007, the groups of Buchwald and Ma contemporaneously reported new strategies to prepare the benzo-fused heterocycles based on transition-metal-catalyzed cross-coupling reactions. Through Pd- or Cu-catalyzed C−N bond-forming steps, the imidazolyl nitrogen atom was functionalized prior to cyclization, thus avoiding regioselectivity issues. Both *N*-aryl-[276] and *N*-alkylbenzimidazoles,[277,278] as well as 1*H*-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones[279] were prepared following this approach. Recently, the groups of Clark[280] and Buchwald[281] developed related methods involving primary amide coupling steps to rapidly access benzimidazoles and derivatives with well-defined substitution patterns (Scheme 80). The one-pot preparation of imidazopyridines and -pyrazines reported by Clark and co-workers is shown in Scheme 80a. The synthesis began by cross-coupling primary amides with N-substituted (hetero)chloroanilines (**355**), to afford intermediate **356**. Subsequent condensation/dehydration steps gave rise to benzimidazole derivatives. Hindered di-*tert*-butylphosphino biaryl ligands, such as **L20** and **L21**, in combination with $Pd_2(dba)_3{\cdot}CHCl_3$ and K_2CO_3 were optimal, providing the fused heterocycles in 60−99% yield.[282] Jui and Buchwald disclosed the regio- and chemocontrolled synthesis of *N*-arylbenzimidazoles, which involved two consecutive C−N bond-formation reactions with readily available starting materials (Scheme 80b).[281] Initial Pd-catalyzed aniline N-arylation enabled in situ preparation of halo- or sulfonoxyaniline precursors **358a** and **358b**. Next, amide coupling facilitated by the same Pd catalyst followed by ring closure afforded the final N-substituted benzimidazole. This three-step cascade was easily performed in one-pot and a single operation. The distinct reactivities of the starting materials are the basis of the reaction's excellent regioselectivity. The weakest bond of the 1,2-(sulfonoxy)chloro arene starting material **357** (OTf < Cl < OMs) undergoes preferential oxidative addition, which dictates the coupling site with the more reactive aniline. Subsequent reaction of the less-reactive halogen with the less-reactive primary amide, followed by cyclization, completes the process. The nature of the pseudohalide in compound **357** determines the regioselectivity of the final product: for Z = OTf, the reaction will deliver 5-substituted benzimidazoles, whereas if Z = OMs, the analogous 6-substituted heterocycle will be formed. A notable advantage of this methodology is that the complementary electrophiles can be obtained from the same chlorophenol precursor. Utilizing 1 equiv of aniline, 1.3 equiv of amide **L20**-G3 precatalyst, and Cs_2CO_3 in *t*-BuOH, a variety of related regioisomers were successfully prepared in 62−82% yield with predictable selectivity.

6.1.2. Applications of the Coupling of Primary Amides in Medicinal Chemistry. Examples of Pd-catalyzed coupling of amides in drug development are shown in Scheme 81. Peifer and co-workers developed a protocol to couple primary amides and hindered ortho-substituted aryl bromides to obtain a series of 3,4-diarylquinolinones (Scheme 81a).[283] Similar to the aforementioned method for the synthesis of 4-quinolones (Scheme 79b),[274] the desired compounds were obtained via an intermolecular amide coupling/base-promoted aldol condensation sequence. The Pd-catalyzed N-arylation reaction occurred in the presence of a catalyst based on **L7** using Cs_2CO_3 as base

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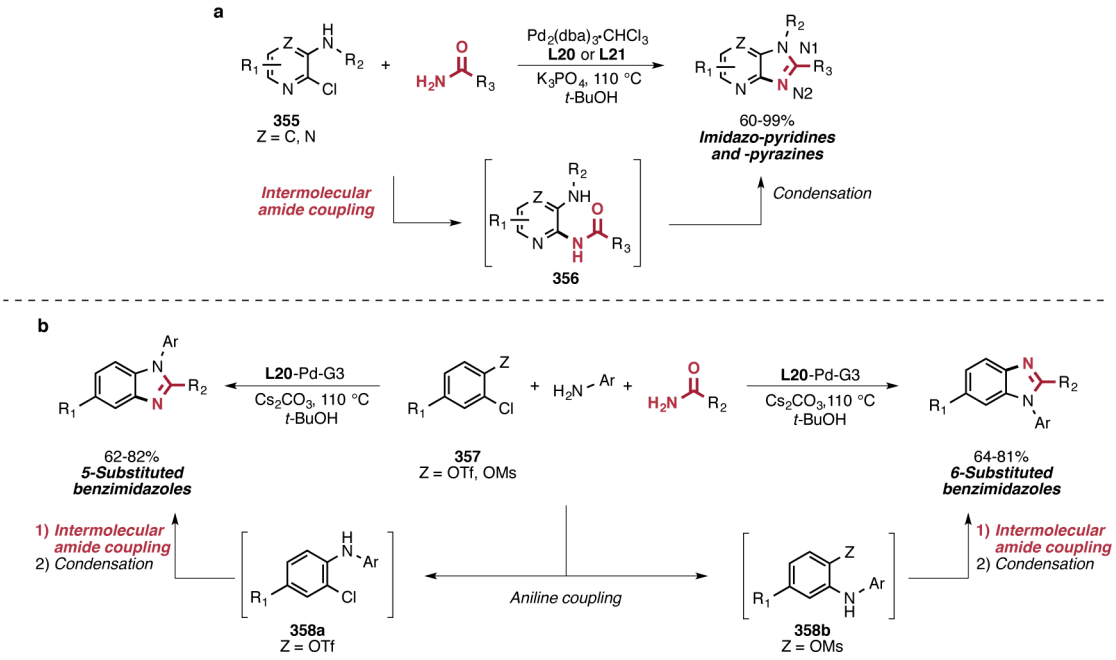
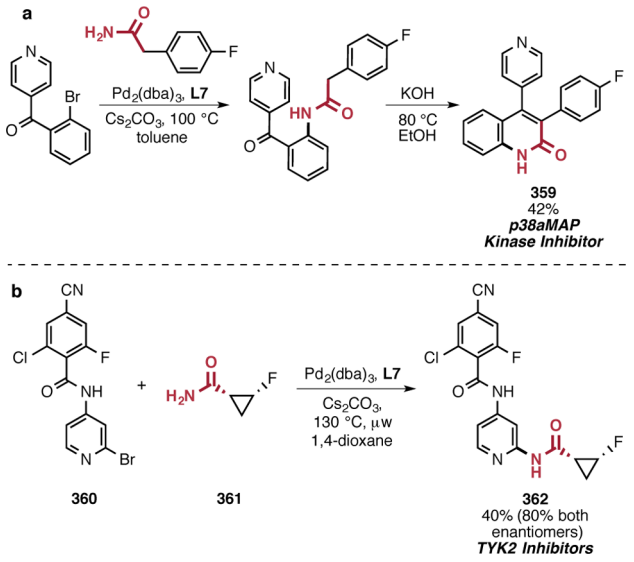
Scheme 80. Benzimidazole Synthesis via Intermolecular Primary Amide Coupling



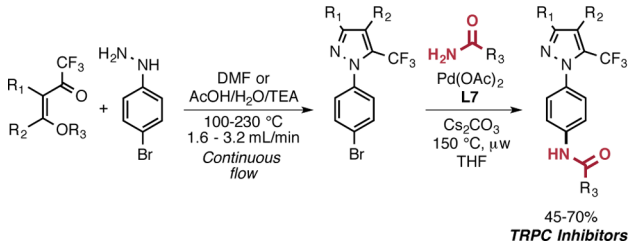
Scheme 81. Synthesis of Drug Candidates via Primary Amide Coupling



in toluene at 100 °C. Among the new series of heterocycles, compound **359** was a lead structure for developing p38a inhibitors, potent candidates to treat inflammation. In addition, chemists at Genentech, ChemPartners, and WuXi AppTec arrived at compound **362** during the optimization process to find new TYK2 inhibitors, therapeutic agents for the treatment of psoriasis and inflammatory bowel diseases (Scheme 81b).[284] Primary amides could be selectively coupled with aryl bromide **360** in the final step of the synthesis, allowing for the exploration of several amide substitution patterns. Using amide **361**, a racemic mixture of TYK2 inhibitor **362** was obtained by employing the same catalyst system under microwave heating in 1,4-dioxane. The reaction tolerated reactive nitrile and amide reactive groups by using a weak base.

6.1.3. Applications of the Coupling of Primary Amides in Process Chemistry. Aiming to develop a general, scalable process, Glasnov, Kappe, and their co-worker reported a procedure for the synthesis of 4-[trifluoromethyl(pyrazol-1-yl)]carboxanilides involving a final C−N cross-coupling (Scheme 82).[285] These compounds had previously been

Scheme 82. Continuous Flow Synthesis of TRPC Inhibitors



disclosed by Mori and co-workers and proved to be active inhibitors of TRPC.[286] The original three-step sequence was improved to a two-step protocol based on continuous flow and microwave-heating technologies. This setup dramatically accelerated the process, reducing the time for the synthesis from days to minutes. The formation of the pyrazole ring was carried out under continuous flow conditions, whereas the $Pd(OAc)_2$/L7-catalyzed N-arylation was accomplished in microwave batch conditions due to the heterogeneous nature of the coupling reaction. The two steps were integrated into one process, generating the desired products in 45−70% overall yield (four examples) and was applied on a multigram scale.

6.1.4. Applications of the Coupling of Primary Amides in the Synthesis of Natural Products. Pd-catalyzed arylations of primary amides have also been applied to the preparation of natural products. Witulski and co-workers employed this transformation in the first total synthesis of antiostatin A1, an alkaloid with antioxidant properties (Scheme 83a).[287] Using a catalyst based on $Pd_2(dba)_3$ and **L7**, the acetamide was coupled to sterically hindered ortho,ortho-

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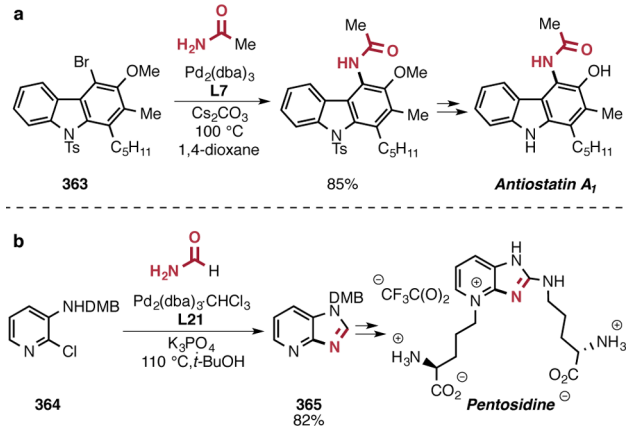
Scheme 83. Examples of Primary Amide Coupling in Synthesis of Natural Products



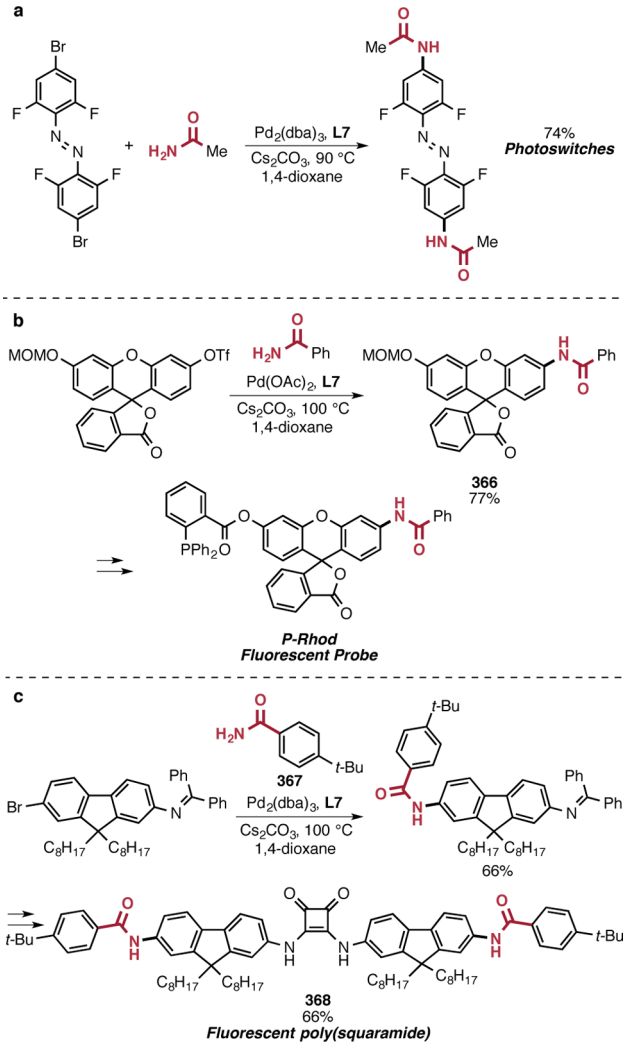
[a]DMB = 2,4- dimethoxybenzyl.

disubstituted aryl bromide **363** in 85% yield. Shortly after their report of the synthesis of imidazopyridine (Scheme 80a),[280] the Clark group applied the same protocol in their six-step route to pentosidine, an advanced glycation end-product (AGE) with fluorescent properties (Scheme 83b).[288] Commercially available 3-amino-2-chloropyridine, protected as the corresponding 2,4-dimethoxybenzyl (DMB) amine (**364**), was coupled with formamide using **L21** as ancillary ligand. Subsequent cyclization afforded the fused heterocycle in 82% yield on a gram scale. The one-pot assembly of the heterocyclic core was a highly chemoselective alternative to monofunctionalization of the benzimidazole product, which is known to be challenging.[275,281] Further modification of **365** led to the desired natural product in six steps in 30% overall yield.

6.1.5. Applications of the Coupling of Primary Amides in Materials Chemistry and Chemical Biology. Compounds displaying interesting optical properties often contain amides conjugated with adjacent aromatic rings (Scheme 84). Bléger and co-workers installed amide groups onto *o*-fluoroazobenzenes in order to modify their absorption spectra (Scheme 84a).[289] The diamide product, which behaved as a potential photoswitch, was obtained in 74% yield in 1 h. Scheme 84b shows the synthesis of P-Rhod, a fluorescent probe used in living cells that was reported by Nakagawa and colleagues.[290] A MOM ether and a triflate group were introduced to differentiate the hydroxy groups of the starting rhodol scaffold, followed by selective cross-coupling between benzamide and the triflate, providing the desired product **366** in 77% yield on a 5-g scale. Taylor and co-workers prepared a series of fluorescent poly(squaramide) polymers for the detection of anions, a function applicable to medical diagnostics, environmental monitoring, and nuclear waste remediation.[291] In the course of their research, they synthesized by Pd-catalyzed cross-coupling nonpolymeric compound **368**, containing the basic unit of the polymers, as a model structure (Scheme 84c). Aryl amide **367** was added to the bromofluorene precursor in the presence of an **L7**-based catalyst, providing the corresponding intermediate in 66% yield.

The Zhang laboratory has used several Pd-catalyzed cross-coupling reactions, including arylation of primary amides, to install a variety of functional groups onto brominated porphyrin precursors.[292] Furthermore, D_2-symmetric chiral porphyrins, useful for asymmetric catalysis, can be accessed using chiral

Scheme 84. Synthesis of Optically Active Compounds via Primary Amide Coupling



amide nucleophiles.[293] Scheme 85a shows a series of amidophenylporphyrins successfully prepared by amide coupling of the tetrabromo derivative **369**. High catalyst loadings [10−40% $Pd(OAc)_2$ and 20−80% **L7**] were employed to promote the four C−N bond-forming reactions. Additionally, a large excess of the corresponding amides and Cs_2CO_3 (16 equiv) and long reaction times (48−96 h) were necessary to obtain the desired products in ∼80% yield. The high yield of this 4-fold transformation is impressive given the steric hindrance of the electrophile. The cobalt(II) complexes of the resulting ligands are efficient catalysts for cyclopropanation,[294,295] $C(sp^3)$−H amination,[296] and aziridination[297] reactions, in some cases asymmetrically, and demonstrate excellent reaction selectivities and catalyst turnovers.[298]

The Masson and Zhu groups collaboratively published an enantioselective aza-Morita−Baylis−Hillman reaction catalyzed by quinuclidine **372** and *β*-naphthol (Scheme 85b).[299] The bifunctional *β*-isocupreidine (*β*-ICD) catalyst was obtained from intermediate **370** by selective Pd-catalyzed intermolecular coupling with amide **371**. The cross-coupling reaction provided the desired catalyst in 73% with catalytic amounts of $Pd_2(dba)_3$ and **L7** in the presence of Cs_2CO_3 as the base.

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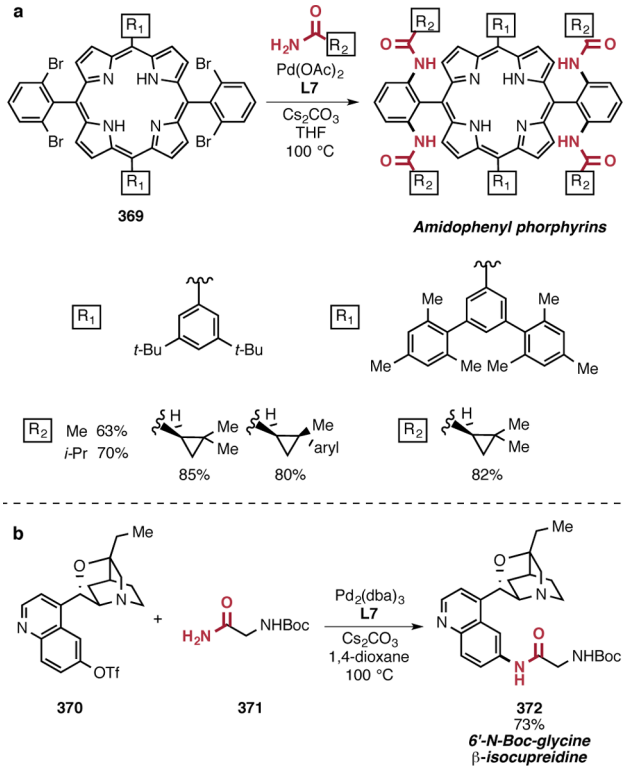
Scheme 85. Ligand Synthesis via Primary Amide Coupling

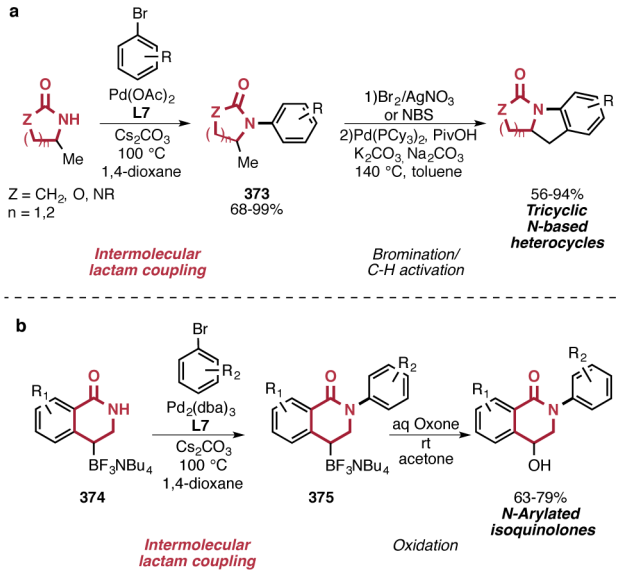


6.2. Secondary Amides

Although numerous methods exist for the N-arylation of primary amides and lactams with (pseudo)aryl halides, far fewer are known for the intermolecular coupling of acyclic secondary amides.[300] As with primary amides, secondary amides are challenging coupling partners due to their reduced nucleophilic nature. The additional steric hindrance at the nitrogen atom can diminish coordination to the palladium center and slow down subsequent deprotonation. Other than early reports of intramolecular N-arylation of secondary amides[301] and scattered examples of intermolecular processes,[302] there is only one detailed report of the intermolecular cross coupling of secondary amides.[303] In this paper, a highly electron-withdrawing diarylbiarylphosphine enabled the coupling of a variety of acyclic secondary amides with aryl nonaflates, triflates, and chlorides. However, **L7** and **L17** remain the most widely used ligands to date for this transformation.

6.2.1. Applications of the Coupling of Secondary Amides in the Synthesis of Heterocycles. In general, the Pd-catalyzed N-arylation of lactams is much easier than that of acyclic secondary amides. Guyonnet and Baudoin employed this transformation in his direct route from γ- and δ-lactams (Z = CH_2, n = 1 and 2, respectively, Scheme 86a) to the corresponding fused tricyclic derivatives found in bioactive alkaloids.[304] Three consecutive steps—lactam N-arylation, regioselective bromination, and C(sp^3)−H arylation—furnished the rigid nitrogen-based systems in an efficient manner. First, five- and six-membered ring lactams were successfully coupled to electron-poor aryl bromides in 68−99% yield using a $Pd(OAc)_2$/**L7** combination, although attempts to expand the reaction to ε-lactams (n = 3) were unsuccessful. In addition, five- and six-membered ring N-arylated carbamates and ureas (Z = O, N) were successfully obtained under the same reaction conditions. Subjecting the N-arylated lactams **373** to electrophilic bromination conditions, followed by intramolecular C−H functionalization, lead to the desired fused 6,5,6- and 6,5,5-membered ring structures. The combined efforts of the groups of Molander and Rombouts (Janssen Pharmaceutical) resulted in a novel Rh(III)-catalyzed annulation reaction to prepare 4-trifluoroborato tetrahydroisoquinolones **374** under mild conditions (Scheme 86b).[305] The boron-containing lactams underwent chemoselective Pd-catalyzed N-arylation, with none of the competing Suzuki−Miyaura cross-coupling product observed. Lactam coupling, enabled by a $Pd_2(dba)_3$/**L7** catalyst, followed by Oxone oxidation (without purification of intermediate **375**), generated the corresponding N-arylated 4-hydroxyisoquinolinones in good yield (63−79%).

Scheme 86. Heterocycle Synthesis via Lactam Coupling



Lactam-containing heterocycles can also be assembled via the intramolecular N-arylation of aryl halides to form δ-lactams (Scheme 77a, section 6.1.1). On the basis of a previous report for the synthesis of indoles,[306,307] Willis and chemists at AstraZeneca disclosed a method to selectively access 2-quinolones via Pd-catalyzed aminocarbonylation followed by intramolecular amidation (Scheme 87a).[308] The two independent C−N bond-forming steps were facilitated by a combination of $Pd_2(dba)_3$ and a ligand (**L3b**, **L7** or **L30**) to achieve high yield. The Larock group reported two strategies to obtain tricyclic lactams involving intramolecular amide coupling steps (Scheme 87b). Fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates **376** was a practical means to generate highly electrophilic arynes, which after Pd-catalyzed annulation afforded N-substituted phenanthridinones[309] and *N*-acylcarbazoles.[310] In the presence of $Pd(OAc)_2$/**L31**, Na_2CO_3, and CsF as the fluoride source, *o*-halobenzamides delivered N-substituted phenanthridinones in 36−87% yield. An excess of benzyne precursor **376** (2 equiv) and CsF (5 equiv), as well as the slow generation of benzyne (promoted by a toluene/acetonitrile mixture), were key to the reaction's success. Similarly, *N*-acylcarbazoles were obtained in 33−77% yield with a catalyst based on $Pd(dba)_2$ and **L9** from *o*-halo-*N*-phenylamides.[311]

The postfunctionalization of Ugi multicomponent reaction (MCR) products by the intramolecular cross-coupling of secondary amides is an interesting synthetic application.[312,313] Using the operationally simple, sequential Ugi MRC/N-

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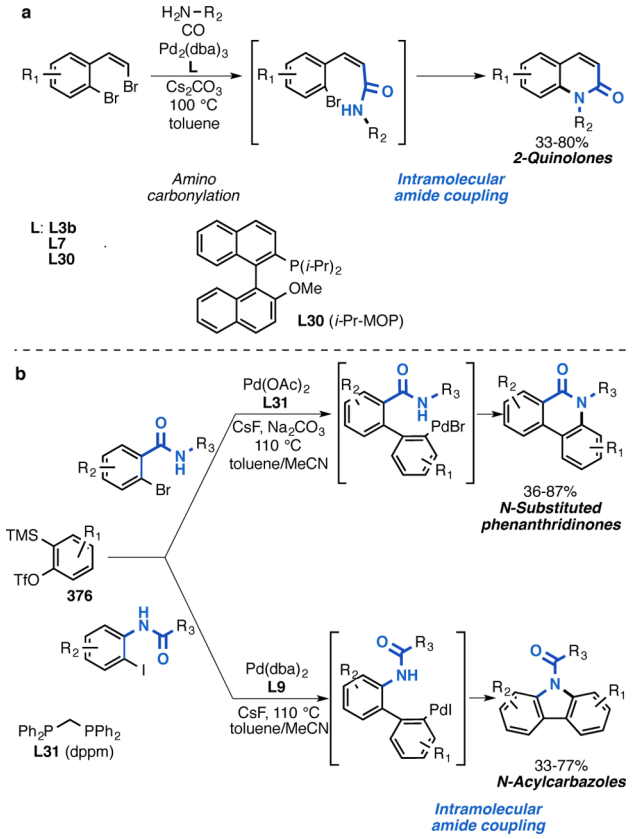
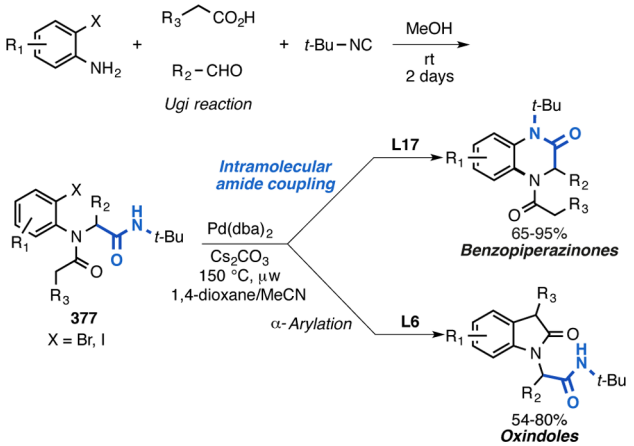
Scheme 87. Heterocycle Synthesis via Intramolecular Secondary Amide Coupling



arylation reactions, compounds with a high level of diversity can be efficiently obtained from readily available starting materials. The structural variability offered by MCR adducts makes them attractive precursors for a wide range of heterocycles.[314] Following this approach, Neuville, Zhu, and their co-worker developed a direct route to benzopiperazinones and oxindoles by exploiting the amide reaction sites of a single Ugi adduct (**377**, Scheme 88).[315] The reaction pathway was dictated by the combination of ligand choice and the presence of a hindered *tert*-butylamide (derived from *tert*-butyl isocyanide). In the presence of dialkylbiarylphosphine **L17**, intramolecular N-

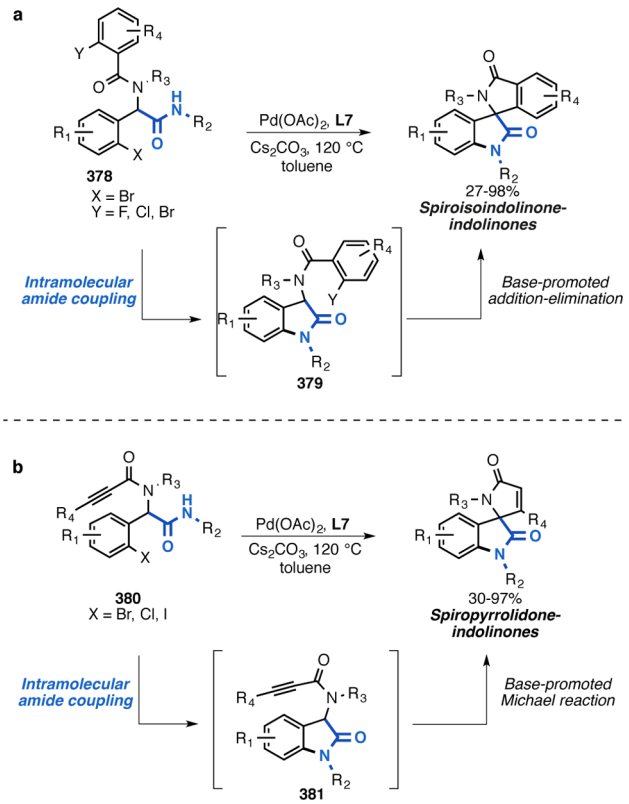
Scheme 88. Post-Ugi Functionalization via Intramolecular Secondary Amide Coupling



arylation afforded bioactive 3,4-dihydroquinoxalin-3-ones (benzopiperazinones) in 65−95% yield. The reaction gave better results with aryl iodides and bromides, whereas low conversions were observed with aryl chlorides. With **L6** as supporting ligand, intramolecular α-arylation of an in-situ-formed amide enolate occurred to generate 2-(2-oxoindolin-1-yl)acetamides (oxindoles). The excellent chemoselectivity of the two reactions can be ascribed to the differences between a mono- or bidentate ligand: amide coordination is facilitated with **L17**, a monodentate ligand, and a C−N bond results. The chelating ligand **L6** prevents coordination of the bulky *tert*-butyl amide and enolate formation, and subsequent five-membered ring closure is the predominant outcome.

Van der Eycken and co-workers published a related post-Ugi functionalization to construct complex spiroindolinones from analogous intermediates (Scheme 89). From Ugi precursor **378**

Scheme 89. Synthesis of Spiroindolinones



featuring a tertiary benzamide group, spiroindolinone−isoindolinones were formed in moderate to excellent yield (27−98%) through sequential amide coupling/addition−elimination steps via intermediate **379**.[316] Likewise, alkyne-containing Ugi adduct **380** was transformed into spiropyrrolidone−indolines (30−97% yield) by domino amide N-arylation and Michael addition reactions involving intermediate **381**.[317] These methods represent an ideal alternative to traditional isatin functionalization protocols to obtain spirooxindoles[318] due to the simplicity of the reaction setup and the broader scope offered.

Liu and co-workers viewed the Ugi reaction/postfunctionalization sequence as a valuable approach for preparing large libraries of structurally diverse fused heterocycles with druglike properties (Scheme 90).[319] In addition to altering the peripheral substituents of drug candidates, the group focused

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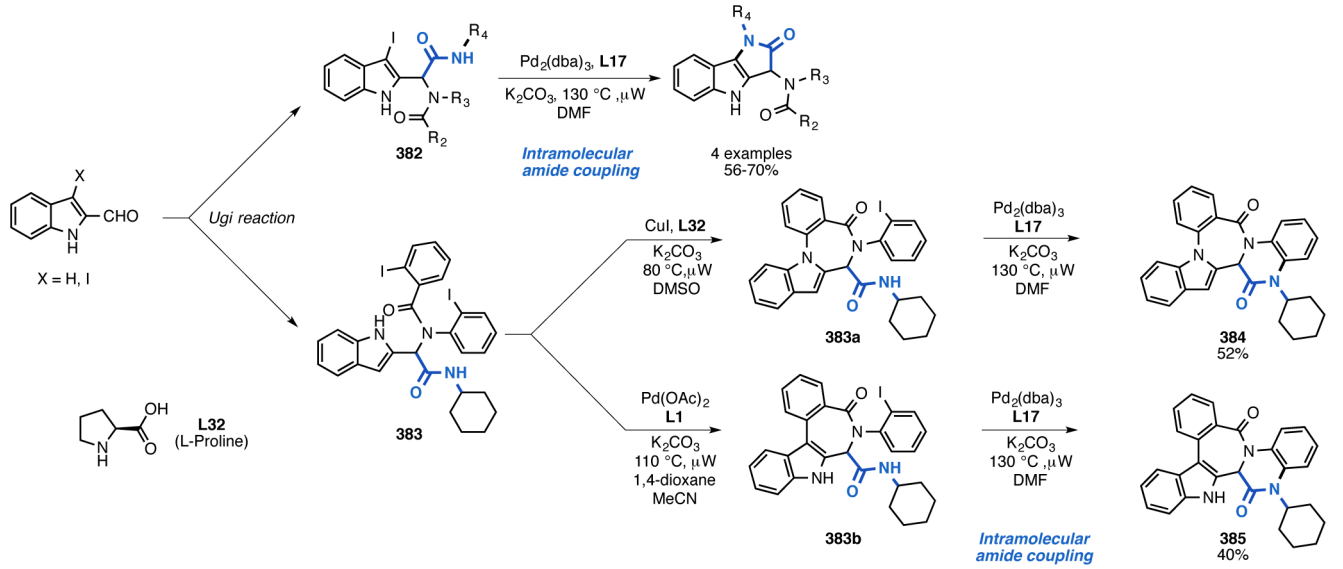
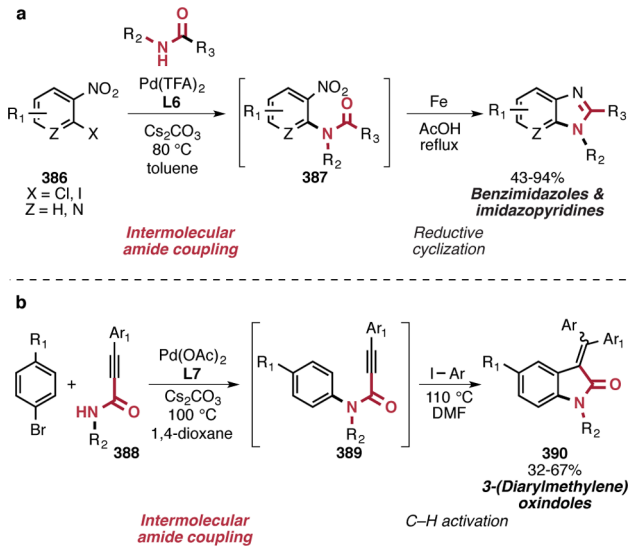
Scheme 90. Post-Ugi Functionalization via Intramolecular Secondary Amide Coupling



on increasing their diversity of core structures, something that is not typically explored. Thus, a library of 50 indole-based compounds bearing 10 distinct scaffolds was obtained in a maximum of three steps from commercially available small molecules through sequential Ugi four-component reactions and a variety of microwave-assisted postcyclizations. Ugi adduct **382** was directly transformed into a variety of 6,5,5-polycyclic heterocycles via the Pd-catalyzed amide coupling between the secondary amide and the 3-iodoindole present in the molecule. Initial attempts using a copper-based catalyst resulted in large amounts of reduction product, whereas the use of Pd catalysis provided the desired products in moderate to good yields (56–70%). A more functionalized Ugi precursor (**383**), incorporating two aryl iodides, multiplied the reaction possibilities, giving rise to more complex heterocycles. First, a cyclization involving the more-electron-deficient aryl iodide to form a seven-membered ring provided intermediates **383a** and **383b** using Cu and Pd catalysis conditions, respectively. Intramolecular coupling between the cyclohexylamide group and the remaining aryl iodide afforded the polycyclic compounds **384** and **385** in moderate yield. The cross-coupling reactions were carried out using a $Pd_2(dba)_3$/**L17** catalyst and K_2CO_3 as base. High temperatures of 130 °C with microwave-heating conditions allowed for short reaction times of only 20 min with DMF as the reaction solvent. Overall, this strategy provided a large number of high-complexity compounds using an operationally simple setup.

The intermolecular Pd-catalyzed coupling of secondary amides with aryl halides and pseudohalides has also been applied to the synthesis of heterocycles. For example, Lindenschmidt and co-workers (Sanofi-Aventis) developed a protocol to access medicinally relevant N-substituted benzimidazoles and imidazopyridines (Scheme 91a).[320] Amide coupling and subsequent reductive amino cyclization reactions could be carried out in a single flask and gave rise to a series of benzo-fused heterocycles in 43–94% yield with complete regiocontrol. Although 2-halonitroarenes are often problematic substrates for Pd-catalyzed amidation reactions,[41,321] the use of $Pd(TFA)_2$/(*R*)-**L6**[322] successfully transformed **386** and substituted amides into intermediate **387**. The use of weak base in the reaction was crucial due to the presence of the base-

Scheme 91. Heterocycle Synthesis via Intermolecular Secondary Amide Coupling



sensitive nitro group. Furthermore, excellent levels of selectivity were observed with di(halo)nitroarene reagents, which underwent C–N bond formation exclusively at the halide ortho to the nitro group. A different approach was followed by Neuville, Zhu, and their co-worker to obtain unsymmetrically substituted 3-(diarylmethylene)oxindoles from secondary alkynyl amides (Scheme 91b).[323] In a three-component process, a single Pd catalyst facilitated a cross-coupling and a Heck reaction/C–H activation sequence to afford the final products in 32–67% yield. First, selective N-arylation of amide **388** with electron-poor aryl bromides generated intermediate **389**. Subsequent addition of a DMF solution of aryl iodide provided *E*/*Z* mixtures of oxindole isomers **390** via sequential carbopalladation/C–H activation steps.[324] Conveniently, the reaction was carried out in one-pot using a $Pd(OAc)_2$/**L7** catalyst that promoted both C–N and C–C bond-forming steps.

6.2.2. Applications of the Coupling of Secondary Amides in Medicinal Chemistry. Yang and co-workers employed Pd-catalyzed N-arylation of lactams to arrive at a

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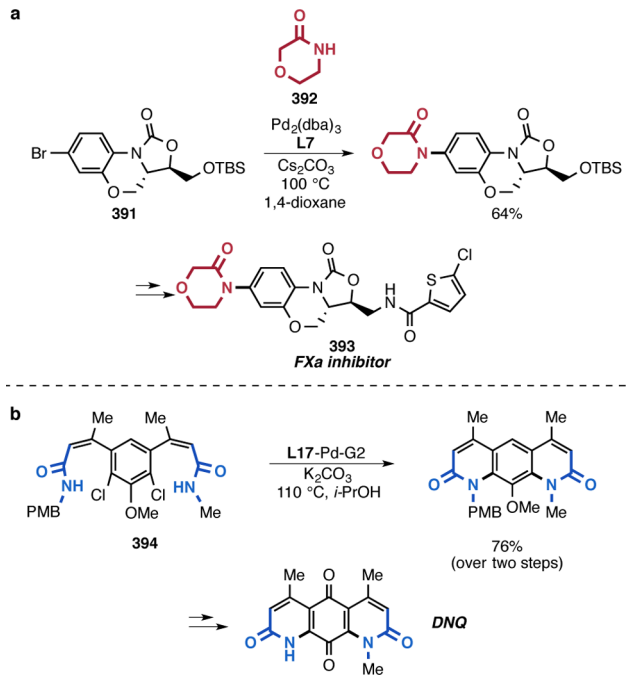
potent anticoagulant drug candidate (**393**, Scheme 92a).[325] Previously, a series of cyclic amides had been successfully

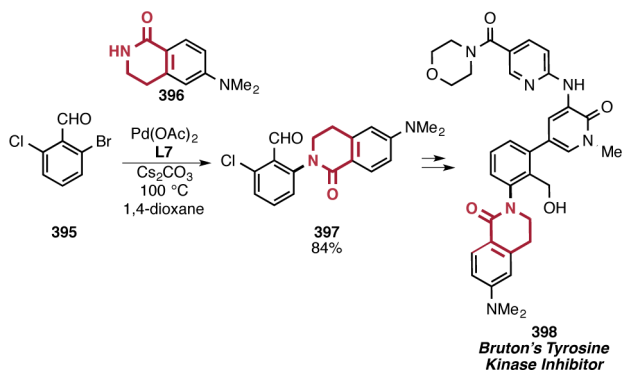
Scheme 92. Synthesis of Drug Candidates via Coupling of Lactams or Intramolecular Coupling of Secondary Amides



combined with tricyclic oxazolidinone **391** in the presence of $Pd_2(dba)_3$, **L7**, and Cs_2CO_3; the δ-lactam **392** gave rise to the most active compound. The Hergenrother group developed an efficient multistep route to prepare the potential anticancer agent DNQ and study its mechanism of action (Scheme 92b).[326] The key steps of the synthesis were Pd-catalyzed cross-coupling reactions: Suzuki–Miyaura coupling, Miyaura borylation, and two intramolecular amidation reactions. Double ring closure of aryl chloride **394** was achieved with **L17**–Pd-G2 precatalyst, in the presence of additional **L17**, and K_2CO_3 as the base, in 76% yield.

6.2.3. Applications of the Coupling of Secondary Amides in Process Chemistry. Hong and co-workers (Roche) developed a scalable synthesis of Bruton's tyrosine kinase inhibitor **398** to potentially treat autoimmune and inflammatory diseases (Scheme 93).[327] The target compound

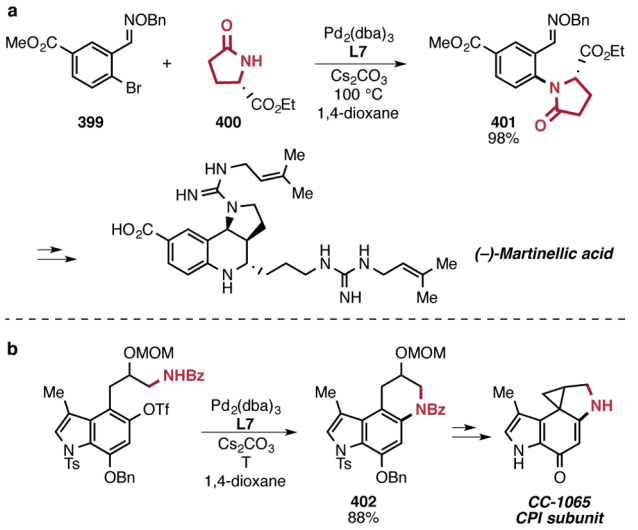
Scheme 93. Scalable Synthesis of Bioactive Compound 30 via Lactam Coupling



was assembled from four building blocks that were connected by S_NAr and Pd-catalyzed reactions. Dihaloarene **395** was selectively coupled with δ-lactam **396** in the presence of **L7** and a slight excess of the electrophile.[328] Intermediate **397** was accessed on a several hundred gram scale (375g) in 84% yield.

6.2.4. Applications of the Coupling of Secondary Amides in the Synthesis of Natural Products. Miyata, Naito, and their co-workers published an improved total synthesis of the alkaloid (−)-martinellic acid using a Pd-catalyzed lactam coupling (Scheme 94a).[329] After initial

Scheme 94. Examples of Lactam and Intramolecular Secondary Amide Coupling in Natural Products Synthesis



attempts to use CuI as a catalyst with no success, C–N bond formation between aryl bromide **399** and chiral cyclic amide **400** (L-pyroglutamic acid ethyl ester) was accomplished using $Pd_2(dba)_3$/**L7** to provide intermediate **401** in 98% yield. Kerr described the total synthesis of the CPI (1,2,8,8a-tetrahydrocyclopropa[*c*]pyrrolo[3,2-*e*]indol-4-one) subunit found in potent antitumor agent CC-1065 employing an intramolecular amide coupling (Scheme 94b).[330] Starting from commercially available 5-fluoro-2-nitrophenol, the route involved a Diels–Alder reaction and Pd-catalyzed amide coupling as key steps. The pyrrolotetrahydroquinoline intermediate **402** was obtained in excellent yield (88%) via an intramolecular triflate amidation using a catalyst based on $Pd_2(dba)_3$ and **L7**.

6.3. Sulfonamides

In the preparation of *N*-arylsulfonamides, Pd-catalyzed cross-coupling methods offer significant advantages in comparison to the more traditional condensation of anilines and sulfonyl chlorides protocols. This is because, in the latter, both the starting materials and the sometimes formed sulfonate byproducts are known to be genotoxic; therefore, avoiding their use is desirable.[331] Since the first example of Pd-catalyzed intramolecular sulfonamide coupling by Buchwald and co-workers,[61] great progress has been achieved in the intermolecular version of the reaction. Scattered examples of the coupling of primary and secondary sulfonamides with aryl chlorides,[266,303] bromides,[117,332] triflates and nonaflates,[303,332] are found in the literature, whereas few sulfonamide-specific methodologies have only more recently been developed. In 2003, Cao and co-workers developed a protocol to combine

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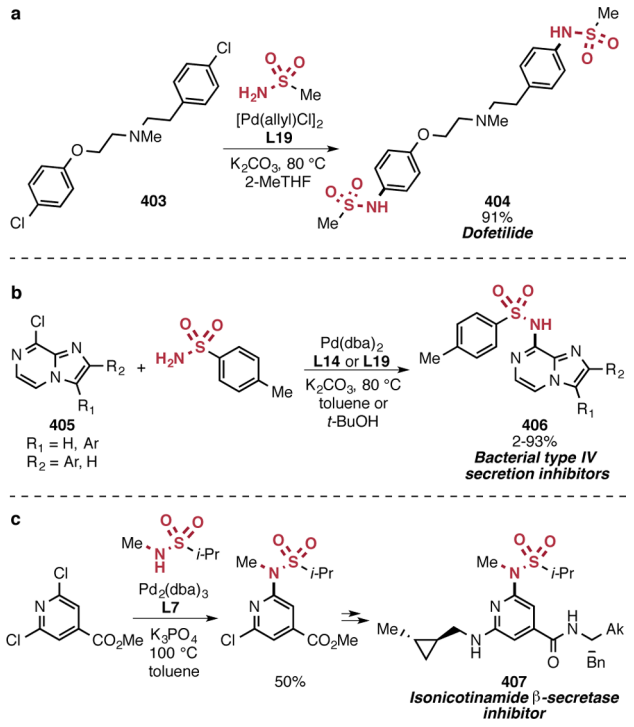
primary sulfonamides with aryl chlorides under microwave-heating conditions.[333] Later, Ruble, Beauchamp, and their co-workers (Eli Lilly) reported a method to couple methanesulfonamide and related nucleophiles to aryl chlorides and bromides.[331] Contemporaneously, Shekhar and co-workers (Abbvie) disclosed a related strategy for sulfonamide coupling with aryl nonaflates.[334] After exploring a series of ligands, both groups identified **L19** as the most efficient.[335−337] The cross-coupling of sulfonamides with aryl halides and sulfonates is an important transformation in the pharmaceutical industry, where catalysts based on **L7** and *tert*-butylbiarylphosphine-type ligands have been the most commonly employed.

6.3.1. Applications of the Coupling of Sulfonamides in Medicinal Chemistry. To demonstrate the utility of their method, Ruble, Beauchamp, and their co-workers synthesized dofetilide (**404**, Scheme 95a), an antiarrhythmic agent

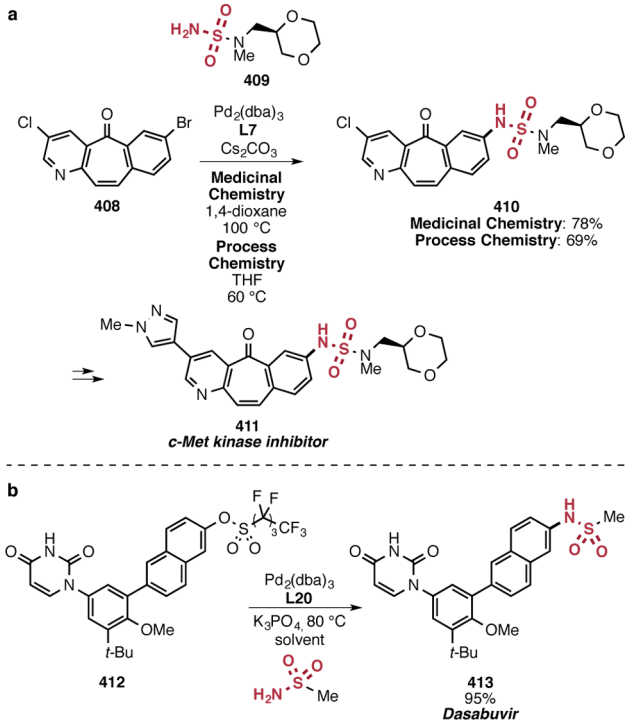
Scheme 95. Synthesis of Drug Candidates via Sulfonamide Coupling



marketed as Tikosyn by Pfizer, using two Pd-catalyzed C−N bond-forming reactions of previously described intermediate **403**.[331] The desired product was prepared in excellent yield (91%) using 2.5 equiv of methanesulfonamide. In an effort to employ industrially friendly reaction conditions, K_2CO_3 was used as base in lieu of Cs_2CO_3, and 2-MeTHF was chosen as the reaction solvent. Tabor discovered a series of 8-sulfamide imidazopyrazines with high potency as antibacterial agents (**406**, Scheme 95b).[338] Employing either **L14** or **L19** as the supporting ligand, *p*-toluenesulfonamide was coupled with a variety of heteroaryl chlorides (**405**) using toluene or *t*-BuOH as solvent. This method proved to be very substrate dependent, but an alternative S_NAr approach did not provide a significant improvement. Stanton and co-workers (Merck) discovered that isonicotinamide **407** displays potent activity for the treatment of Alzheimer's disease (Scheme 95c).[339] With a $Pd_2(dba)_3$/**L7** catalyst, 2,6-dichloroisonicotinate underwent C−N bond formation as the first step of the synthesis of the drug candidate, providing an example of the N-arylation of secondary sulfonamides in modest yield (50%).

6.3.2. Application of the Coupling of Sulfonamides in Process Chemistry. The groups of Katz and Stewart (Merck) developed the medicinal and process chemistry routes, respectively, to access promising anticancer drug **411** (Scheme 96a).[340,341] Due to the low nucleophilicity of the corresponding

Scheme 96. Large-Scale Synthesis of Biologically Active Compounds 411 and 413 via Sulfonamide Coupling



tricyclic aniline and the low yield obtained utilizing sulfamoyl chloride electrophiles, both research teams used Pd-catalyzed cross-coupling as a means to install the sulfamide fragment. Chemoselective cross-coupling of the aryl bromide of the dihaloketone **408** with sulfamide **409** afforded **410** in 78% yield. The challenges of scaling up the medicinal chemistry route did not pertain to the cross-coupling reaction, allowing this step to be retained in the process route. By using a more desirable solvent (THF vs 1,4-dioxane), reducing the temperature to 60 °C, and increasing the reaction time to 24 h, compound **411** was obtained in 69% yield on a multikilogram scale. In addition, a new sulfonamide-containing NS5B polymerase inhibitor (dasabuvir, **413**, Scheme 96b) developed at AbbVie has been recently approved for treatment of hepatitis C.[342] The last step in the synthesis of Exviera involved the reaction between intermediate **412** and methanesulfonamide in the presence of a $Pd_2(dba)_3$/**L20** catalyst.

6.4. Ureas

In 2001, Beletskaya and co-workers reported the first examples of the Pd-catalyzed N-arylation of urea employing an **L7**-based catalyst system.[19,343] A major challenge of urea cross-coupling reactions is the potential formation of mixtures of mono-arylated and diarylated products. In the past years, the reaction has evolved from exclusively enabling the cross-coupling of urea and activated aryl bromides to include a diverse array of substrates, such as unactivated aryl chlorides and bromides,

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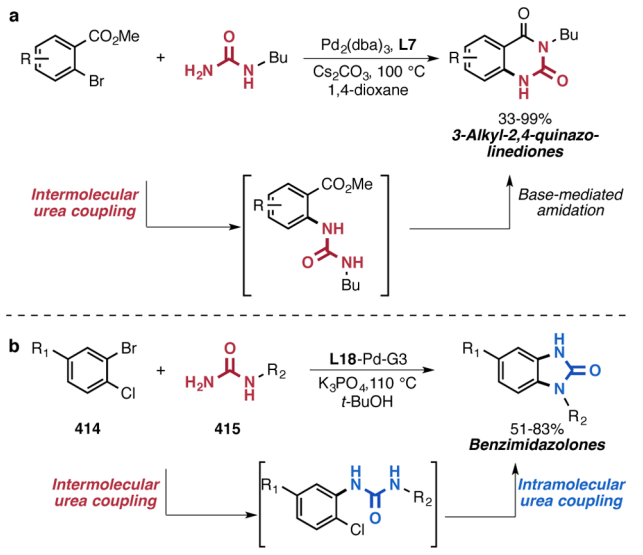
heteroaryl halides, and monosubstituted ureas.[344−346] The N-arylation of ureas has been employed to build benzo-fused heterocycles and unsymmetrical bioactive compounds.

6.4.1. Applications of the Coupling of Ureas in the Synthesis of Heterocycles. Ureas are precursors to a variety of heterocycles. Tandem processes involving the Pd-catalyzed cross-coupling between monosubstituted ureas and 1,2-disubstituted arenes can often provide heterocyclic products as a single regioisomer in one-pot procedures (Scheme 97).

Scheme 97. Heterocycle Synthesis via Urea Coupling



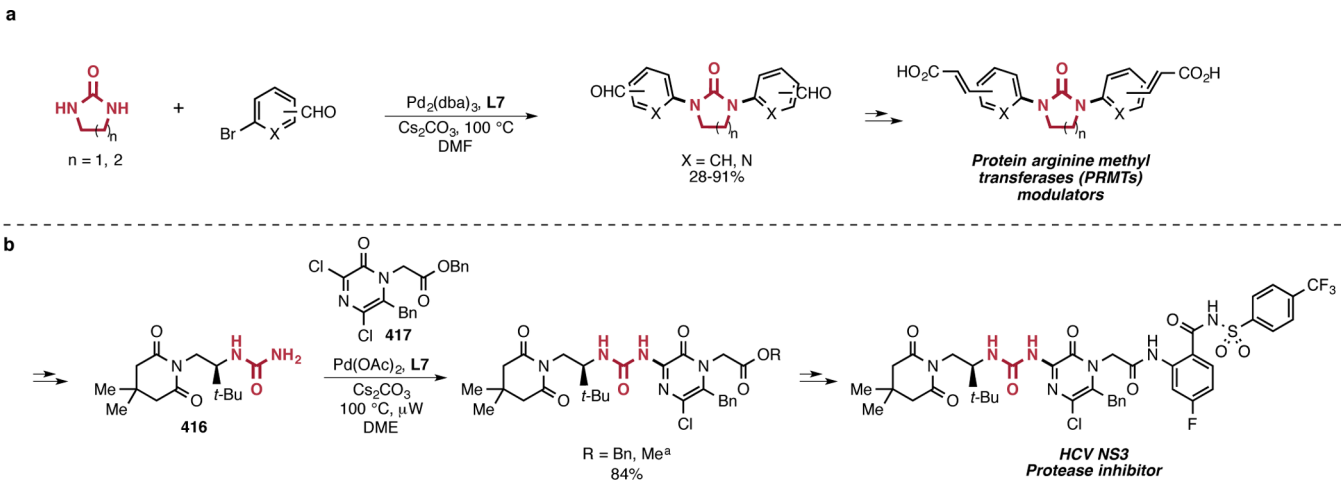
Alternative methods of exclusive N1- or N3-functionalization typically require the use of protecting groups or they result in the formation of mixtures of regioisomers. Illustrative is the synthesis of *N*3-alkylquinazolinediones reported by Willis and co-workers (Scheme 97a).[347] N-Arylation of the urea NH_2 with an *o*-halobenzoate occurs first. Subsequent ring closure takes place via base-promoted intramolecular amidation, leading to the formation of a single regioisomer. In addition, Buchwald and co-workers reported an approach to access related compounds, benzimidazolones (Scheme 97b).[348,349] A sequence of two individual C−N bond-formation steps between 1,2-dihaloarenes (**414**) and monosubstituted ureas (**415**) affords the corresponding heterocycle as a single regioisomer. In this case, the regioselectivity is controlled by the C−X bond strength, which favors preferential oxidative addition of the aryl bromide. As in the previous example, the more reactive free NH_2 of the urea is arylated first. Conveniently, commercially available **L18**−Pd-G3 precatalyst facilitated both cross-coupling steps.

6.4.2. Applications of the Coupling of Ureas in Medicinal Chemistry. $Pd_2(dba)_3$·$CHCl_3$/**L7** enabled the preparation of a series of symmetrical ureas that serve as modulators of protein arginine methyl transferases (Scheme 98a).[350] Álvarez, de Lera, and their co-workers carried out the diarylation of cyclic ureas with aldehyde-containing aryl and pyridyl bromides in moderate to good yield, contaminated with only small amounts of the monosubstituted products (1−4%). However, the direct coupling of these electrophiles with urea itself was unsuccessful. Additionally, the use of **L7** gave superior results compared to when other bidentate ligands (e.g., dppe and **L11**) were employed for the Pd-catalyzed cross-coupling of monosubstituted ureas and chloropyrazinone **417**, a structural unit for the development of complex protease inhibitors.[351] Belfrage and co-workers applied this transformation to couple urea **416** in the synthesis of a new hepatitis C virus (HCV) NS3 protease inhibitor candidate (Scheme 98b). The corresponding intermediate was obtained in excellent yield (84%) as a mixture of methyl and benzyl esters.

To access unsymmetrical diaryl ureas, Buchwald and co-workers applied a two-step method that was illustrated with the synthesis of omecamtiv mecarbil (Scheme 99).[345] This protocol allows for the stepwise, selective installation of substituents on each of the urea nitrogen atoms, providing an alternative to traditional methods for the synthesis of ureas. According to the protocol, benzylurea was initially coupled with 5-bromo-2-methylpyridine, followed by one-pot deprotection of the benzyl group. Subsequent N-arylation of the unsubstituted end of the urea provided the desired product in 81% yield. Dialkylbiarylphosphine **L20**, in combination with $Pd(OAc)_2$, was suitable for facilitating both cross-coupling steps.

6.4.3. Applications of the Coupling of Ureas in Process Chemistry. In 2009, Kotecki and co-workers

Scheme 98. Synthesis of Biologically Active Compounds by the Coupling of Ureas



[a]Methyl ester formation was due to the presence of MeOH in the DME.

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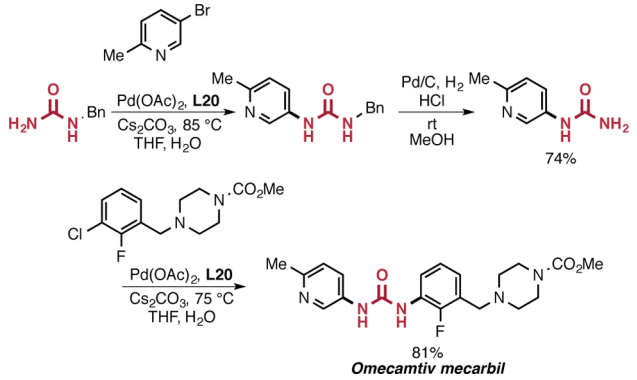
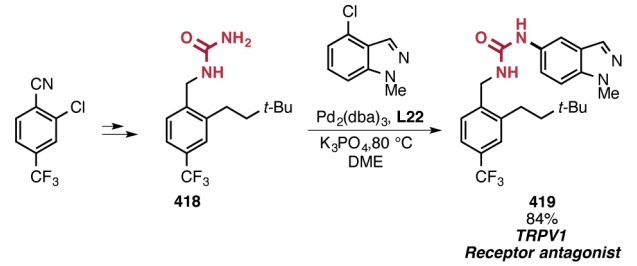
Scheme 99. Synthesis of Omecamtiv Mecarbil via Urea Coupling



(Abbvie) reported a method for accessing unsymmetrically substituted ureas from their monosubstituted counterparts.[344] When a catalyst system based on $Pd_2(dba)_3$ and **L7** gave moderate conversion to products, they found that **L22** was the optimal ligand for the desired transformation. The method efficiently transformed a wide range of aryl bromides and (hetero)aryl chlorides. This protocol was applied by Yu and co-workers (Abbvie) in the large-scale preparation of the potent TRPV1 receptor antagonist, a nonopioid, non-NSAID pain reliever (**419**, Scheme 100).[352] The key step of the synthesis

Scheme 100. Scalable Synthesis of Drug Candidate 419 via Urea Coupling



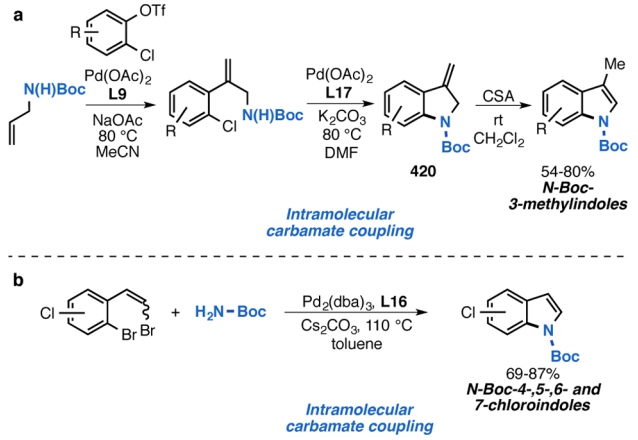
was the cross-coupling of 4-chloro-1-methylindazole and benzyl urea **418**, which provides the desired product in 84% yield (Scheme 100). The previous synthesis of **419** utilized unstable 4-amino-1-methylindazole, making the Pd-based synthetic route an attractive alternative (five steps, 71% overall yield).

6.5. Carbamates

Among carbamates, *tert*-butyl carbamate (NH_2Boc) is the most frequently used in cross-coupling reactions, owing to its role as an ammonia surrogate to access Boc-protected primary anilines. Furthermore, NH_2Boc is a readily available and easy to handle solid. Since Hartwig and co-workers's initial report using **L3a** as a supporting ligand,[353] only two NH_2Boc-specific methods have been developed. The first, by Hornberger and colleagues (GlaxoSmithKline), described the coupling reaction with aryl bromides at room temperature with **L19** as the supporting ligand.[354] Zou, Wu, and their co-workers expanded the substrate scope of this reaction to (hetero)aryl bromides and chlorides using **L17**.[355] Additionally, the coupling of fluorous-tagged carbamates[356] and carbamic acid 2-trimethylsilylethyl ester[357] has been reported. Examples of other reactions of coupling carbamates are found in reports of the N-arylation of amide-type nucleophiles.[18] In general, catalysts based on **L7** or biarylphosphine-type ligands have been the most frequently used.

6.5.1. Applications of the Coupling of Carbamates in the Synthesis of Heterocycles. Baxter and co-workers (Merck) developed an efficient and regioselective route to substituted 3-methylindoles via an intramolecular carbamate coupling (Scheme 101a).[358] The three-step process starts with

Scheme 101. Synthesis of Indoles via Carbamate Coupling



a Heck reaction between a 1,2-chlorotriflate (readily accessible from the corresponding 1,2-chlorophenol) and *N*-Boc-allylamine in the presence of $Pd(OAc)_2$/**L9**. The more reactive triflate reacts in preference to the chloride with complete selectivity. Switching solvent from MeCN to DMF, followed by addition of a new catalyst ($Pd(OAc)_2$/**L17**) along with K_2CO_3, delivered intermediate **420** via intramolecular carbamate-aryl chloride coupling. CSA-induced isomerization of the *exo*-olefin led to the formation of *N*-Boc-3-methylindoles. This method proved to be scalable, affording the heterocycles in good overall yield (54−80%) starting with 1−120 g of substrate. Shortly thereafter, Willis, Lindon, and their co-worker reported the preparation of *N*-Boc-protected 4-, 5-, 6-, and 7-chloroindoles[359] (Scheme 101b) based on previous methods that had been devised for the synthesis of indoles[306,307] and 2-quinolones[308] (Scheme 87a). Using **L16** as the supporting ligand, NH_2Boc first reacts at the bromoalkene, and subsequent intramolecular coupling with the aryl bromide provides the corresponding indoles in 69−87% yield.

6.5.2. Applications of the Coupling of Carbamates in Medicinal Chemistry. In the multistep synthesis of drug candidates, the presence of free amines can be problematic due to their basicity and nucleophilicity. When installing an amino group early in a synthetic route, medicinal and process chemists have utilized ammonia surrogates for cross-coupling reactions to access the protected aniline. Scheme 102 presents two examples of this strategy, in which the Boc group was removed in the final stages of the sequence. Xiao and co-workers (Tetraphase Pharmaceuticals) prepared a series of 9-amino-pentacyclines with antibacterial activity based on Myers's synthesis of tetracycline analogues.[360] The research team employed a Pd-catalyzed carbamate coupling to install amines on the E ring of the polycycle (**424**, Scheme 102a). Under Pd-catalyzed conditions with **L3a** as the supporting ligand, aryl bromide **421** reacted with *tert*-butyl carbamate to produce the desired product in 64% yield on a gram scale. After several

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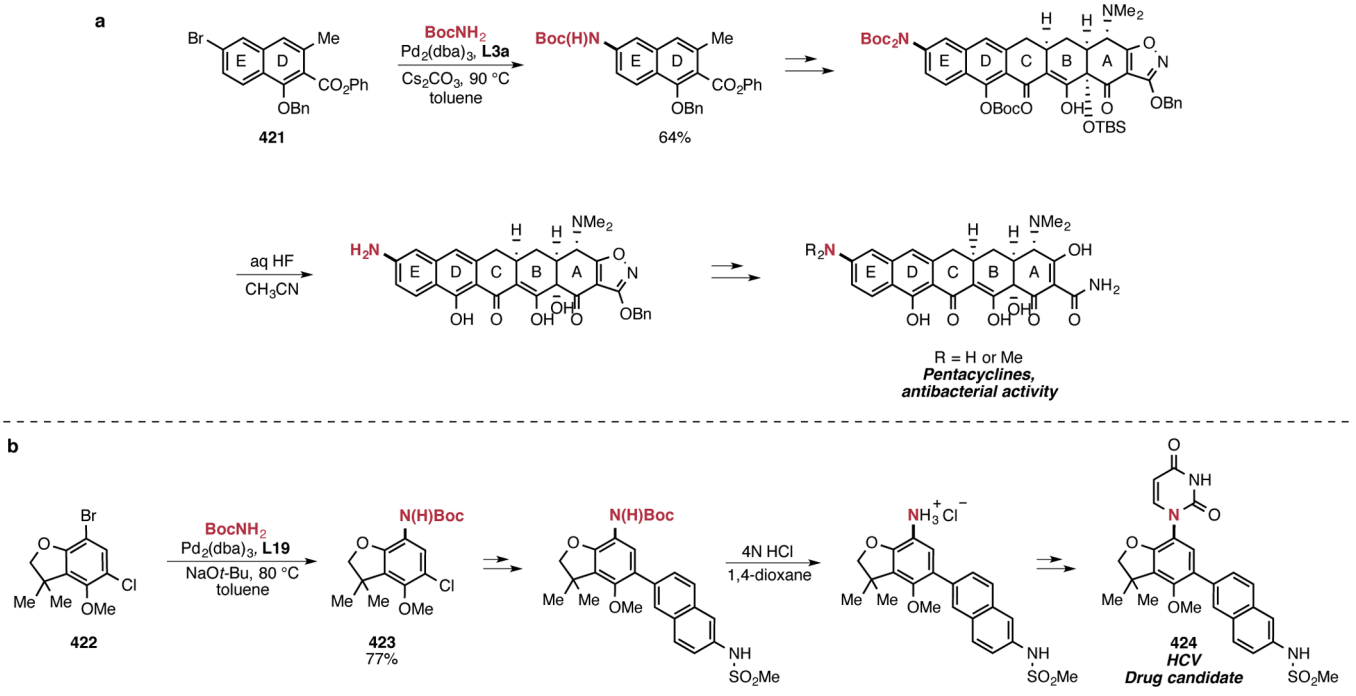
Scheme 102. Carbamate Coupling in Medicinal and Process Chemistry

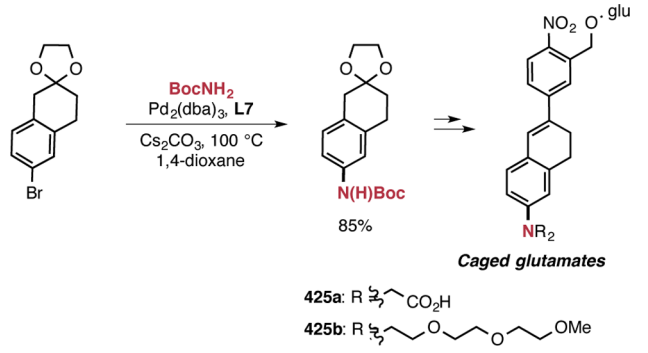


steps, the Boc group was removed to provide the 9-aminopentacyclines.

6.5.3. Applications of the Coupling of Carbamates in Process Chemistry. Wang and Briggs (Hoffmann-La Roche) followed a similar approach as described above for the scalable synthesis of an HCV drug candidate (Scheme 102b).[361] Chemoselective Pd-catalyzed carbamate coupling of aryl bromide **422** was carried out with a $Pd_2(dba)_3$/**L19** catalyst and NaO-*t*-Bu, providing compound **423** in 77% yield on a 1-g scale. Moreover, the reaction was exceptionally fast, finishing in approximately 10 min at 80 °C. Subsequent Suzuki−Miyaura coupling of the aryl chloride followed by Boc deprotection with further functionalization of the aniline's amino group gave the final product. This route produced the ammonium chloride precursor of **424** in 40% overall yield, a vast improvement to the 5% overall yield realized in the medicinal chemistry group's synthesis.

6.5.4. Applications of the Coupling of Carbamates in Materials Chemistry and Chemical Biology. Pd-catalyzed cross-coupling reactions of carbamates have also been used to prepare compounds with interesting optical properties. Scheme 103 shows the synthesis of caged glutamates by Abe, Katan, and their co-workers.[362] Compounds **425a** and **425b** are attractive reagents for physiological studies, specifically in neuroscience, due to their absorption properties and chromophoric activity. Early in the sequence, an amino group was installed through Pd-catalyzed coupling with NH_2Boc. The transformation was carried out with **L7** as the ancillary ligand and yielded the desired product in 85% yield. The reaction was rapid, taking only 5 h on a 4-g scale. Similarly, Lavis and co-workers investigated the conversion of carbofluoresceins (**426**) to the corresponding carborhodamines (**427**) via Pd-catalyzed N-arylation reactions (Scheme 104).[363] Both **426** and **427** are fluorescent compounds that are practical for live-cell-imaging experiments and super-resolution microscopy, among other applications. **L7** and **L17** were suitable ligands for the installation of a variety of *N*-alkyl, aryl, and acyl nucleophiles

Scheme 103. Synthesis of Optically Active Caged Glutamates via Carbamate Coupling



onto the carbofluorescein core. Scheme 104 shows specific examples of carbamate coupling reactions leading to *N*-Boc-protected carborhodamines **427a** and **427b** and the more complex compound **427c** bearing *o*-nitroveratryl carbamates. Using Cs_2CO_3 as a base, the reaction tolerated esters, lactones, and nitro groups.

6.5.5. Applications of the Coupling of Carbamates in the Synthesis of Ligands. Kitagaki and co-workers explored [2.2]paracyclophanes as planar chiral cores for thiourea-type organocatalysts (Scheme 105).[364] The research group utilized *tert*-butyl carbamate coupling as the means to append primary amino groups onto this unique aromatic structure. In the presence of $Pd_2(dba)_3$ and **L12**, optically pure bromo[2.2]-paracyclophenyl triflate **428** successfully underwent double amination to afford compound **429**. An excess of NH_2Boc (6 equiv) and the use of a NaOPh were required to obtain the desired product in 63% yield. Subsequent N-deprotection with TFA provided the corresponding diamine, which was transformed into the final [2.2]paracyclophane bis(thiourea) **430**. Catalyst **430** was highly efficient for the asymmetric Henry reaction.

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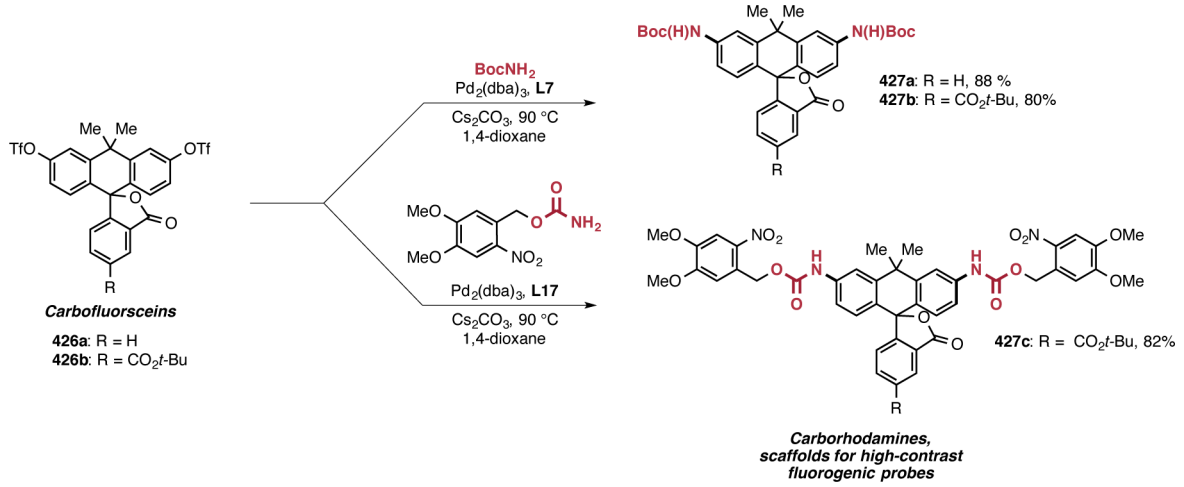
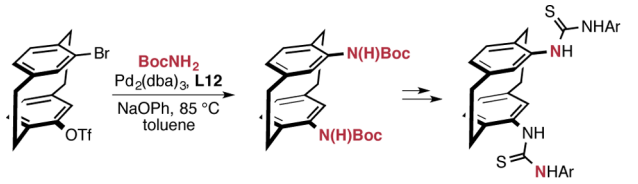
Scheme 104. Synthesis of Optically Active Materials via Carbamate Coupling



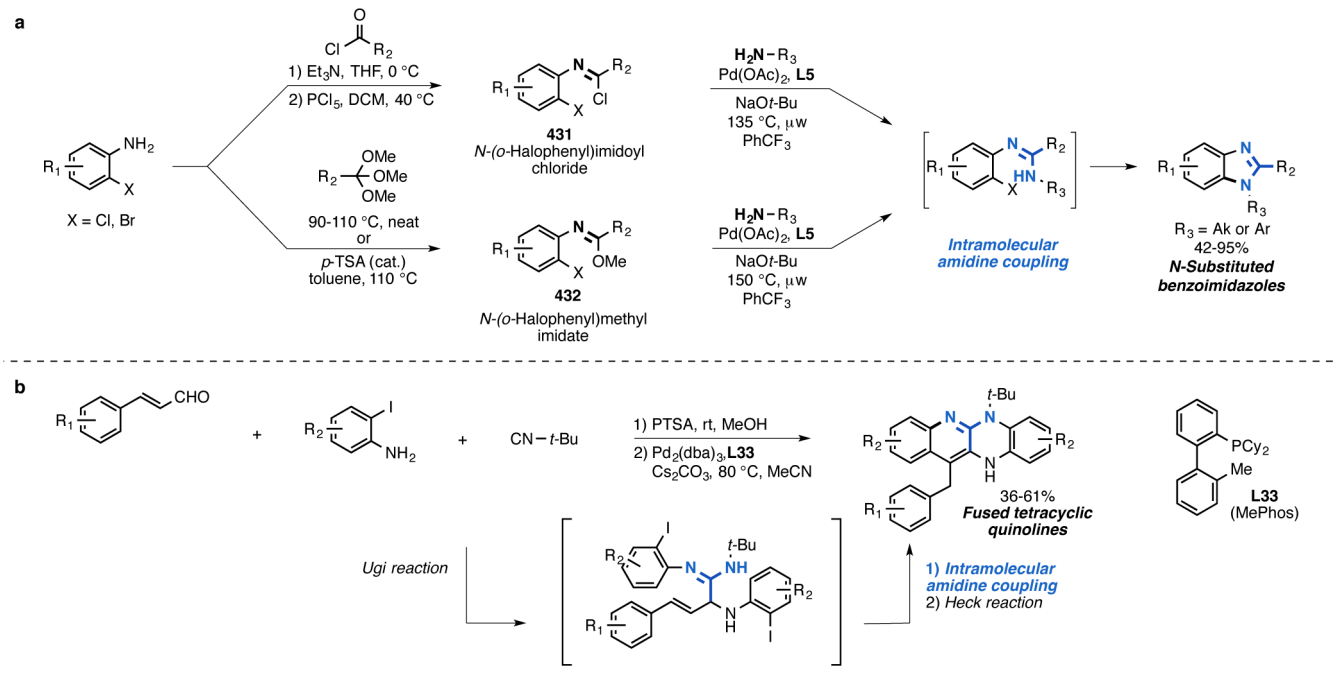
Scheme 105. Synthesis of Thiourea-Based Organocatalysts via Carbamate Coupling



6.6. Amidines

Amidines are a challenging substrate for Pd-catalyzed C−N cross-coupling reactions for several reasons.[208] First, strong coordination to the transition metal can occur, leading to catalyst deactivation. For this reason, the amidine reagent is typically added into the reaction mixture as the corresponding HCl salt for the slow generation of the active nucleophile. Additionally, amidines often have low solubility in many of the commonly used solvents for C−N coupling; thus, more polar solvents (MeCN, *t*-BuOH, or *t*-AmOH) need to be employed. Finally, the formation of both N1- and N3-substituted regioisomers or diarylation products can occur due to the presence of two nucleophilic nitrogen centers. The first Pd-catalyzed amidine coupling was published in 2002 by Brain and co-workers (Novartis)[365,366] and was utilized to synthesize N-substituted benzimidazoles. The method involved the in situ preparation of *o*-bromoarylamidines and their subsequent intramolecular coupling catalyzed by Pd(**L1**)$_4$ to afford the desired heterocycle. Shortly thereafter, Boykin and colleagues reported the N-arylation of protected *O*-methylamidoximes with aryl bromides and iodides using **L7** as the supporting ligand.[367] Since then, few methods have been developed for urea-specific coupling, but several protocols for heterocycle synthesis have incorporated this transformation. A variety of

Scheme 106. Synthesis of Benzimidazoles via Intramolecular and Intermolecular Amidine Coupling



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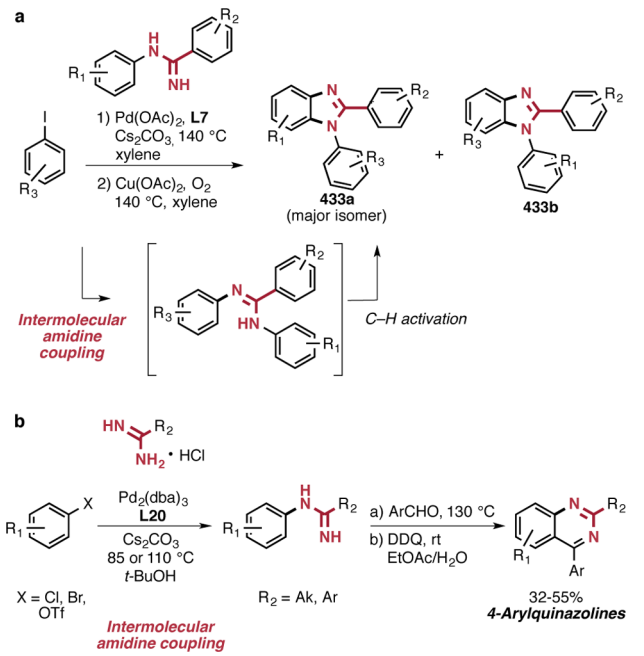
catalysts have been utilized for the intra- and intermolecular N-arylation of amidines, with the ones based on **L7** and dialkylbiarylphosphines being the most common.

6.6.1. Applications of the Coupling of Amidines in the Synthesis of Heterocycles. Building on a well-stablished strategy,[365,368] Willis and co-workers reported the synthesis of benzimidazoles via intramolecular amidine N-arylation (Scheme 106a).[369] Two related precursors **431** and **432** reacted with a variety of *N*-nucleophiles to form the respective five-membered heterocycle product in a two-step, one-pot process. It was demonstrated that amidine formation likely occurs first, followed by Pd-catalyzed ring closure. The reaction was carried out with $Pd(OAc)_2$ in combination with **L5** in trifluoromethylbenzene, under conditions of microwave heating. Imidoyl chlorides (**431**) reacted more efficiently with alkylamines, whereas the corresponding methylimidate (**432**) afforded a higher yield with anilines. Similar to the previously mentioned post-Ugi functionalization strategies (Schemes 88, 89, and 90), Che, Lin, and their co-workers reported a method to obtain fused tetracyclic quinolines (Scheme 106b).[370] Sequential Ugi-MRC and Pd-catalyzed bisannulation transformed relatively simple starting materials into complex polycyclic molecules in a convenient one-pot process. The combination of cinnamaldehyde, *o*-iodoaniline, and *tert*-butyl isocyanide gave rise to the α-aminoamidine intermediate, which then underwent sequential N-arylation and Heck coupling to afford the desired heterocycles in 36−61% yield.

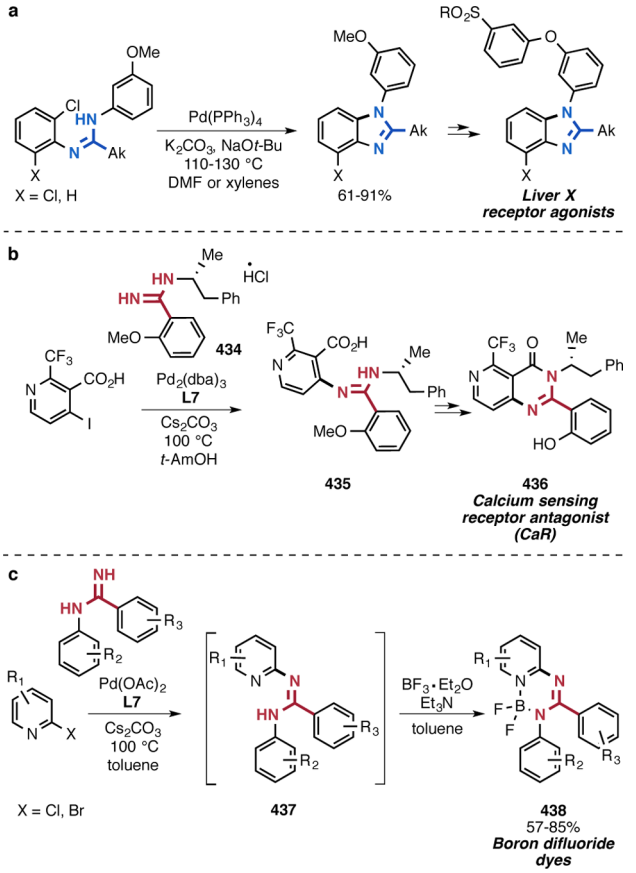
Bao and co-workers developed a technique to obtain substituted benzimidazoles through the intermolecular coupling of amidines (Scheme 107a).[371] In a one-pot protocol, 1,2-diarylimidazoles were obtained through the Pd-catalyzed coupling of *N*-arylbenzamidines and iodobenzenes and subsequent Cu-catalyzed C−H activation. Formation of two isomers was possible, compound **433a** being the major one in most cases. In 2012, Buchwald and co-workers published another method for the Pd-catalyzed intermolecular N-arylation of amidines (Scheme 107b).[372] An array of alkyl and aryl amidines were successfully coupled with aryl chlorides, bromides, and triflates in the presence of a $Pd_2(dba)_3$/**L20**-based catalyst. Notably, excellent selectivity for monoarylated products was observed with N-unsubstituted amidines. Grinding of the base was required to achieve better conversion, and better results were observed when the free base of the amidine was used. This transformation was applied to the one-pot synthesis of 4-arylquinazolines, as shown in Scheme 107b. After formation of the arylated amidine, the unsubstituted nitrogen was condensed with an aryl aldehyde by base-promoted imine formation. Subsequent electrocyclization followed by DDQ oxidation provided the desired 4-quinazolines in moderate yield (32−55%) over three steps. A variety of relatively electron-rich alkyl, aryl, and heterocyclic amidines, as well as heterocyclic and polyhalogenated aldehydes, were successfully converted into the corresponding 4-arylquinazolines.

6.6.2. Applications of the Coupling of Amidines in Medicinal Chemistry. For the synthesis of liver X receptor agonists, Bernotas and co-workers (Wyeth) expanded Brain's method to aryl chlorides coupling partners to prepare N-substituted benzimidazoles (Scheme 108a).[152] This was advantageous due to the greater availability of the starting chloroanilines. The intramolecular coupling occurred in the presence of $Pd(\mathbf{L1})_4$ and the combination of K_2CO_3/NaO-*t*-Bu as a base as in the parent method, using DMF or xylenes as the solvent (61−91% yield).

Scheme 107. Heterocycle Synthesis via Intramolecular and Intermolecular Amidine Coupling



Scheme 108. Benzimidazole Synthesis, Large-Scale Preparation of Bioactive Compound 436, and Synthesis of Boron-Based Dyes



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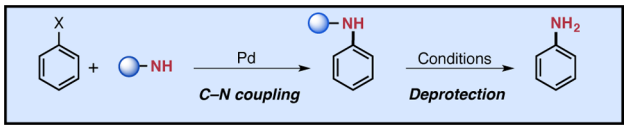
6.6.3. Applications of the Coupling of Amidines in Process Chemistry. Li and co-workers (Pfizer) developed a procedure for the large-scale synthesis of quinazolin-4(3*H*)-ones.[373] Targeting quinazoline **436** (Scheme 108b), the research group initially examined a Cu-catalyzed approach to access intermediate **435**. However, they only observed low conversion to the desired product. In contrast, a catalyst based on $Pd_2(dba)_3$ and **L7** efficiently coupled 3-trifluoro-4-iodonicotinic acid and amidine **434** to exclusively give the product of reaction at the unsubstituted nitrogen atom. Attempts to use the phenolic amidine directly resulted in competing O-arylation, necessitating the use of methyl ether as the protecting group. Compound **435** was then cyclized to give the desired quinazolin-4(3*H*)-one. This shorter process route to **436** allowed for the production of the drug candidate on a several hundred gram scale. In addition to **436**, various quinazolin-4(3*H*)-ones were prepared from 2-bromo- or 2-iodobenzoate esters in a one-pot method with yields ranging from 44% to 89% (not shown).

6.6.4. Applications of the Coupling of Amidines in Materials Chemistry. The You group designed a new class of nonplanar asymmetric aza-boron dyes (**438**) that displayed full-color-tunable emissions and mechanochromic luminescence (Scheme 108c).[374] These compounds possessed a core constituted by a nitrogen-based heterocycle (most frequently pyridine or pyrazine) and a diaryl amidine unit. A library of fluorophores was conveniently built in a one-pot process. First, Pd-catalyzed regioselective coupling of 1,2-diaryl amidines and 2-(hetero)aryl halides using **L7** afforded intermediate **437**. This was treated with boron trifluoride−diethyl etherate to afford the BF_2/amidine complexes in 57−85% yield.

7. AMMONIA EQUIVALENTS AND AMMONIA

The formation of primary anilines is a crucial process in synthetic chemistry due to their presence in organic molecules that are used in biological studies and advanced materials.[375] Moreover, the aniline nitrogen atom often serves as a handle for the assembly of N-based heterocycles embedded in larger molecules or is further transformed into other functional groups (e.g., amides). Although ammonia is an ideal coupling partner for primary aniline production, the use of ammonia gas is limited by safety and handling considerations. Furthermore, direct amination using ammonia often results in formation of polyarylated products. Given these difficulties, alternative reagents have been developed as ammonia equivalents.[376] Conveniently, ammonia surrogates are commercially available and safe compounds that give rise to N-protected aniline intermediates. Even though an additional deprotection step is required, the presence of a protecting group can be beneficial in multistep syntheses (Scheme 109). Moreover, the Pd-catalyzed coupling of ammonia surrogates is a milder alternative to traditional methods such as a nitration/reduction sequence and its use also allows for better access to regiochemically pure anilines.

Scheme 109. General Reaction Scheme of the Use of Ammonia Equivalents

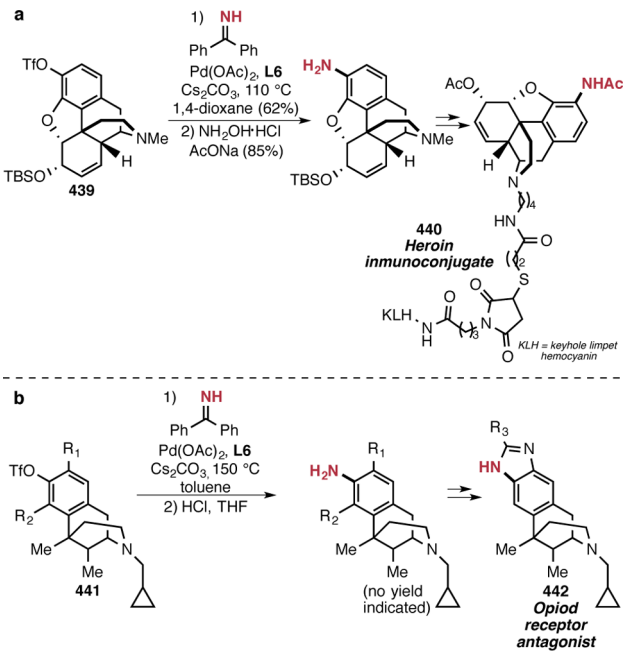


7.1. Benzophenone Imine

Benzophenone imine is a commercially available, inexpensive, and easy to handle alternative to ammonia for the generation of primary anilines. Note, however, that it is often desirable to distill the commercially obtained material in order to achieve good yields in coupling reactions in which it is employed. The relatively low steric hindrance and its inability to form diarylation side products make benzophenone imine a practical nucleophile for Pd-catalyzed C−N bond-forming reactions. The resulting *N*-aryl imine is frequently preserved as a protecting group due to its stability and straightforward removal, which can be accomplished by reaction with hydroxylamine hydrochloride, citric acid, aqueous HCl, or hydrogen in the presence of a transition-metal catalyst.[377] An early report by Buchwald employed a catalyst based on **L6** combined with NaO-*t*-Bu or Cs_2CO_3 as the base to couple the ammonia surrogate with aryl halides and triflates, respectively.[377] Contemporaneously, Hartwig and co-workers developed a method for the N-arylation of benzophenone imine with aryl bromides using **L9** as the supporting ligand.[20] More recent examples have been shown with catalysts derived from other ligands[378,379] such as dialkylbiarylphosphines by Buchwald and co-workers,[380] **L24** by Nolan and colleagues,[381] or **L19** by Hornberger and co-workers[382] (GlaxoSmithKline).

7.1.1. Applications of the Coupling of Benzophenone Imine in Medicinal Chemistry. Medicinal chemists have utilized benzophenone imine to access primary anilines that are typically further functionalized. The preparation of compounds **440** and **442** by Bremer and Janda[383] and Wentland and co-workers[384] (parts a and b of Scheme 110) are illustrative examples. To generate the morphinan derivatives, potential candidates to treat heroin (Scheme 110a) and cocaine (Scheme 110b) addiction, benzophenone imine was successfully coupled with the corresponding aryl triflates **439** and **441** in the presence of an **L6**-based catalyst. Subsequent cleavage of the

Scheme 110. N-Arylation of Benzophenone Imine in Medicinal Chemistry



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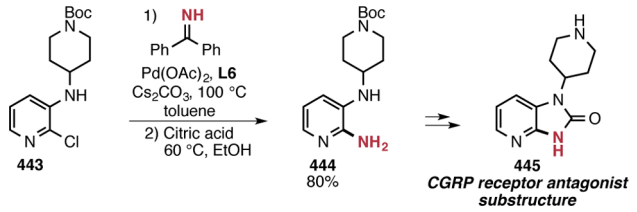
resulting imines readily delivered the target primary anilines, which were then carried on to the desired final compounds.

7.1.2. Applications of the Coupling of Benzophenone Imine in Process Chemistry. The Pd-catalyzed cross-coupling of benzophenone imine to 2-chloropyridine **443** was a key step in Leahy and co-workers's (Bristol-Myers Squibb) large-scale synthesis of compound **445** (Scheme 111), a

Scheme 111. Large-Scale Coupling of Benzophenone Imine

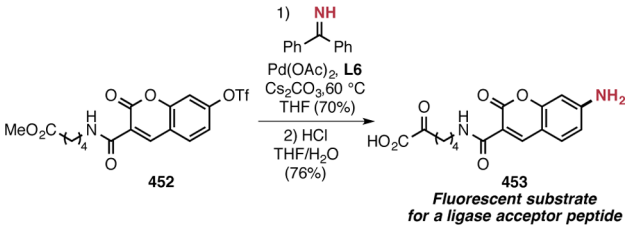


substructure present in >1000 CGRP receptor antagonists used to combat migraine headaches.[385] This novel route represented a significant improvement from previous reports by enabling the use of less costly starting materials. The direct generation of primary aniline **444** was initially attempted with nucleophiles such as LHMDS or ammonia gas, which led to low conversions and undesired diarylation products. In contrast, utilizing benzophenone imine cleanly furnished the target aniline after removal of the imine with citric acid. Although requiring an additional deprotection step, the sequence was highly efficient, providing compound **445** in 80% yield (over two steps).

7.1.3. Applications of the Coupling of Benzophenone Imine in the Synthesis of Natural Products. Tyagi and co-workers exploited the protected product of coupling benzophenone imine in their bioinspired synthesis of **449**, a metabolite of the fungicide sedaxane (Scheme 112a).[386] **L6** was a suitable supporting ligand for the reaction between chiral aryl bromide **446** and benzophenone imine, furnishing intermediate **447** in 67% yield. Prior to cleavage of the imine, a Kulinkovich cyclopropanation was carried out, and subsequent in situ acidic deprotection gave rise to the target primary aniline **448** in 54% yield. Ohmori, Suzuki, and their co-worker also employed the N-arylation of benzophenone imine in their asymmetric synthesis of (−)-cavicularin (**451**, Scheme 112b), the enantiomer of a unique natural product consisting of a very strained polycyclophane ring.[387] Interestingly, the ultimate purpose of the cross-coupling transformation was to install an iodide using the amine as directing group and to eventually achieve an overall deoxygenation. First, enantiomerically pure aryl triflate **450** was readily converted into the corresponding aniline using an **L6**-based Pd catalyst followed by treatment with HCl. The newly formed amine group served as a directing group to conduct an α-iodination reaction and was subsequently removed by a deamination step. Lastly, cyclization at the aryl iodide position gave rise to a new six-membered ring in the polycyclic structure of **451**.

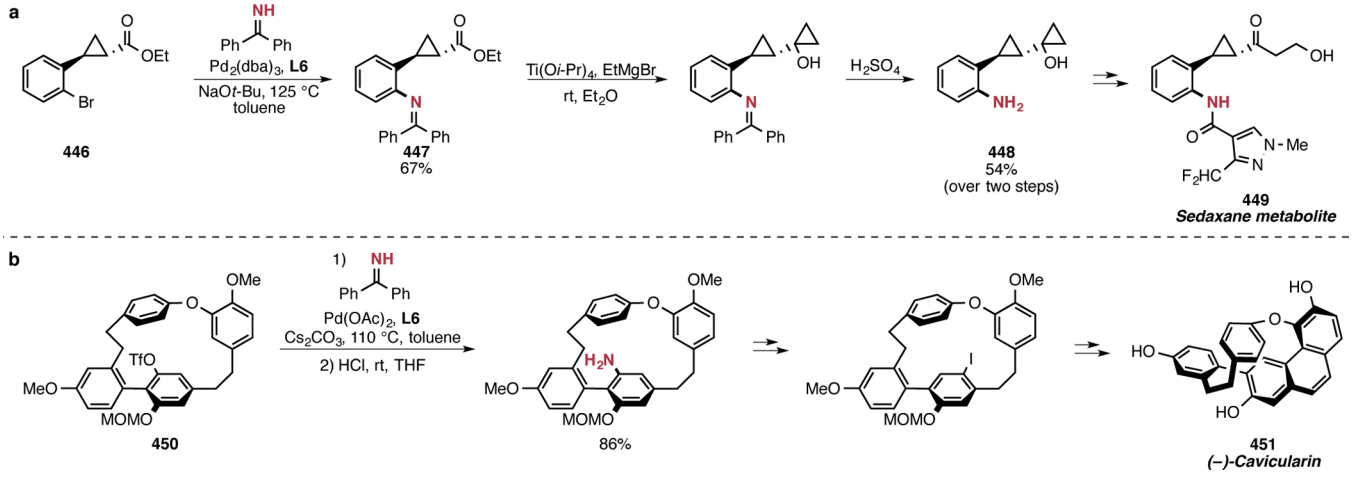
7.1.4. Applications of the Coupling of Benzophenone Imine in Materials Chemistry and Chemical Biology. The use of benzophenone imine in place of ammonia is also well-established in the field of materials science and chemical biology. As an example, Ting and colleagues treated aryl triflate **452** with the ammonia surrogate to prepare primary aniline **453** (Scheme 113), a fluorophore for protein labeling in living

Scheme 113. Coupling of Benzophenone Imine in the Synthesis of a Biological Probe



cells.[388] The C−N coupling reaction was performed in the presence of an **L6**-based catalyst and Cs_2CO_3 as the base in THF, optimal reaction conditions to prevent undesired hydrolysis of the aryl triflate. The target aniline was obtained in 73% overall yield after acidic hydrolysis. Lavis disclosed the synthesis of another organic material for biological purposes through the coupling of benzophenone imine (Scheme 114a).[389] Fluorescent rhodamine **455**, potentially applicable to biological super-resolution microscopy, resulted from the combination of aryl dibromide **454** and benzophenone imine. As in most cases, this transformation proceeded smoothly with a $Pd(OAc)_2$/**L6** catalyst and a weak base. In addition, coupling of the ammonia equivalent was exploited by El-Kaderi and co-

Scheme 112. Applications of the Coupling of Benzophenone Imine in the Synthesis of Natural Products



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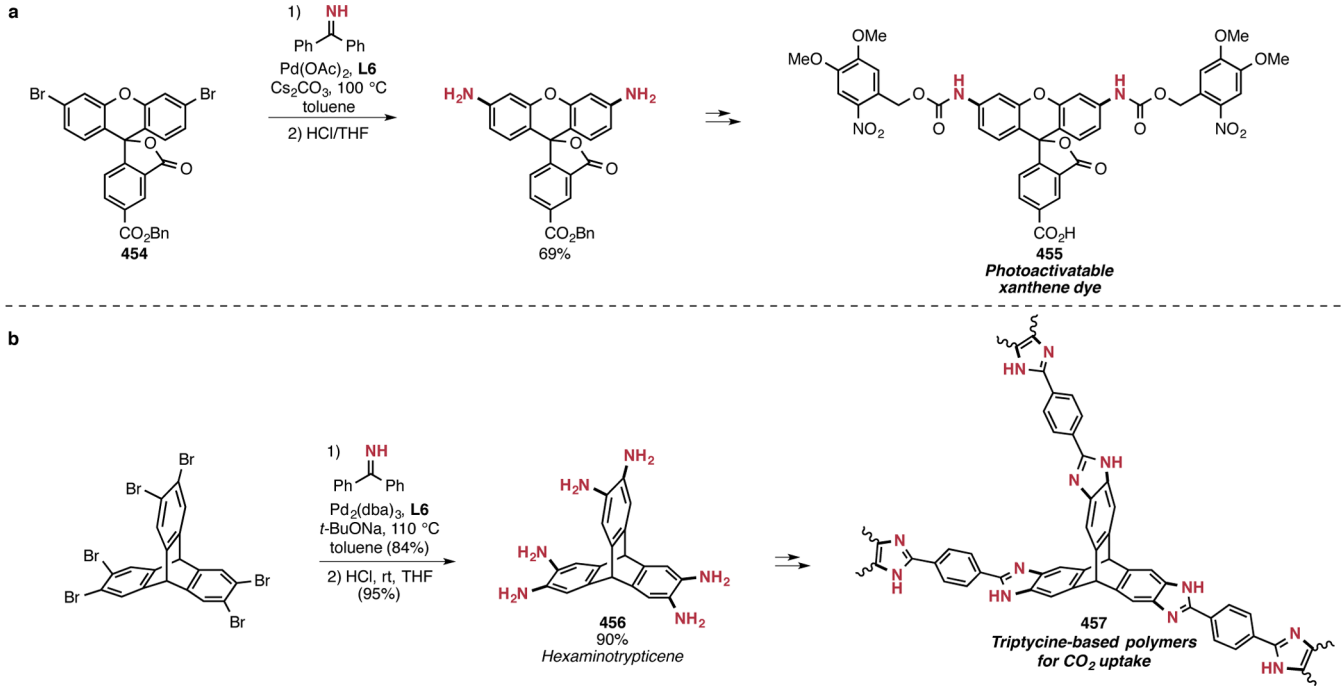
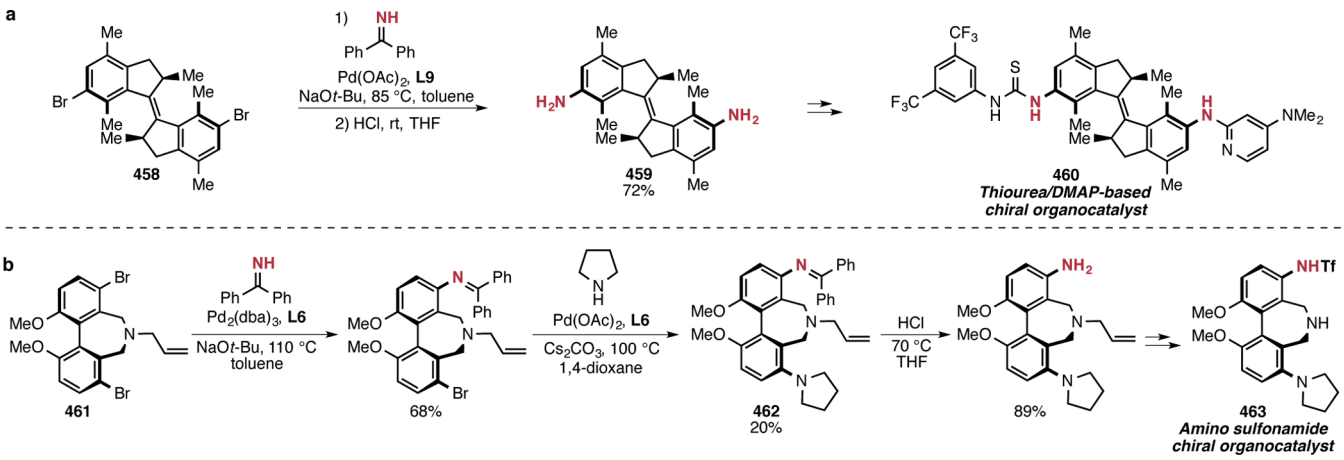
Scheme 114. Applications of the Coupling of Benzophenone Imine in the Synthesis of Organic Materials



Scheme 115. Applications of the Coupling of Benzophenone Imine in the Synthesis of Organocatalysts



workers to access a new nanoporous polymer for selective CO_2 uptake (**457**, Scheme 114b).[390] The trigonal macromolecule integrated a triptycene core with imidazole groups that were rapidly assembled from hexaminotrypticene (**456**), which was generated by six N-arylation reactions with benzophenone imine followed by the corresponding deprotection steps. Interestingly, the formation of **456** occurred in excellent overall yield (90%) for this 6-fold process.

7.1.5. Applications of the Coupling of Benzophenone Imine in the Synthesis of Ligands. The utility of benzophenone imine was also demonstrated in the synthesis of organocatalysts **460** and **463** (Scheme 115a,b). Chiral catalyst **460**, comprised of thiourea and (dimethylamino)-pyridine (DMAP) active sites, was designed by Feringa and co-workers to efficiently perform asymmetric Henry reactions.[391] Benzophenone imine was coupled twice to the enantiomerically pure parent compound **458** using **L9** as ancillary ligand, and subsequent acidic cleavage afforded the desired intermediate **459** in 72% yield. An interesting example of the benefit of obtaining the coupled product in protected form was demonstrated in the synthesis of chiral amino sulfonamide catalyst **463** (Scheme 115b), developed by Maruoka and co-workers to effectively perform asymmetric Mannich reactions.[392] First, 1 equiv of benzophenone imine was coupled with diaryl bromide **461** using a $Pd_2(dba)_3$/**L6** catalyst. Keeping the diarylimine as a protecting group, a second C–N coupling reaction was performed between the remaining aryl bromide and pyrrolidine to form intermediate **462**, which was then readily converted to the desired aniline by treatment with acid.

7.2. LHMDS and Related Nucleophiles

The base lithium hexamethyldisilazide (LHMDS) can also be used as an ammonia surrogate for the synthesis of primary anilines. In comparison to other ammonia substitutes, the cleavage of the silyl groups easily occurs upon acidic workup. Moreover, LHMDS is an inexpensive reagent conveniently available in solution form and does not require a base for the

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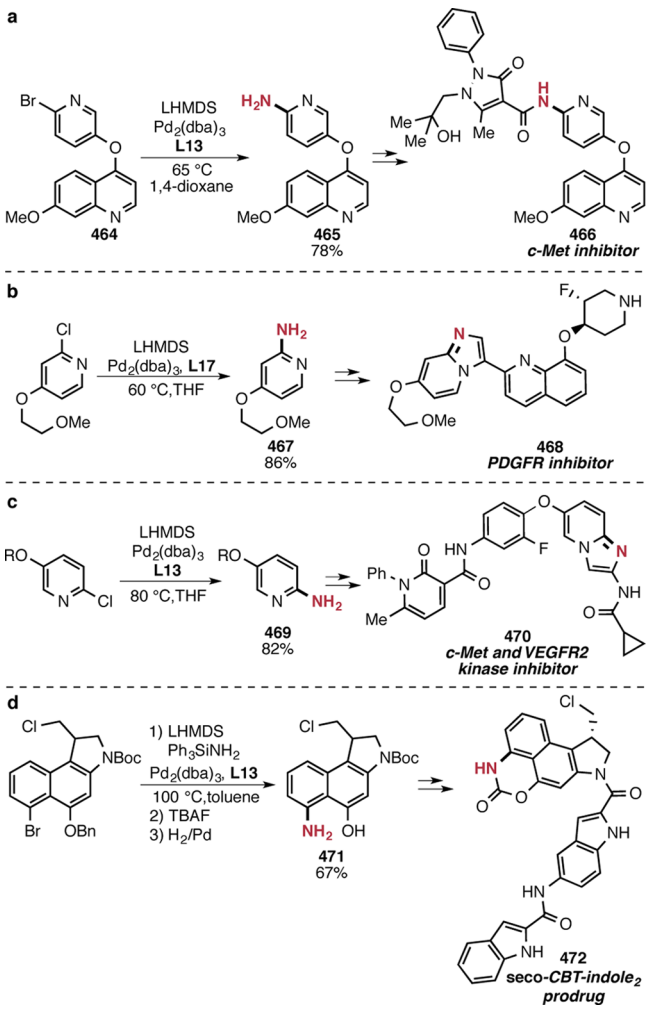
cross-coupling reaction. In 2001, Hartwig and co-workers reported the first N-arylation of LHMDS with aryl chlorides and aryl bromides, which could often be performed at room temperature in the presence of an **L3a**-based catalyst.[393] Contemporaneously, Huang and Buchwald described a related protocol employing **L13** as supporting ligand. In addition, this work addressed the incompatibility of this transformation with sterically hindered aryl halides by employing a less sterically encumbered nucleophile, aminotriphenylsilane (Ph_3SiNH_2), in combination with LHMDS.[394] More recently, Lee and Hartwig expanded the reaction scope to include aryl halides and triflates bearing base-sensitive functional groups or enolizable hydrogens by utilizing zinc bis(hexamethyldisilazide) ($Zn[N(SiMe_3)_2]_2$) as an ammonia surrogate.[395]

7.2.1. Applications of the Coupling of LHMDS in Medicinal Chemistry. The Pd-catalyzed N-arylation of LHMDS is a practical means for the rapid generation of primary anilines in drug discovery. For this transformation, medicinal chemists have typically utilized catalysts based on dialkylbiarylphosphines, most frequently **L13**. Lui and co-workers (Amgen) employed this ligand to furnish heteroarylamine **465** from 2-bromopyridine **464** and LHMDS (Scheme 116a).[396] The final c-Met inhibitor **466** was a potent therapeutic candidate in oncology. In addition, LHMDS couplings have been applied to construct azaheterocycles present in druglike molecules. For instance, Hicken and co-workers (Array BioPharma)[397] and Masumoto and colleagues (Takeda)[398] followed this approach to access heteroarylamines **467** and **469**, respectively, as the source of the imidazopyridine cores in potential cancer therapeutics **468** and **470** (Scheme 116b,c). The corresponding 2-chloropyridines reacted with LHMDS in excellent yield with the assistance of dialkylbiarylphosphine-based catalysts. Following Buchwald's protocol, Boger and co-workers prepared antitumor *seco*-CBI-indole$_2$ prodrug **472**, an analogue of duocarmycin, from precursor **471** (Scheme 116d).[399] Thus, the primary aniline was obtained by combining Ph_3SiNH_2 and LHMDS in the presence of a $Pd_2(dba)_3$/**L13** catalyst. Previous attempts with **A** as an ammonia surrogate or Cu-based catalysts to access compound **471** were unsuccessful. Ultimately, aniline **471** was converted to a cyclic carbamate to produce the target prodrug, which was stable and safer to handle.

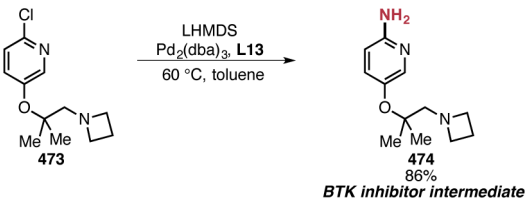
7.2.2. Applications of the Coupling of LHMDS in Process Chemistry. Briggs and co-workers (Hoffmann-La Roche) reported the large-scale preparation of compound **474**, a common precursor of numerous active BTK inhibitors against autoimmune diseases (Scheme 117).[400] Although the final C–N coupling of **473** and LHDMS was common to the medicinal and process synthetic routes, the reaction conditions required substantial modification to be scalable. By slow addition of the LHMDS/THF solution and switching the main reaction solvent from THF to toluene, 443 g of the desired product could be obtained in excellent yield (86%).

7.2.3. Applications of the Coupling of LHMDS in the Synthesis of Natural Products. Scheme 118 depicts the N-arylation of LHMDS in multistep processes toward natural products. In Scheme 118a, Burgos, Vaquero, and their co-workers pursued the synthesis of variolin B to investigate its antileukemia activity.[401] Pd-catalyzed cross-coupling technologies played a key role in their synthetic route, which involved

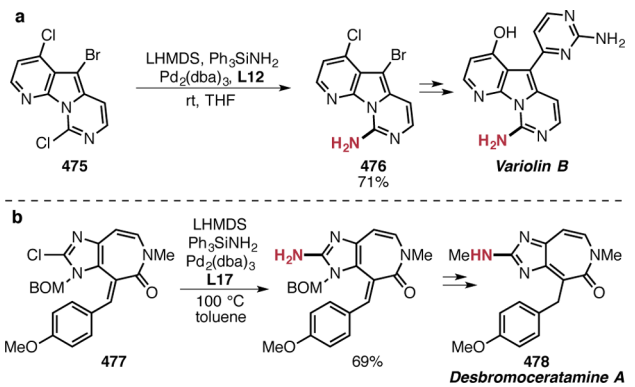
Scheme 116. N-Arylation of LHMDS in Drug Discovery



Scheme 117. Large-Scale Coupling of LHMDS



Scheme 118. N-Arylation of LHMDS in the Synthesis of Natural Products



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three consecutive C−N, C−C, and C−O bond-forming reactions. First, aniline **476** resulted from the chemoselective coupling of Ph_3SiNH_2/LHMDS with trihaloheterocycle **475** at room temperature. Interestingly, the selectivity of the reaction stemmed from the high reactivity of the 2-chloropyrrolopyrimidine group, which reacted preferentially in the presence of an aryl bromide (in contrast to the normal order of reactivity for oxidative addition). Subsequent chemoselective Suzuki and O-arylation steps furnished the final natural product. Related work by Andersen and co-workers demonstrated the reaction between highly active 2-chloroimidazole **477** and a mixture of Ph_3SiNH_2/LHMDS to access ceratamine alkaloid **478** (Scheme 118b).[402] A catalyst based on **L17** enabled the reaction to be carried out in 69% yield after unsuccessful attempts to use S_NAr conditions.

7.2.4. Applications of the Coupling of LHMDS in Materials Chemistry. To date, **L3a** has been the most commonly used ligand for the Pd-catalyzed N-arylations of LHMDS in the field of organic materials. Often, multiple coupling reactions are carried out to access polyanilines, such as the ferrocene **479** (Scheme 119a). Hosono and co-workers prepared tetra(aniline) **479** via a 4-fold LHMDS coupling reaction in 45% yield.[403] This compound was used as a very flexible unit to make polymeric gels for resins and MOFs. In a similar fashion, Choi prepared trigonal structures **482** for anion recognition.[404] Through multiple C−N coupling reactions between triaryl bromide **480** and LHMDS, intermediate **481** was generated in 67% yield (Scheme 119b). Subsequent reaction with iso(thio)cyanate furnished the final (thio)urea units, which are able to selectively establish hydrogen bonds with certain anions. Kaszynski and co-workers employed LHMDS as coupling partner for a rare B−N bond-forming cross-coupling reaction to functionalize *closo*-carbaborates (Scheme 119c).[405] These compounds exhibit three-dimensional aromaticity and are interesting building blocks for the fabrication of electro-optical materials. In analogy to the N-arylation of aryl iodides, the 10-vertex of **483** underwent sequential C−N coupling and diazotization reactions to afford precursor **484**. Notably, earlier experiments with ammonia, **A**, and *t*-Bu carbamate were unsuccessful. The combination of LHMDS with an **L13**-based catalyst and THF as solvent to dissolve the starting material afforded the desired product.

Liebl and Senker explored Pd-catalyzed LHMDS coupling in the construction of *N*-heterocycles embedded in organic oligomers for CO_2 capture (**487**, Scheme 120a).[406] The phthalamide rings of the polymeric network were derived from triazine **486**, which was generated by the 3-fold N-arylation of LHMDS with aryl bromide **485**. Lin accessed aniline **488** via LHMDS coupling (84% yield) in order to form tetrazole-containing compound **489**, which was used to prepare probes for protein imaging in living organisms by two-photon-triggered photoclick chemistry (Scheme 120b).

7.3. *tert*-Butyl Carbamate

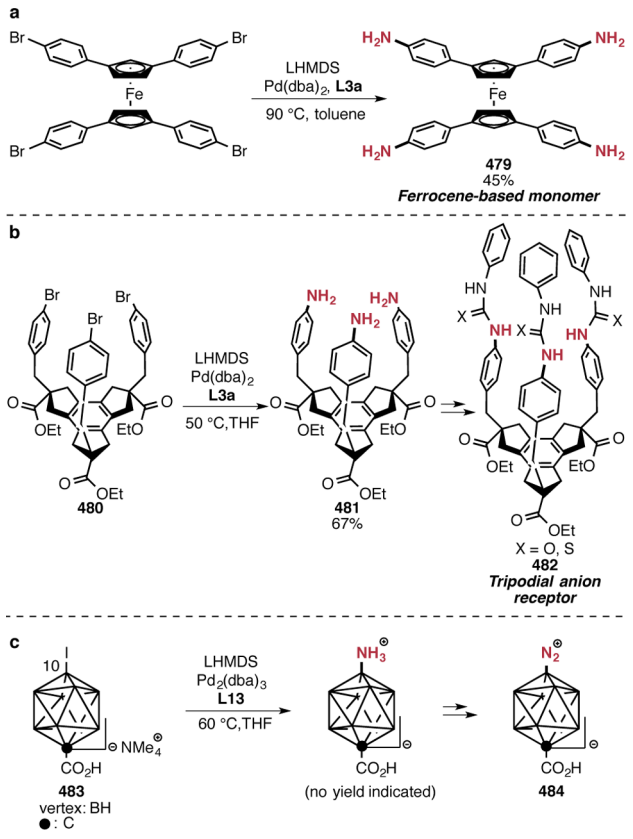
See section 6.5.

7.4. Ammonia

The direct cross-coupling of ammonia has been addressed by several research groups in the past few years.[375,376,407,408] In 2006, the first protocol for coupling ammonia gas as well as lithium amide was reported by Hartwig's group.[409] The transformation occurred using **L10** as supporting ligand and was later expanded by the group to include a broader range of aryl halides and sulfonates.[410] Surry and Buchwald described the use of very bulky dialkylbiarylphosphines for the N-arylation of ammonia in solution to synthesize primary anilines as well as symmetrical and unsymmetrical di- and triarylamines.[411] Several years later, an improved method by the same group allowed for the N-arylation of ammonia with a wide variety of electrophiles, including challenging five-membered heterocycles, using various third-generation palladium precatalysts.[412] Additionally, the use of imidazole-based dialkylmonophosphine ligands for this transformation was reported by Beller's group.[413,414] Stradiotto and co-workers demonstrated the first protocol for the monoarylation of ammonia at room temperature using **L23**, which was an excellent ligand for this reaction.[415,416] Moreover, they demonstrated the C−N coupling reaction with unactivated aryl chlorides as well as in the presence of other primary or secondary amines.

7.4.1. Applications of the Coupling of Ammonia in the Synthesis of Heterocycles. To date, one of the few applications of the direct coupling of ammonia is the synthesis of heterocycles. As part of the work of Stradiotto's group in this area, they reported the synthesis of 2-arylindoles (**492**, Scheme 121a) from 2-alkynylbromoarenes **490** employing this transformation.[417] A commercially available solution of ammonia in 1,4-dioxane was combined with the electrophile (**490**) in the presence of an **L10**-based catalyst. The cross-coupling reaction generated monoarylated intermediate **491**, which readily underwent a base-mediated cyclization step to afford the target heterocycle **492**. Related work by Tsvelikhovsky and Buchwald described the preparation of medicinally relevant dibenzodiazepines **496** and the structural analogues dibenzooxazepines and dibenzodiazepinones, via the direct N-arylation of

Scheme 119. Applications of LHMDS Coupling in Materials Chemistry



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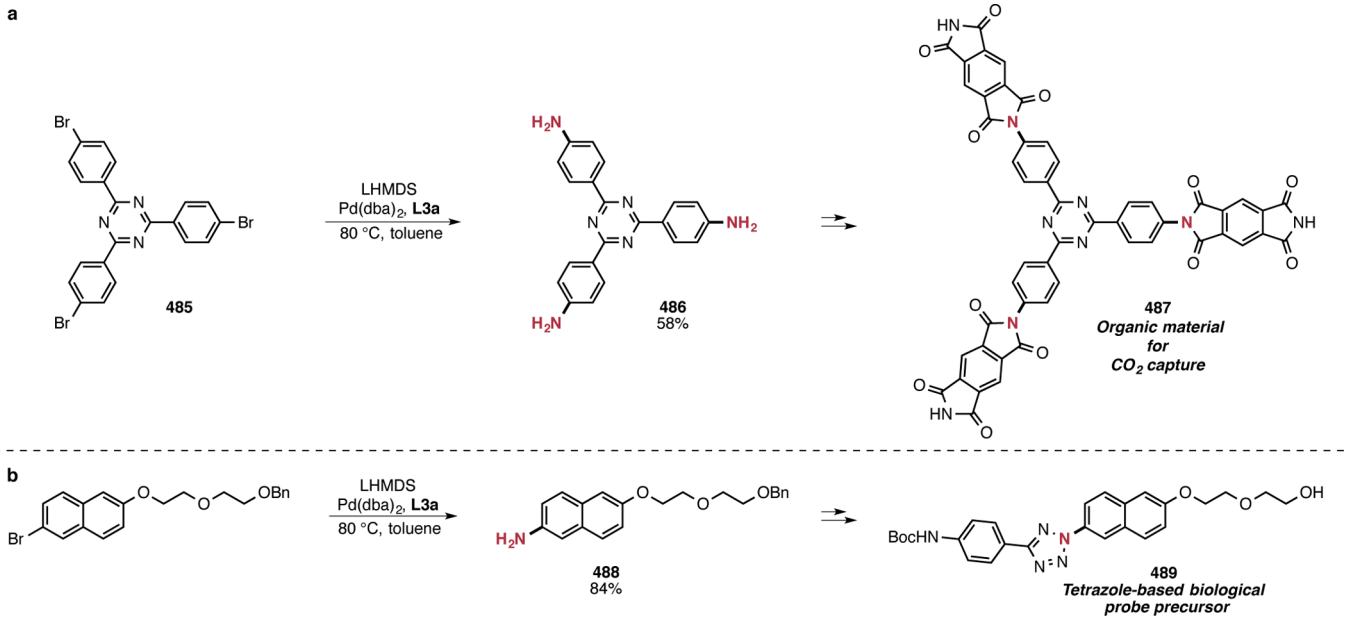
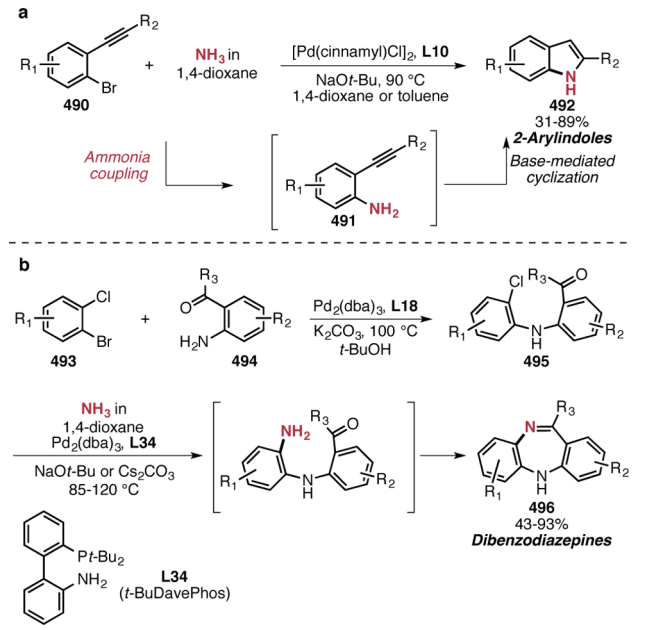
Scheme 120. LHMDS Coupling in Organic Materials



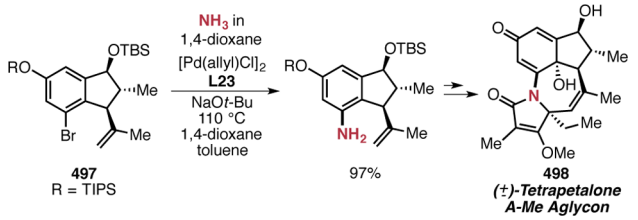
Scheme 121. Direct Coupling of Ammonia in the Synthesis of Heterocycles



ammonia (Scheme 121b, only dibenzodiazepines shown).[418] The key precursor of the heterocycle (**495**) was previously formed by coupling 1,2-dihaloarenes **493** with *o*-carbonylanilines **494** using an **L18**-based catalyst. The cross-coupling of ammonia (5 equiv was required) was then carried out by employing a more bulky dialkylbiarylphosphine ligand, *t*-BuDavePhos (**L34**). Subsequent intramolecular condensation readily afforded the desired dibenzodiazepines in 43−93% yield.

7.4.2. Applications of the Coupling of Ammonia in the Synthesis of Natural Products. Frontier and colleagues employed Stradiotto's method for the coupling of ammonia in the synthesis of (±)-tetrapetalone A-Me aglycon (**498**, Scheme 122), which belongs to a family of natural products with activity

Scheme 122. N-Arylation of Ammonia in the Synthesis of Natural Product 498



against inflammatory diseases.[419] The nitrogen atom embedded in the four-fused-ring core was introduced by reacting aryl bromide **497** with ammonia in the presence of an **L23**-based catalyst (97%). Notably, attempts to couple other primary amines were unsuccessful.

8. HYDRAZINE AND HYDRAZINE DERIVATIVES

The generation of *N*-arylhydrazines is key in the synthesis of numerous nitrogen-containing heterocycles, including indoles, indazoles, and *N*-arylpyrazoles. However, the direct Pd-catalyzed N-arylation of hydrazine to obtain these intermediates has been limited by several intrinsic problems. While the reducing properties of hydrazine can potentially decompose either the reaction catalyst or the aryl halide, metal complexes are also known to cleave the N−N bond, which could lead to undesired side products.[420] Moreover, formation of polyarylated products can result from the existence of two reaction sites. Additionally, hydrazine is a toxic and potentially explosive reagent. In 2010, Lundgren and Stradiotto published the first protocol for the direct monoarylation of hydrazine with aryl chlorides and tosylates using an **L23**-based catalyst.[420] In subsequent work, Buchwald and co-workers developed a continuous flow process aimed at minimizing the potential safety risks of using hydrazine in the presence of metallic compounds.[421] In contrast, hydrazine derivatives, such as aryl- or alkyl-substituted hydrazines, are less susceptible to side reactions and have also been more frequently employed in Pd-catalyzed N-arylation reactions. The groups of Cacci[422,423] and

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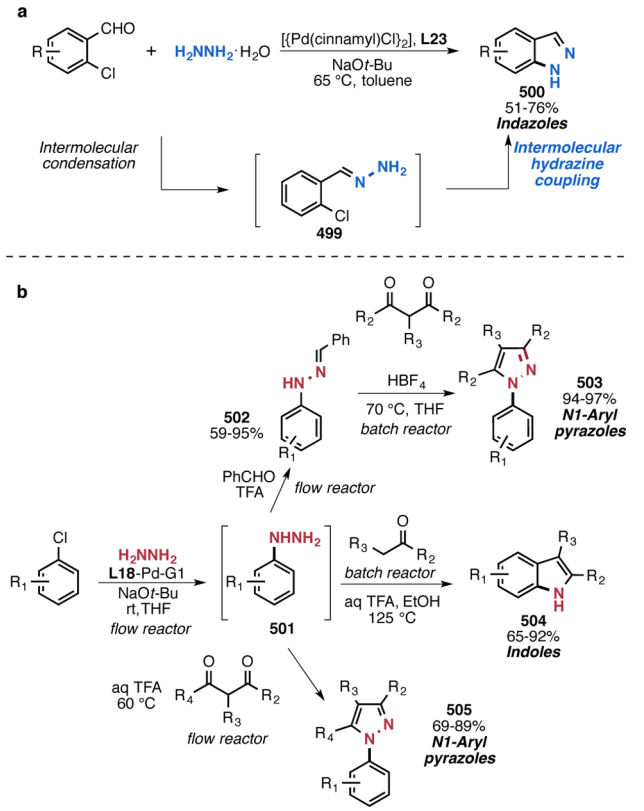
Tsou[424] have reported the synthesis of *N,N*-dialkyl-*N′*-arylhydrazines and Messaoudi and co-workers[425] the synthesis of *N,N*-diaryl-*N′*-arylhydrazines. Alternatively, hydrazides have served as hydrazine surrogates in C−N coupling reactions. In particular, *N*-Boc hydrazides have been employed due to the high regioselectivity of the cross-coupling reaction and the ease of the protecting group removal. Interestingly, Wang and Skerlj described the coupling of *N*-Boc hydrazide at the Boc-protected nitrogen atom.[426] Methods for the *N*-arylation of Boc-protected aryl hydrazides and bis-Boc-protected hydrazide have also been described by the groups of Cho[427] and Zhang,[428] respectively.

8.1. Hydrazine, Substituted Hydrazines, and Hydrazides

8.1.1. Synthesis of Heterocycles via the Coupling of Hydrazines. Several groups have applied the direct coupling of hydrazine to the synthesis of heterocycles (Scheme 123).[420]

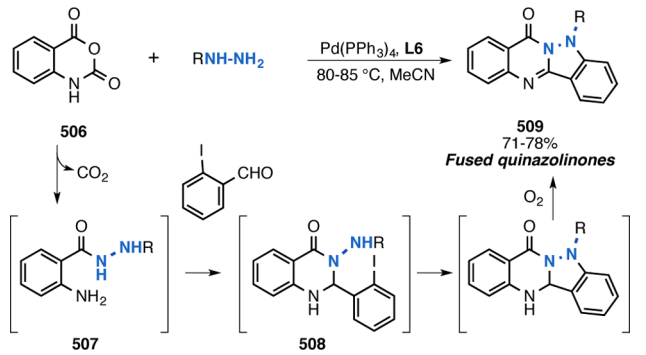
Scheme 123. Synthesis of Heterocycles via Direct Hydrazine Coupling Reactions



Stradiotto and co-workers demonstrated the utility of his method for hydrazine monoarylation to prepare unprotected indazoles, as shown in Scheme 123a. A variety of functionalized indazoles (**500**) were prepared from 2-chlorobenzaldehydes in a one-pot process facilitated by an **L23**-based catalyst. Presumably, condensation between the aldehyde and the hydrazine occurred first to give intermediate **499**. Subsequent intramolecular hydrazine coupling afforded the desired heterocycles in moderate to good yields (51−76%). Similarly, Buchwald and co-workers' continuous flow protocol for the coupling of aryl chlorides and hydrazine was applied to the multistep syntheses of *N1*-aryl pyrazoles **503** and **505** as well as unprotected indoles **504** (Scheme 123b).[421] Both types of heterocycles were derived from a common aryl hydrazine precursor, **501**, which was readily obtained from the corresponding aryl chloride and hydrazine in the presence of the first-generation **L18** precatalyst. Intermediate **501**, was first trapped as the *N*-aryl benzaldehyde hydrazone (**502**) by reaction with benzaldehyde. In a separate operation, the addition of a *β*-dicarbonyl compound under acidic conditions led to the near-quantitative formation of *N1*-arylpyrazoles. Furthermore, addition of either monocarbonyl or *β*-diketone compounds under acidic conditions furnished the target heterocycles **504** and **505** directly from the aryl hydrazine through condensation reactions.

As an alternative, monosubstituted hydrazines are convenient coupling partners that typically react exclusively at the unsubstituted nitrogen center. Alkylhydrazines were among the substrates utilized by Pal and co-workers in a multicomponent reaction (MCR) to access fused heterocycles **509**, as shown in Scheme 124.[429] Through this novel transformation,

Scheme 124. Synthesis of Fused Quinazolinones via the Intramolecular Coupling of Hydrazine



a set of structurally diverse indazoloquinazolinones, potentially active against pulmonary diseases, was rapidly generated in a one-pot protocol. The multistep sequence began by reaction of the hydrazine with isatoic anhydride (**506**) to afford intermediate **507** after loss of CO_2. Subsequent intermolecular condensation and cyclization with *o*-iodobenzaldehyde gave rise to quinazolinone **508**, which underwent Pd-catalyzed intramolecular coupling to give the immediate precursor to **509**. The cross-coupling step was enabled by an **L6**-based catalyst, and further oxidation in the presence of air afforded the fused heterocycles in 71−78% yield.

Intermolecular Pd-catalyzed cross-coupling reactions of N,N-disubstituted hydrazines are shown in Scheme 125. Halland, Lindenschmidt, and their co-workers (Sanofi-Aventis) reported a one-pot method to obtain 1-aminoindoles **512** from 2-halophenylacetylenes (Scheme 125a).[430] Presumably, the tandem reaction begins with the cross-coupling of alkyl and aryl hydrazines **510** to form intermediate **511**, followed by cyclization to close the five-membered ring. The process was general for several N,N-disubstituted nucleophiles such as *N*-Boc-*N*-phenylhydrazine, and *N*-phenylhydrazinecarboxylic acid ethyl ester, as well as hydrazines such as *N*-methyl-*N*-phenylhydrazine and N-heterocyclic hydrazines.[431] Related work by Alami, Messaoudi, and their co-workers demonstrated the utility of the N-arylation of 1-aminoindoles **513** in the construction of polycyclic structures of potential interest to medicinal chemists (**514**, Scheme 125b).[432] The Pd-catalyzed reaction proceeded with **L17** as the supporting ligand, KO-*t*-Bu as the base, and LiCl as an additive. Subsequent benzylation

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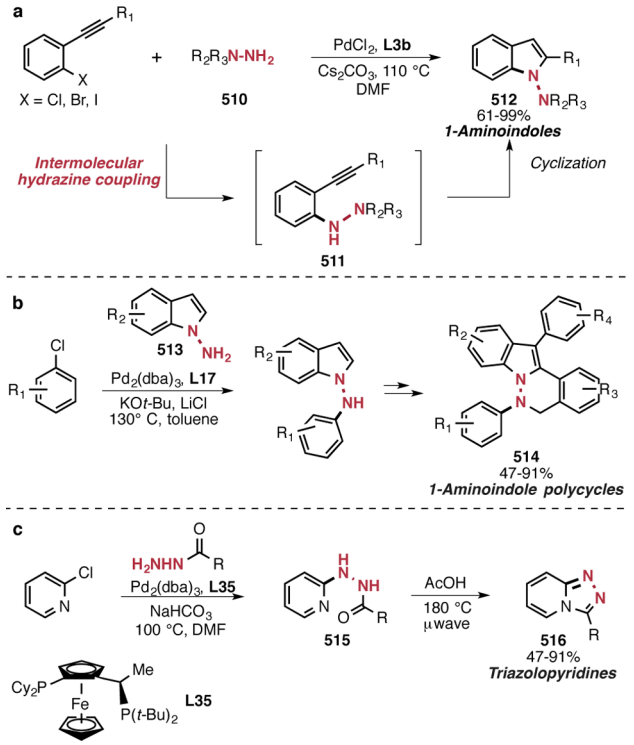
Scheme 125. Synthesis of Heterocycles via the Intermolecular Coupling of Functionalized Hydrazines



and Pd-catalyzed intra- and intermolecular C−H activation steps led to the formation of polycycles **514**.

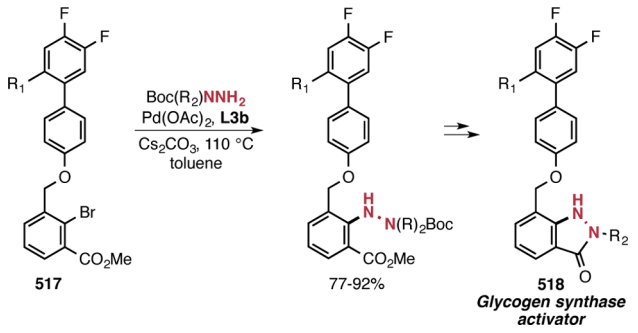
Hydrazides are also efficient coupling partners that incorporate an additional reactive carbonyl group for subsequent transformation. Reichelt and co-workers' (Amgen) synthesis of triazolopyridines **516** bearing different substituents at the C3-position is an illustrative example (Scheme 125c).[433] In two sequential steps, 2-chloropyridine selectively reacted with the terminal nitrogen of the hydrazide to generate intermediate **515**, which led to triazolopyridines by dehydration in acetic acid.

The optimal reaction conditions for the cross-coupling consisted of the combination of $Pd_2(dba)_3$/**L35** with $NaHCO_3$ as the base in DMF.

8.1.2. Applications of the Coupling of Hydrazines in Medicinal Chemistry. In search of novel synthase activators to treat type II diabetes, Qian and colleagues (Hoffmann-La Roche) developed a method to form 2-N-substituted indazolones **518** by the coupling of N,N-disubstituted hydrazines (Scheme 126).[434] Sterically encumbered aryl bromide **517** successfully reacted with several hydrazines using **L3b** as an ancillary ligand and Cs_2CO_3 as the base. Subsequent removal of the Boc group and cyclization under acidic conditions yielded the target heterocycles. A broad series of *N*-Boc-*N*-arylhydrazines and *N*-Boc-*N*-alkylhydrazines were transformed into a range of indazolones.

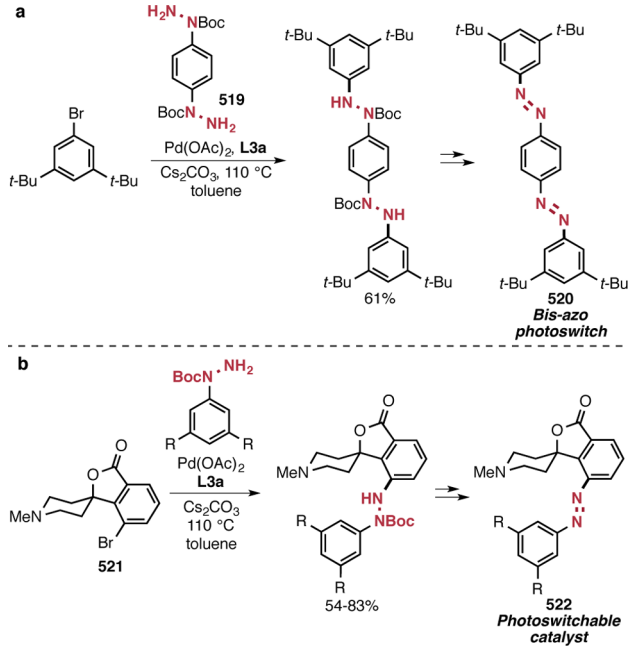
8.1.3. Applications of the Coupling of Hydrazines in Materials Chemistry. The primary application of the Pd-catalyzed cross-coupling of hydrazines in materials chemistry is the synthesis of azo compounds, which are the core of many photoswitchable molecules. These materials are valuable building blocks for nanotechnology because they undergo structural changes when subjected to UV−visible light radiation. Hecht and co-workers have reported several azo

Scheme 126. Hydrazine Coupling in Drug Discovery



compounds derived from the reaction between *N*-Boc-*N*-arylhydrazides and aryl bromides (Scheme 127a,b). Linear bis-

Scheme 127. Syntheses of Photoswitches via Hydrazine Coupling



azobenzene **520** was prepared by 2-fold N-arylation of previously synthesized bis-hydrazide **519** in 61% yield.[435] Additionally, Hecht's group obtained a variety of photoswitchable catalysts **522** by reacting aryl bromide **521** and several *N*-Boc-*N*-arylhydrazines.[436] Both transformations took place under identical conditions using a $Pd(OAc)_2$/**L3a** catalyst and Cs_2CO_3 as the base at 110 °C in toluene. A related contribution by Rebek and co-workers was the preparation of azo-benzene glycoluril **525**, a photocontrolled organogel for drug delivery and sensing applications, among other things (Scheme 128).[437] Although the yield was low (17−21%), the authors demonstrated that it was possible to obtain the product of coupling at the Boc-protected nitrogen atom of $BocNHNH_2$ using a catalyst based on **L19**. The resulting bis-N,N-disubstituted hydrazine **523** underwent a second Pd-catalyzed N-arylation with aryl bromide **524** using **L3b** as an ancillary ligand instead (50−77% yield).

8.2. Hydrazones

Benzophenone hydrazone is a practical alternative to the direct use of hydrazines in Pd-catalyzed C−N coupling reactions. This

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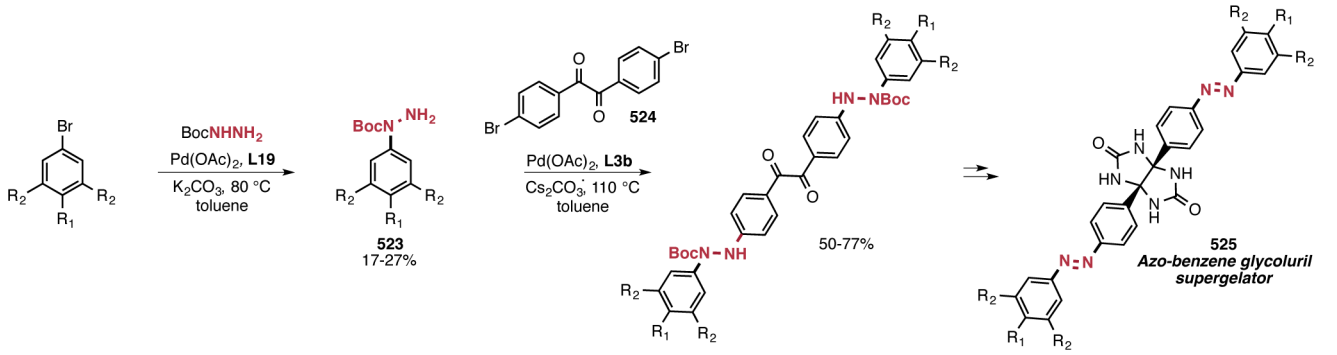
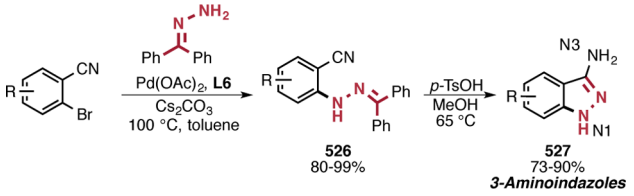
Scheme 128. Syntheses of Photoswitch 525 via Hydrazine Coupling



hydrazine surrogate is commercially available and safer than hydrazine itself and thus has been often used in the synthesis of N-based heterocycles. Hartwig disclosed the first method for the N-arylation of benzophenone hydrazone with aryl bromides in the presence of an **L9**-based catalyst.[438] Shortly thereafter, Buchwald and co-workers demonstrated a broad-scope method and the practicality of benzophenone hydrazone coupling in a variant of the Fischer indole synthesis that avoids the need for toxic and unstable arylhydrazine precursors.[439] Other examples of the coupling of benzophenone hydrazone have been shown using MePhos-,[440,441] **L7**-,[439] **L10**-,[442] and **L17**-based[443] palladium catalysts. The use of these catalysts expanded the scope of the transformation, allowing aryl chlorides and benzenesulfonate substrates to be used, for example.

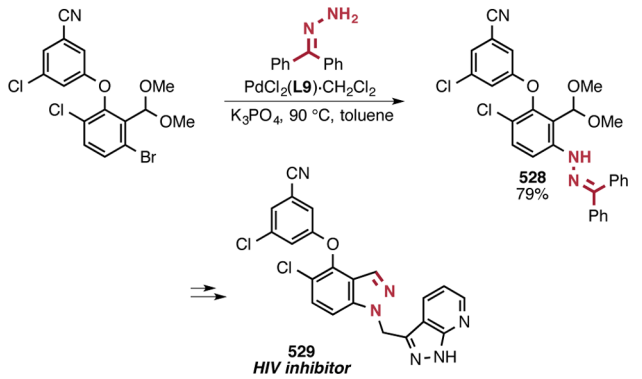
8.2.1. Synthesis of Heterocycles via the Coupling of Hydrazones. A common sequence in the preparation of diazoles is the tandem Pd-catalyzed cross-coupling of a hydrazone followed by condensation. For example, Fabis and co-workers reported an efficient method to access a family of 3-aminoindazoles (**527**, Scheme 129) from 2-bromobenzonitriles.[444] First, the N-arylation of benzophenone hydrazone using **L6** as supporting ligand afforded intermediate **526** in excellent yield (80−99%). The use of Cs_2CO_3 as the base instead of NaO-*t*-Bu was key to preventing an undesired Wolff−Kischner-type reduction of the electron-poor hydrazone. Subsequent sequential acidic deprotection/cyclization steps yielded target heterocycles **527** in 73−90% yield. Furthermore, this protocol offered an alternative synthesis of *N1*-alkyl-3-aminoindazoles that avoids protection of the N3-position, which is typically required, in order to selectively alkylate the N1-site. From intermediate **526**, a N1-alkyation can be carried out regioselectively prior to the standard deprotection and cyclization steps (not shown).[445]

Scheme 129. Use of Hydrazones in the Synthesis of Heterocycles



8.2.2. Applications of the Coupling of Hydrazones in Process Chemistry. In the pharmaceutical industry, the use of benzophenone hydrazone played a key role in the multikilogram-scale synthesis of HIV inhibitor **529** described by Goodyear and co-workers (Merck) (Scheme 130).[446] In the medicinal chemistry route, the core indazole ring of compound **529** was directly constructed using hydrazine hydrate, an undesirable reagent for large-scale operations due to its toxicity. Moreover, the sequence lacked regioselectivity in the direct N1-alkylation of the indazole. To circumvent these limitations, the synthetic approach was redesigned using a Pd-catalyzed arylation of benzophenone hydrazone. The cross-coupling reaction led to the generation of intermediate **528**, allowing for the desired selective N1-alkylation step, which was followed by the standard deprotection and cyclization steps to afford the substituted indazole (**529**). The cross-coupling reaction was carried out with a $PdCl_2$(**L9**)·CH_2Cl_2 catalyst, since the use of very active ligands such as **L6**, **L15**, or **L17** produced significant amounts of the diarylated product. In addition, the use of NaO-*t*-Bu as the base resulted in hydrazone addition to the nitrile group, and thus, a milder base (K_3PO_4) was selected instead. Due to the heterogeneous nature of the solution, very effective mixing was key to the success of the reaction. The new scalable synthetic route improved the overall yield for the preparation of **529** from 5% to 35%.

Scheme 130. Medicinal and Process Synthetic Routes of Drug Candidate 529



8.2.3. Applications of the Coupling of Hydrazones in the Synthesis of Ligands. Ma and co-workers employed hydrazone coupling to synthesize novel chiral ligand **531** (Scheme 131), which was active in the Cu-catalyzed asymmetric conjugate borylation reactions to form secondary alkylboronates.[447] The 1,2,4-triazolium salt portion of the planar ligand was built from *N*-arylhydrazone **530**, previously obtained by reacting enantiomerically pure 4-iodo[2.2]-paracyclophane and benzophenone hydrazone. The cross-

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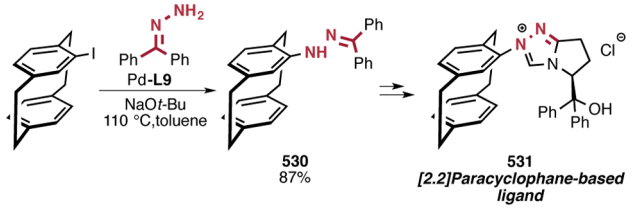
Scheme 131. Application of Benzophenone Hydrazone Coupling to the Synthesis of Organocatalyst 531



coupling proceeded in excellent yield with an **L9**-based catalyst and NaO-*t*-Bu.

9. NH-HETEROCYCLES

Although N-arylated (benzo)azoles are prevalent structures in medicinal compounds and organic materials, there are few methods for their preparation with Pd-based catalysts. In contrast, the Cu-catalyzed N-arylation of azoles is a well-established and widely used transformation.[8] Many more examples of monoazole coupling exist in the literature than those with diazoles, which still remain very challenging coupling partners. In general, bulky ligands are required for the N-arylation of azoles for two reasons: (1) in many cases, coordination of the N-heterocycle to the $L_nPd(Ar)X$ is difficult and the use of bulkier ligands increases the amount of $L_1Pd(Ar)X$, the species to which the heterocycles can best bind, and (2) reductive elimination is rather difficult from small electron-rich five-membered ring palladium complexes.[448] One additional complication is that these coupling reactions can suffer from a lack of chemoselectivity, giving rise to C-arylated (monoazoles) or N′-arylated (diazoles) products instead.[8]

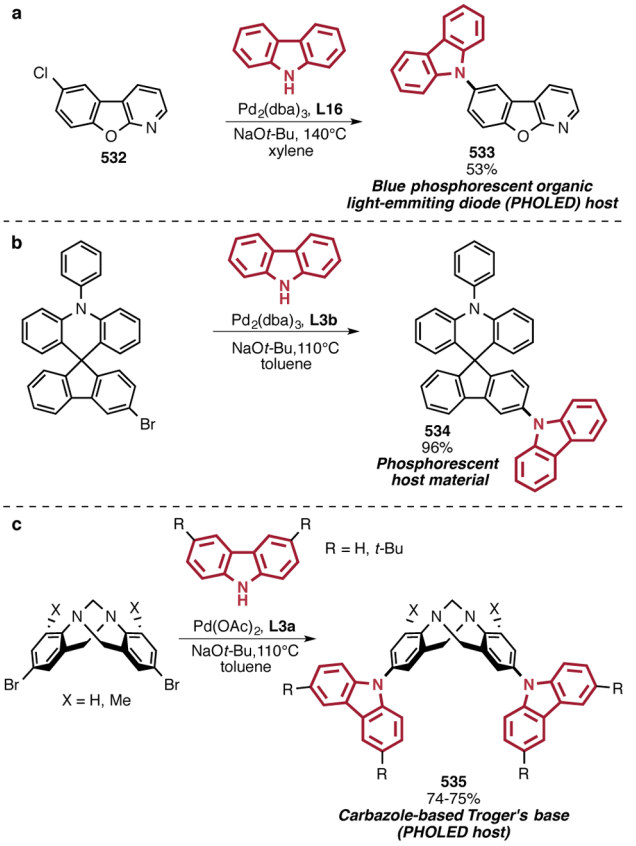
9.1. Carbazole

Although there are no recent methodological papers focusing on the direct Pd-catalyzed N-arylation of carbazoles, this transformation has been widely used in the field of materials chemistry. The most up-to-date report on this topic is the N-arylation of *N*-carbazolyl magnesium chloride (made in situ from carbazole and methyl magnesium chloride) with a catalyst based on Mo-Phos (cBRIDP) by Nakayama and co-workers.[449] However, the coupling of carbazole and carbazole derivatives is a versatile reaction that has been demonstrated with numerous Pd/L complexes, with those based on **L3a** and dialkylbiarylphosphines being most common. Typically, the reaction requires high temperatures and NaO-*t*-Bu as the base.

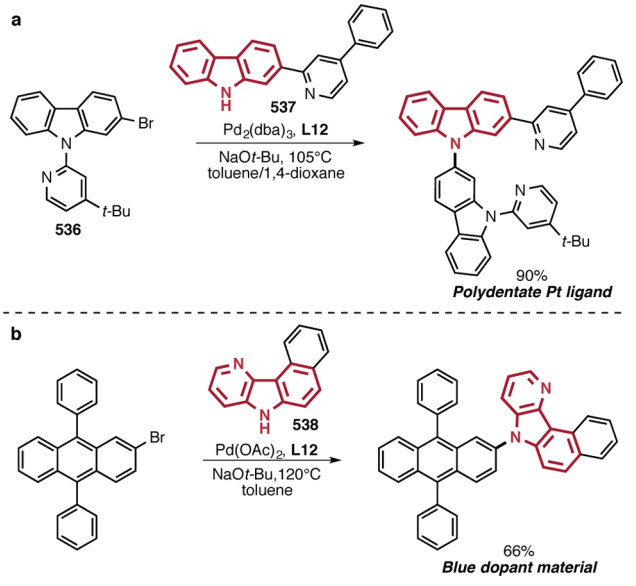
9.1.1. Applications of the N-Arylation of Carbazoles Coupling in Materials Chemistry. *N*-Arylcarbazoles are prevalent units in host materials for organic light-emitting diodes (OLEDs). Very often, the C−N bond of these structural units is produced via Pd-catalyzed cross-coupling reactions. Examples of the N-arylation of carbazole are shown in Scheme 132. Lee synthesized blue phosphorescent diode **533** from heteroaryl chloride **532** using **L16** as ancillary ligand (Scheme 132a),[450] while Jiang, Liao, and their co-workers obtained spiro compound **534** by coupling carbazole in the presence of a $Pd_2(dba)_3$/**L3b** catalyst (Scheme 132b).[451] Additionally, Chow, Moorthy, and their co-workers prepared a series of V-shaped Tröger's bases (**535**, Scheme 132c) as PHOLED hosts via the 2-fold N-arylation of carbazoles facilitated by an **L3a**-based catalyst.[452]

Additional examples of the C−N coupling with carbazole derivatives are shown in Scheme 133. Li and co-workers employed a dialkylbiarylphosphine to effect the reaction

Scheme 132. N-Arylation of Carbazoles Applied to the Synthesis of OLEDs



Scheme 133. Use of Carbazole Coupling in the Synthesis of Fluorescent Materials



between heteroaryl bromide **536** and substituted carbazole **537** (90% yield, Scheme 133a).[453] The resulting tetradentate species formed Pt(II) complexes used to prepare red phosphorescent OLEDs. Similarly, Kim, Yoon, and and their co-workers were able to couple *δ*-carboline **538** and 7-bromo-9,10-diphenylanthracene under comparable reaction conditions

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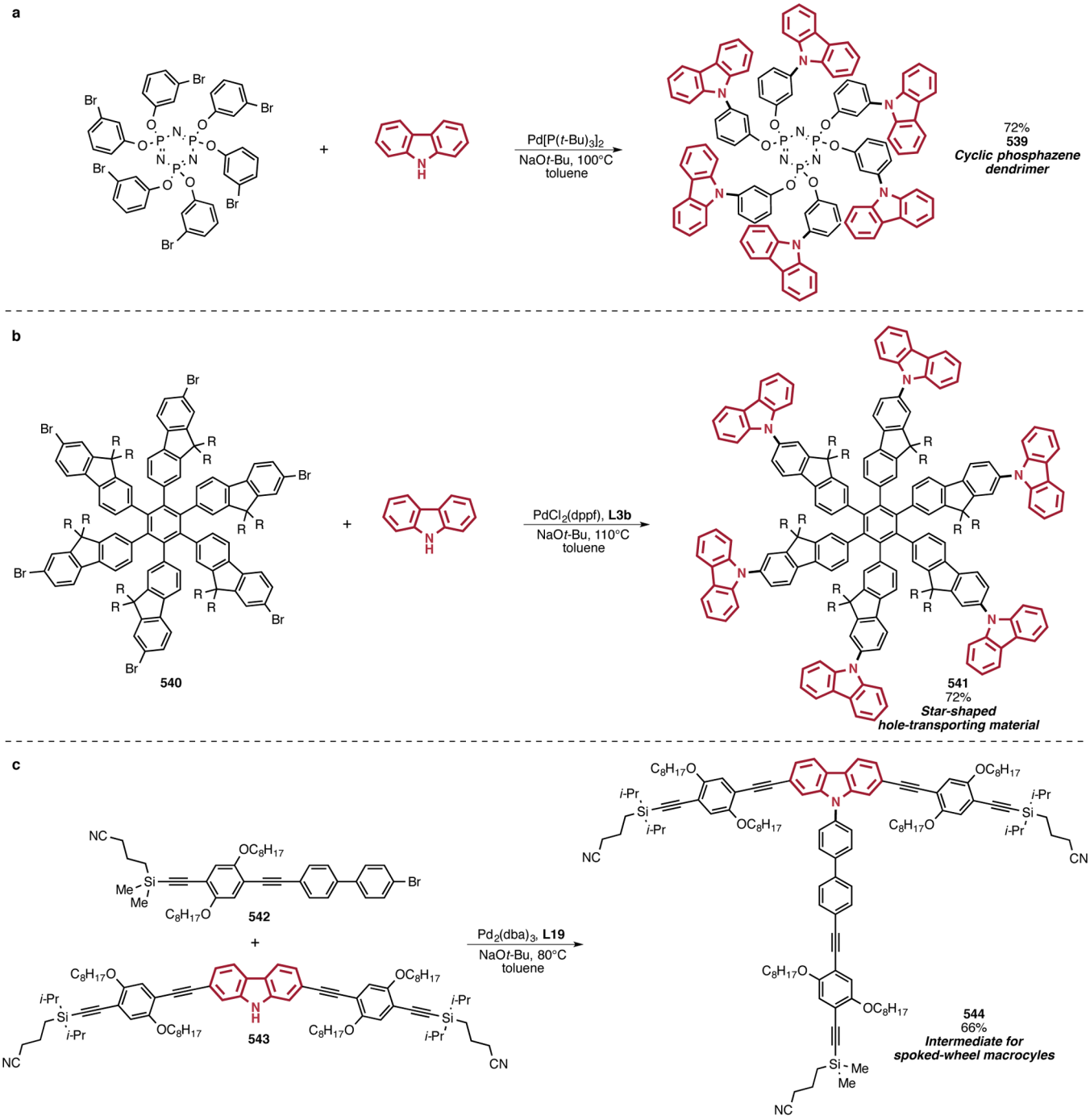
Scheme 134. Carbazole Coupling in the Synthesis of High Molecular Weight Materials



using an **L12**-based catalyst and NaO-*t*-Bu in toluene (Scheme 133b).[454]

High molecular weight compounds could also be prepared using C−N coupling reactions with carbazole-type molecules (Scheme 134). Cyclic phosphazene dendrimer (**539**, Scheme 134a), a host material for blue and green OLEDs, was prepared in this manner by Sellingerand co-workers.[455] The outer sphere of the macromolecule was functionalized with carbazole groups using multiple N-arylation reactions facilitated by an **L3a** catalyst. Similarly, Ma, Yang, and their co-workers prepared new hole-transporting materials for OLEDs (**541**) via the cross-coupling of carbazole and hexakis(9,9-dihexyl-9*H*-fluoren-2-yl)benzene core **540** (Scheme 134b).[456] The star-shaped compound was generated in 70% yield using **L3b** as ancillary ligand. Lastly, in order to study the energy-transfer mechanisms occurring in OLEDs, Höger, Lupton, and their co-workers prepared a series of π-conjugated spherical macromolecules derived from intermediate **544** (Scheme 134c).[457] To access this compound, aryl bromide **542** and functionalized carbazole **543** were combined in the presence of an **L19**-based catalyst. Six units of **544** were then connected to a hexagonal core, leading to the target spherical macromolecule.

9.2. Indole

The formation of *N*-arylindoles, which are common structural components in clinically relevant molecules, has typically been

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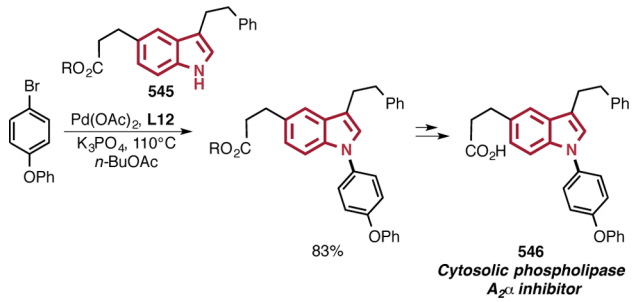
achieved via Ullman coupling and S_NAr-type reactions.[458−460] In contrast, the first Pd-catalyzed N-arylation of indoles was demonstrated in 1998.[20] Hartwig and co-workers reported the C−N bond-forming reaction between indoles and aryl bromides using a catalyst based on **L9**. Later they studied the use of **L3a** as a ligand, which allowed the reaction to occur under much milder conditions.[16] Shortly thereafter, Buchwald's group developed the first general method for the N-arylation of indoles, expanding the scope to substituted indoles, hindered aryl halides, and aryl triflates, by virtue of bulky electron-rich phosphines.[443,461] Additionally, examples of indole *N*-arylation have been reported by Nolan, using SIMesHCl as supporting ligand,[381] and by Stradiotto and co-workers with **L22**.[23]

9.2.1. Applications of the Coupling of Indoles in Medicinal Chemistry. Through Pd-catalyzed indole coupling, Tomoo and co-workers prepared a family of cytosolic phospholipase $A_2\alpha$ inhibitors active against inflammatory and respiratory diseases (Scheme 135).[462] The N-arylation of indole **545** with a large number of functionalized aryl bromides ultimately gave rise to species **546** as the most effective drug candidate. The cross-coupling reaction was enabled by an **L12**-based Pd catalyst and a weak base to avoid undesired reactions of the ester group.

Scheme 135. An Example of the N-Arylation of Indole in Medicinal Chemistry



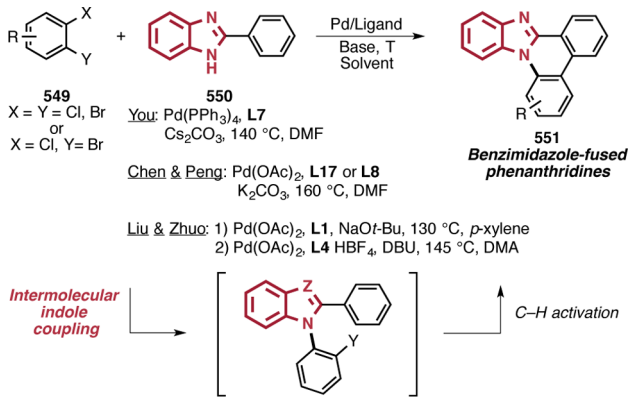
9.2.2. Applications of Indole Coupling in the Synthesis of Natural Products. Boyd and Sperry employed Pd-catalyzed cross-coupling in the total synthesis of (−)-aspergilazine A (**548**, Scheme 136), a bisindole alkaloid isolated from a marine fungus.[463] The interest in this compound stems from its unique N1′−C6 bisindole bond, only observed in one other natural product. The formation of the C−N bond was attempted with typical Cu catalysts previously used in the synthesis of natural products. However, these conditions led to C9 epimerization at high temperatures or no product formation at low temperatures. Thus, the less-explored Pd-catalyzed N-arylation of indoles emerged as an alternative. **L17** was a suitable ligand to achieve the coupling with high selectivity in the presence of two additional N-arylation sites. Notably, the *N*-Boc aryl bromide **547** was employed as coupling partner due to the instability of the unprotected analogue under the reaction conditions. The target product was obtained in 79% yield without any epimerization at C9, demonstrating the applicability of Pd-catalyzed N-arylation of indoles in the synthesis of natural products.

9.3. Diazoles

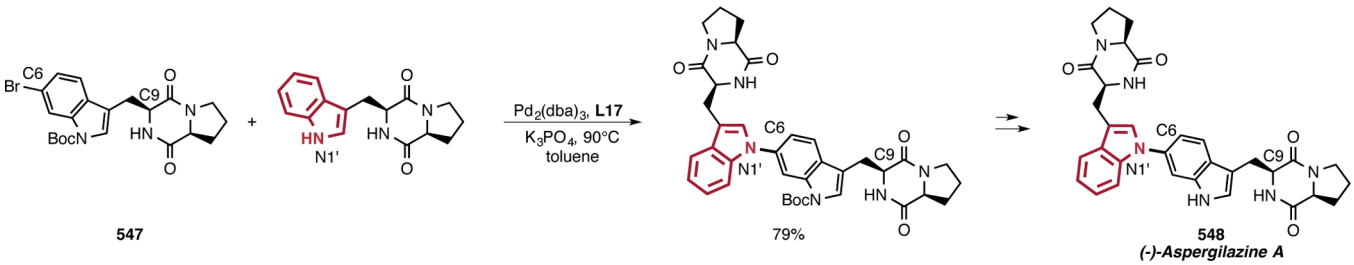
The Pd-catalyzed N-arylation of diazoles and their benzo derivatives has not been extensively developed, presumably due to the low nucleophilicity of these heterocycles. In 2006, Buchwald and co-workers showed that the use of bulky ligands enabled the coupling of pyrazoles and indazoles (**L19**), as well as benzimidazoles (**L21**).[210] There have also been reports about the N-arylation of pyrazoles using **L1** as supporting ligand[464] or **L13**,[465] although these methods were restricted to only one type of electrophile, 2,6-dibromopyridine and 4-(trifluoromethylsulfonyloxy)coumarins, respectively. Additionally, Buchwald's group disclosed the N1-arylation of unsymmetric imidazoles with aryl halides and triflates,[466] as well as the regiospecific synthesis of *N*-arylbenzimidazoles using biarylphosphine ligands.[276]

9.3.1. Applications of the Coupling of Diazoles in the Synthesis of Heterocycles. Three research groups contemporaneously reported related methods for the synthesis of benzimidazole-fused phenanthridines **551** (Scheme 137). The interest in these N-heterocyclic structures stems from their optoelectronic properties, such as blue-emitting performance, high quantum yields, and long fluorescence lifetimes. The three protocols described the transformation of 1,2-dihaloarenes (**549**) and 2-aryl-*N*-heterocycles (**550**) into the corresponding phenanthridines via a domino-type process, although the order

Scheme 137. Alternative Methods for the Synthesis of Fused Phenantridines



Scheme 136. Synthesis of (−)-Aspergilazine a via Indole Cross-Coupling



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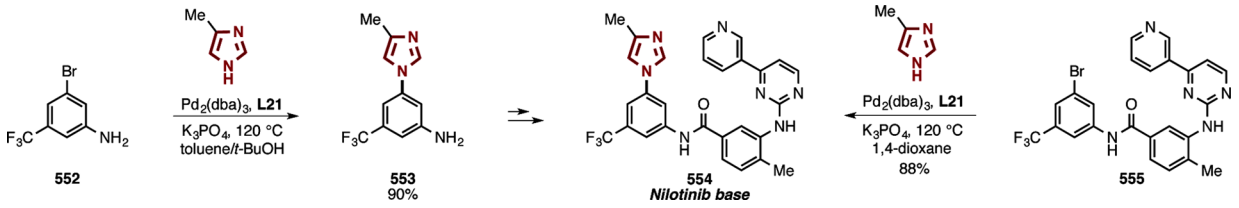
Scheme 138. Two Synthetic Strategies To Access Nilotinib

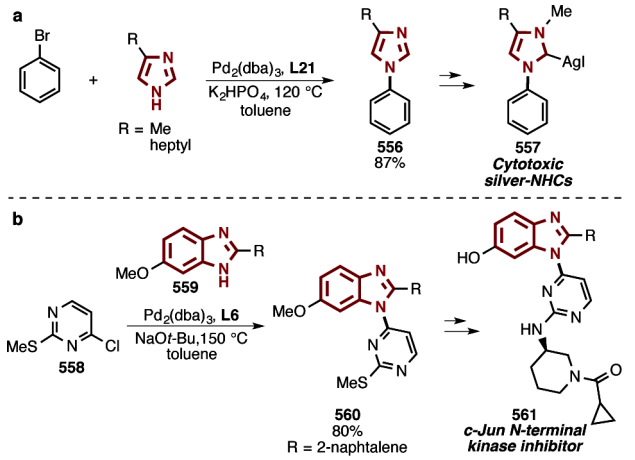


of the two Pd-catalyzed steps, namely, C−N coupling and C−H activation, is unclear. You and co-workers reported conditions giving rise to a broad reaction scope in which (benzo)-imidazoles, indoles, and pyrroles were all suitable coupling partners.[467] When starting from 1,2-dihaloarenes bearing different halogens, he observed exclusively one regioisomer due to the differing reactivity of the halides. You's method was carried out at 140 °C with an **L7**-based catalyst and Cs_2CO_3 in DMF. Chen, Peng, and their co-workers employed 1,2-bromoarenes and 2-arylbenzimidazoles to form benzimidazole-fused phenanthridines.[468] Their reaction conditions consisted of $Pd(OAc)_2$/**L17** or $Pd(OAc)_2$/**L8** catalysts in the presence of K_2CO_3, at 160 °C in DMF. Lastly, Liu, Zhuo, and their co-workers developed a one-pot two-operation process using different catalysts for each step: (1) $Pd(OAc)_2$, **L1**, NaO-*t*-Bu (C−N coupling) and (2) $Pd(OAc)_2$, **L4**·HBF_4, DBU (C−H activation).[469] The authors also employed 2,3-dihalopyridines and 2-heteroarylbenzimidazoles as coupling partners, increasing the heterocycle content of the final products.

9.3.2. Applications of the Coupling of Diazoles in Medicinal Chemistry. Buchwald and co-workers reported a practical method for the N1-selective arylation of unsymmetrical imidazoles and used it to synthesize nilotinib (Tasigna, Scheme 138), a drug for the treatment of chronic myelogenous leukemia.[466] The Pd-catalyzed approach was an alternative to the previous synthesis of the pharmaceutical, in which the introduction of the imidazole via Cu-catalyzed or S_NAr reactions suffered from poor regioselectivity. They reported two viable synthetic routes in which 4-methylimidazole was coupled with different aryl bromides using the same catalyst system, $Pd_2(dba)_3$/**L21**. In one approach, intermediate **553** was obtained in 90% as a single regioisomer from aryl halide **552**. Due to the presence of a nucleophilic amino group in both **552** and **553**, an excess of the imidazole, the use of a low concentration of the aryl halide, and a solvent mixture of toluene/*t*-BuOH were required. As an alternative, late-stage introduction of the imidazole into aryl bromide **555** readily provided the target compound in 88% yield. Interestingly, mechanistic studies of the imidazole coupling suggested that the heterocycle was able to bind to the palladium center when forming the catalyst in situ but was not able to displace the ligand once the complex was generated. Thus, to prevent catalyst deactivation, the active catalytic species was prepared prior to the reaction by preheating the palladium source and the ligand together.

Adopting Buchwald's method, Bjørsvik and co-workers prepared metallodrugs **557** (Scheme 139a), which showed activity against leukemic cells.[470] The functionalized imidazole underwent regioselective N1-arylation with the previously reported catalyst, affording the desired intermediate **556** in 87% yield. In addition, Hah and co-workers obtained benzimidazole derivative **561** (Scheme 139b), a potent candidate against neurodegenerative diseases, by selective C−N bond formation.[471] The cross-coupling of 4-chloropyrimidine **558** and benzimidazole **559** in the presence of an **L6**-based catalyst efficiently provided the desired intermediate **560** in 80% yield.

Scheme 139. Imidazole-type N-Arylations for the Synthesis of Biologically Active Compounds



10. FIVE-MEMBERED HETEROARYL HALIDES

Given the prevalence of five-membered heterocycles in biologically active compounds, natural products, and organic materials, this review includes a specific section about the N-arylation of five-membered heteroaryl halides with any class of N-based coupling partner. Despite the increased use of Pd-catalyzed C−N coupling reactions, this transformation remains limited in scope due to (1) the ability of many of the substrates to bind to the LPd(Ar)X intermediates and to deactivate the catalyst and (2) the small size and more-electron-rich nature of five-membered heterocycles compared to their benzenoid counterparts. In many instances, the rate-determining step of Pd-catalyzed coupling reactions with five-membered heteroaryl halides is reductive elimination.[448,472,473] Moreover, these substrates have great structural diversity. Five-membered heterocycles can have one or more heteroatoms (O, S, and N), be benzo-fused, or contain free NH groups. All of these features make the development of general methods for the coupling to five-membered heterocyclic halides a challenging task.

The first N-arylation reactions of halofurans and halothiophenes were reported by Hartwig and co-workers using **L3a**[474] and **L9**[448] as supporting ligands. Significantly, they observed great differences in reactivity, depending on the position of the halide (C2- vs C3-position). Only a few examples of the coupling of haloazoles (bearing a nitrogen and an additional heteroatom) have been reported. Although the decreased electron density of azoles compared to heterocycles with one heteroatom[474] should facilitate cross-coupling reactions, these

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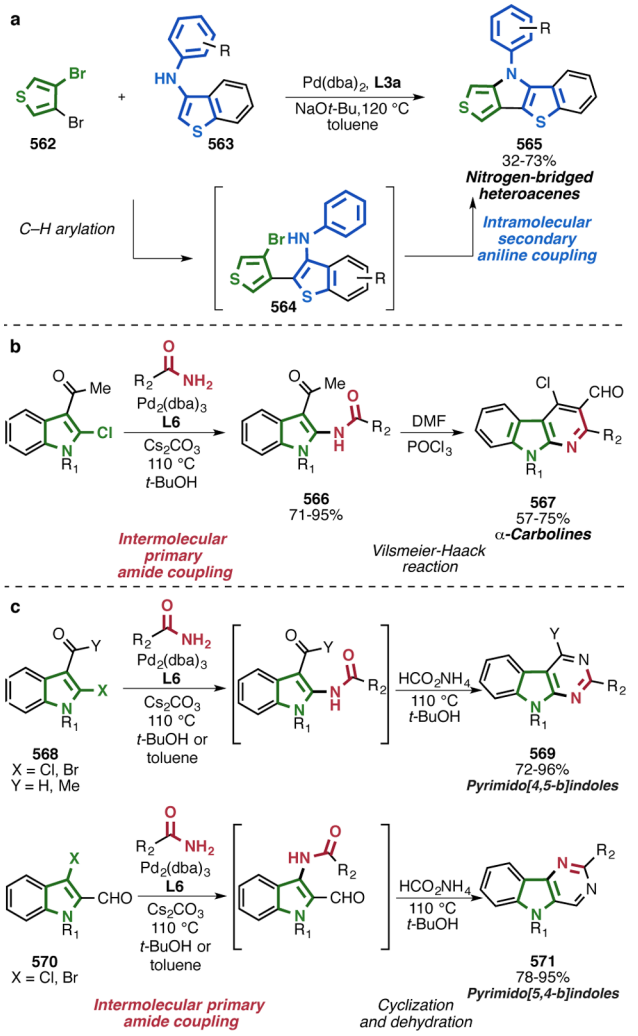
substrates are challenging due to the presence of an sp^2-hybridized nitrogen atom that can coordinate to the palladium center.[472] Hartwig and co-workers showed that the use of an **L3a**-based catalyst allowed for the C−N coupling of halothiazoles, -imidazoles, and -oxazoles with a limited number of amines.[474] Recently, Buchwald and co-workers established the first general methods for the N-arylation of five-membered heteroaryl halides with amides[472] and amines.[245] First, a series of thiazole, furan, protected pyrazole, and protected imidazole electrophiles were successfully coupled with primary amides with the use of the bulky and electron-rich ligand AdBrettPhos. Shortly after, the reaction between alkyl and aromatic amines and halopyrazoles and that between anilines and haloimidazoles bearing free NH groups were reported. These unprotected heterocycles are problematic types of coupling partners and the procedure developed utilized an **L20**-based catalyst with LHMDS as the base. Additional protocols for the coupling of unprotected indoles, triazoles, benzimidazoles, and azaindoles have been reported by the groups of Buchwald[475,476] and Viaud-Massuard.[477] However, the majority of literature examples involving five-membered heteroaryl halides utilize traditional phosphine supporting ligands, such as **L3a**, **L6**, and **L7**, typically in the presence of a weak base to minimize decomposition of the heterocycles.

10.1. Applications of the Coupling of Five-Membered Heteroaryl Halides in the Synthesis of Polycyclic Heterocycles

The N-arylation of five-membered ring heteroaryl halides has been employed for the rapid assembly of fused polycycles (Scheme 140). Through a Pd-catalyzed tandem process, Waldvogel and co-workers prepared a family of nitrogen-bridged heteroacenes **565** (Scheme 140a), which are relevant materials for the construction of OFEDs and OLEDs.[478] Upon combining aryl halide **562** and heteroarylaniline **563**, C−H activation at the C2-position of the nucleophile occurred preferentially to produce intermediate **564**. Subsequent intramolecular N-arylation of the secondary aniline afforded the desired π-extended compound **564**. Among the ligands explored (including dialkylbiarylphosphines, **L6**, **L9**), **L3a** provided the best yields for the overall transformation (32−73%). In a different approach, Nagarajan developed several methods to obtain α-carbolines[479] and related compounds[480] (Scheme 140b,c). These transformations began with the coupling of a primary amide with either a 2- or 3-haloindole using a $Pd_2(dba)_3$/**L6** catalyst and Cs_2CO_3 as the base. Specifically, for the synthesis of α-carbolines (**567**), 3-acetyl-2-chloroindoles were converted into intermediate **566**, which was isolated in excellent yield (71−95%). A subsequent cyclization/Vilsmeier−Haack reaction was carried out to generate the highly functionalized pyridine ring. Shortly thereafter, this methodology was expanded to the one-pot syntheses of pyrimido[4,5-*b*]- (**569**) and pyrimido[5,4-*b*]-indoles (**571**) by replacing the second step with a cyclization reaction in the presence of an ammonia source. The reaction conditions for the Pd-catalyzed C−N coupling from compounds **568** and **570** were identical to those described above, with the exception that toluene was used as the solvent for 2- and 3-bromoindoles. Although the synthesis of **569** and **571** could be carried in a one-pot process, isolation of the corresponding intermediates and sequential addition of HCO_2NH_4 resulted in higher yields.

Scheme 140. Synthesis of Fused Heterocycles via the Coupling of Five-Membered Heteroaryl Halides



10.2. Applications of the Coupling of Five-Membered Heteroaryl Halides in Medicinal Chemistry

Given the ubiquity of sulfur- and nitrogen-containing five-membered heterocycles in pharmaceutically relevant compounds, the N-arylation of their corresponding halides is a recurring reaction in medicinal chemistry. Scheme 141 shows several Pd-catalyzed C−N coupling reactions used to synthesize thiophene-based drug candidates. Chao and co-workers (Merck) successfully coupled aryl bromide **572** and benzophenone imine as part of a multistep route to amido-phenol bioisostere **573**, which was investigated for the treatment of inflammatory diseases (Scheme 141a).[481] In addition, the N-arylation of hydrazine derivatives such as alkylhydrazines and benzophenone hydrazone with halothiophenes was demonstrated by Canales and colleagues (Gilead Sciences) to form HCV inhibitor **574** (Scheme 141b)[482] and by Bindi and co-workers (Nerviano) to obtain anticancer drug candidate **575** (Scheme 141c),[483] respectively. Benzothiophene **576** also underwent C−N coupling at the C3-position in the synthesis of **577** reported by Romagnoli et al. (Scheme 141d).[484] Additionally, Scheme 141e shows the use of 2-bromothiazole **578** in a C−N coupling process by Huang, Shipps, and their co-workers.[485] The heterocycle was combined with an array of

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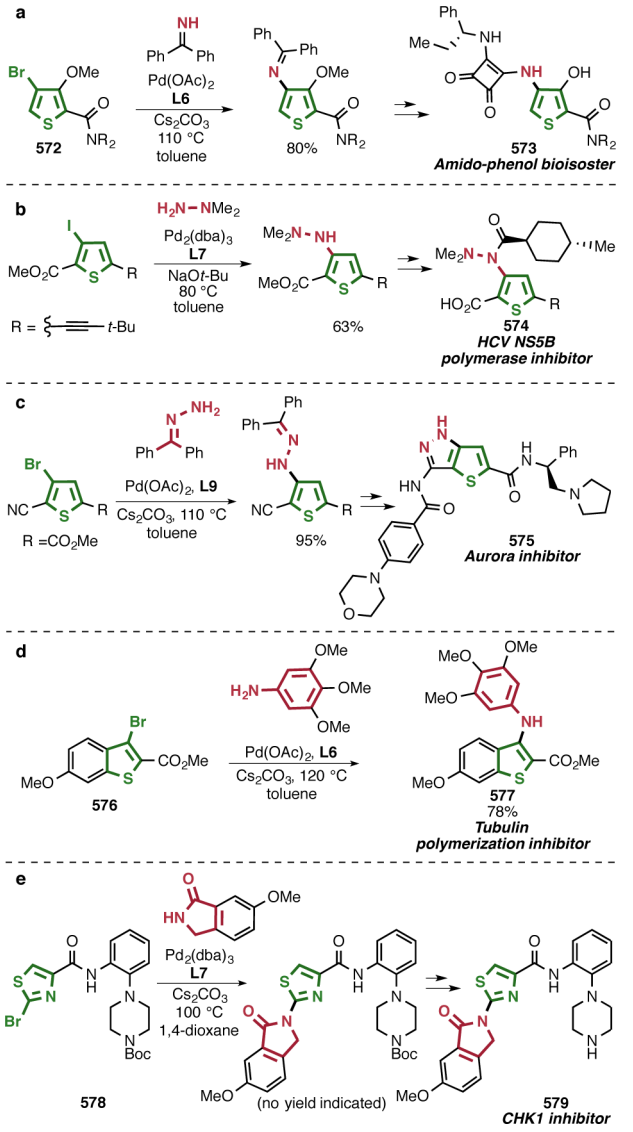
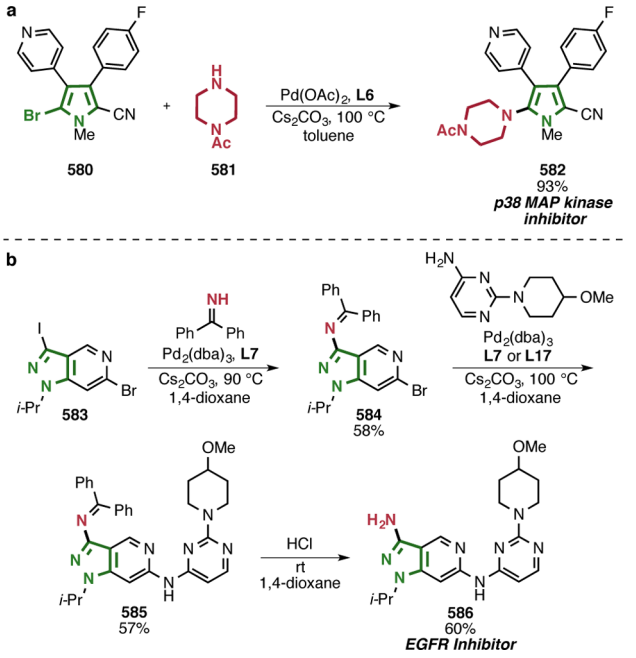
Scheme 141. N-Arylation of S-Based Heterocycles in Drug Discovery



amines and amides using **L7** or **L17** as ancillary ligands, with compound **579** being the most active of those prepared.

Despite the intrinsic difficulties of cross-coupling reactions involving nitrogen-based heterocycles, the N-arylation of halopyrroles, -pyrazoles, -imidazoles, and their benzo-fused analogues has been a research interest for medicinal chemists. A variety of catalysts promote these C−N coupling reactions, although no examples involved five-membered heteroaryl halides bearing a free NH group. Bullington and co-workers (Johnson & Johnson) prepared p38 map kinase inhibitor **582** for potential treatment of inflammatory diseases in excellent yield (93%) by reacting sterically congested 2-bromopyrrole **580** and acetylpiperazine **581** in the presence of $Pd(OAc)_2$/**L6** (Scheme 142a).[486] Additionally, Hanan and co-workers (Genentech) constructed a series of epidermal growth factor receptor (EGFR) inhibitors **586** via two consecutive C−N coupling steps.[487] First, aryl iodide **583** was combined with an ammonia equivalent in the presence of an **L7**-based catalyst to yield intermediate **584** in 58% yield (Scheme 142b). Subsequently, a second N-arylation took place at the 2-

Scheme 142. N-Arylation of Azoles in the Synthesis of Biologically Active Compounds



bromopyridine carbon, leading to **585**. Removal of the protecting group revealed target primary amine **586**.

N-Arylation reactions with haloimidazole derivatives have been performed at every position of the five-membered ring, highlighting the versatility of this substrate (Scheme 143). For instance, Roberge, Andersen, and their co-workers synthesized ceratamine A analogue **588**, an oncology drug candidate, via the Pd-catalyzed C−N coupling of fused imidazole **587** at the C2-position (Scheme 143a).[488] Employing LiHMDS/Ph_3SiNH_2 as a substitute for ammonia, 2-chloroimidazole **587** was readily transformed into the corresponding primary aniline in 71% yield using **L17** as a supporting ligand. Similarly, the C4-position of imidazopyridines **589** (Scheme 143b) and **592** (Scheme 143c) was functionalized to obtain analogues **591**[489] and **594**,[490] which showed activity for tumor inhibition. Peterson, Boezio, and their co-workers (Amgen) initially arrived at **590** via the N-arylation of aminopyrazole **589** using **L10** as an ancillary ligand, whereas Stec and co-workers (Amgen) reacted 4-chlorobenzimidazole **592** and heteroaniline **593** in the presence of the **L18** first-generation palladium precatalyst. 5-Bromoimidazole **595** also underwent C−N cross-coupling in the preparation of promising antimalarial drug **597** by Chatterjee and co-workers (Novartis) (Scheme 143d).[491] Aniline **596** was coupled to the heteroaryl halide using an **L7**-based catalyst in excellent yield (89%). A variety of imidazolopiperazines were obtained in this manner, with **597** being the most active.

10.3. Applications of the Coupling of Five-Membered Heteroaryl Halides in Process Chemistry

In order to fulfill the need for substantial amounts of compound **600** for the investigation of new kinase inhibitors, Weintraub and colleagues (Sanofi-Aventis) developed two scalable synthetic routes.[492] One of them, based on a Pd-catalyzed C−N cross-coupling reaction, is shown in Scheme 144a. Azine **598** was readily converted into intermediate **599** by reaction with benzophenone hydrazone in the presence of a $Pd(OAc)_2$/**L9** catalyst and a weak base. Subsequent hydrolysis

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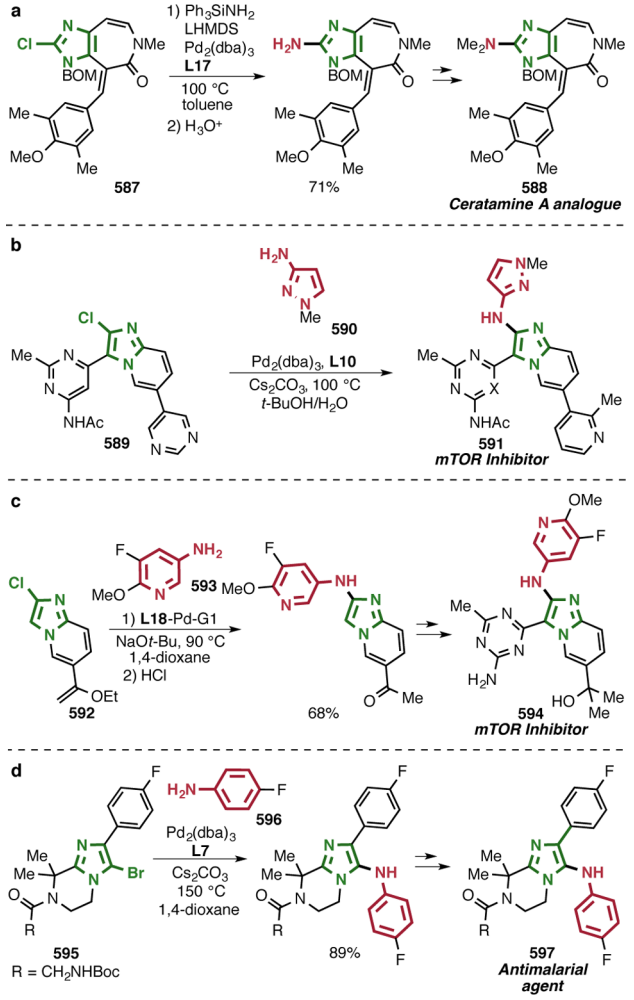
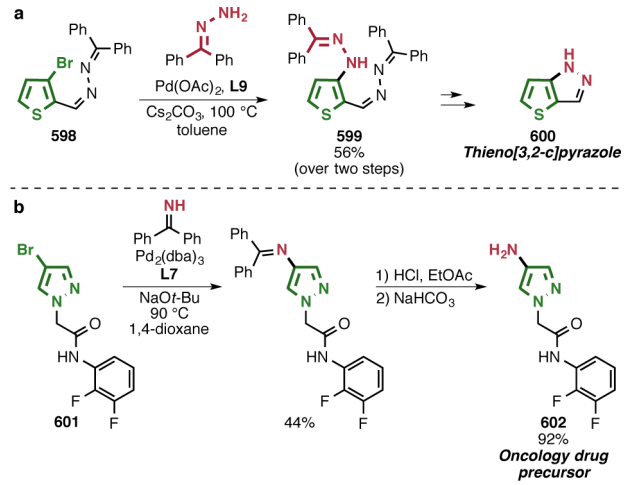
Scheme 143. Pd-Catalyzed C−N Coupling Reactions of Haloimidazole Derivatives



Scheme 144. Large-Scale Reactions of Five-Membered Heteroaryl Halides



and cyclization steps yielded the title compound **600**. Although the overall process significantly increased the yield compared to previous routes, its low atom economy ultimately led to the use of an alternate strategy. Another large-scale operation was reported by Hill and Mortlock (AstraZeneca) to form **602**, a key building block for several oncology drugs (Scheme 144b).[493] While earlier reports employed the potentially explosive 4-nitropyrazole derivative to arrive at the desired primary amine, this alternative introduced the amino group via C−N coupling. Thus, 4-bromopyrazole **601** and benzophenone imine reacted in the presence of an **L7**-based catalyst, which, after cleavage of the imine and deprotonation, yielded **602** in moderate overall yield.

10.4. Applications of the Coupling of Five-Membered Heteroaryl Halides in Materials Chemistry and Chemical Biology

Thiophene is a common structural unit in organic materials, and Pd-catalyzed C−N bond-forming reactions are a practical way to functionalize this heterocycle. For example, Wenger and co-workers developed a family of host materials for optoelectronic devices by connecting thiophene-based linkers of variable size with redox-active anilines (Scheme 145a).[494] The target compound **605** was obtained via a 2-fold Pd-catalyzed coupling of terthiophene **603** and secondary aniline **604** in 38% yield. Additionally, Wang et al. prepared azaborines **609** through two sequential C−N bond-forming steps involving halothiophenes (Scheme 145b).[495] First, dimeric species **606** was combined with benzophenone imine in the presence of an **L6**-based catalyst. Acidic cleavage of the protecting group afforded intermediate **607**, followed by a second N-arylation, using **L3a** as supporting ligand, with an additional equivalent of **606** providing the azathiophene unit **608** in 61% yield. After incorporation of a boron atom, the target compound **609** was employed in the fabrication of organic field-effect transistors (OFETs). Through a double C−N coupling process, Balaji and Valiyaveettil synthesized symmetrical thiophene-based heteroacene **611**, which is also potentially useful for the formation of OFETs (Scheme 146a).[496] Although the preparation of π-extended units of more that four conjugated rings was generally challenging, the target compound was efficiently generated in a two-step synthetic route. A catalyst based on **L3b** promoted successive intra- and intermolecular N-arylation reactions between 2,3-dibromobenzothiophene **610** and 4-hexylaniline in 55% yield.

The N-arylation using haloazoles as electrophiles has also been applied in materials chemistry, albeit to a lesser extent than in the pharmaceutical industry. For instance, Carpenter and Verkman utilized a Pd-catalyzed C−N coupling for a concise synthesis of imidazole-based K^+ sensor **612** for biosensing in aqueous media applications (Scheme 146b).[497] Two C−N bonds were established between diaza-18-crown-6 and 2-chloroimidazole via a microwave-assisted coupling using a QuinaPhos (**L36**)-based catalyst. This is an impressive transformation given the high yield achieved (93%) and, more importantly, the use of free NH imidazoles as coupling partners.

As shown in section 5.1.1, modification of porphyrins has often been accomplished by Pd-catalyzed C−N cross-coupling reactions. These are important compounds due to their wide applicability as biomimetic light-harvesting systems, organocatalysts, and optoelectronic materials. As part of Shinokubo and co-workers' extensive work on porphyrins, he prepared a new class of dimeric systems **615** via the N-arylation of benzophenone imine (Scheme 147a).[498] Aminoporphyrin **614** was generated by reacting triflate **613** and the ammonia surrogate with **L7** as supporting ligand. Subsequent oxidative dimerization readily provided the title pyrazine-fused dipor-

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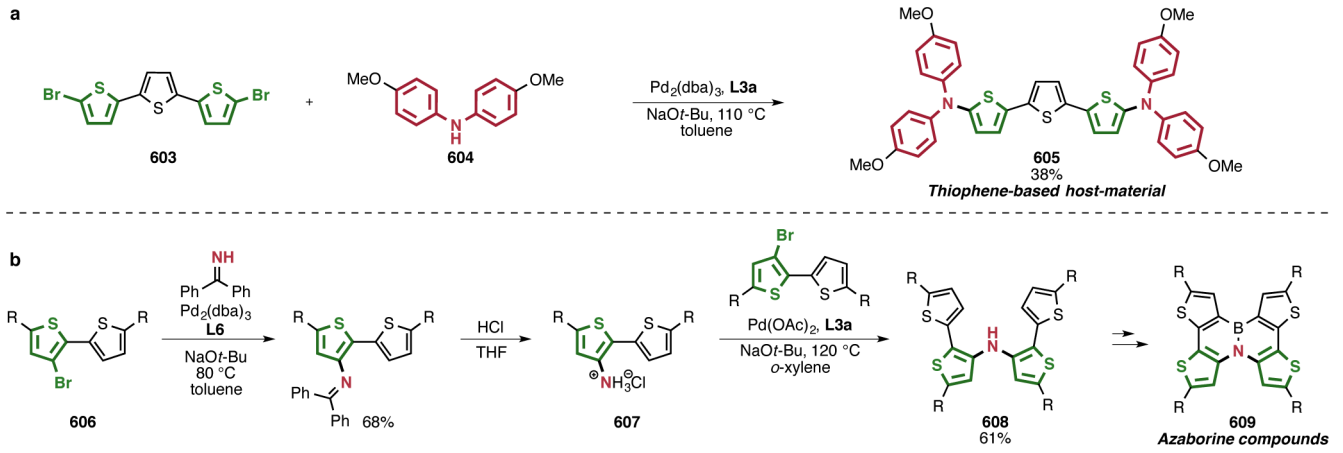
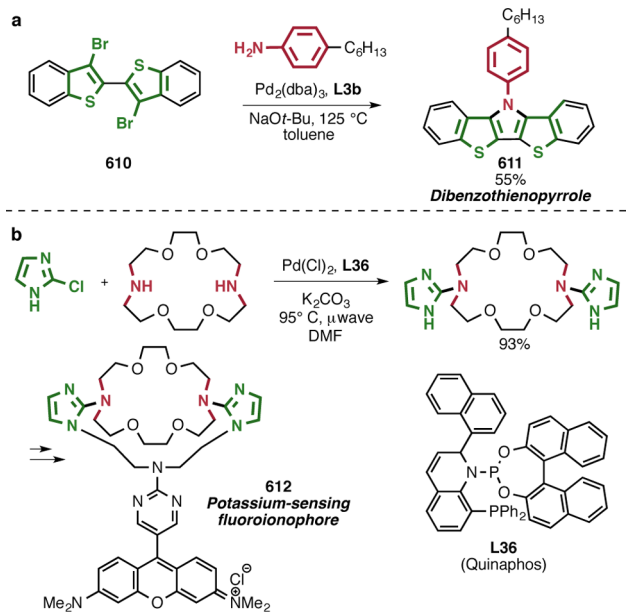
Scheme 145. Thiophene Couplings in Materials Chemistry



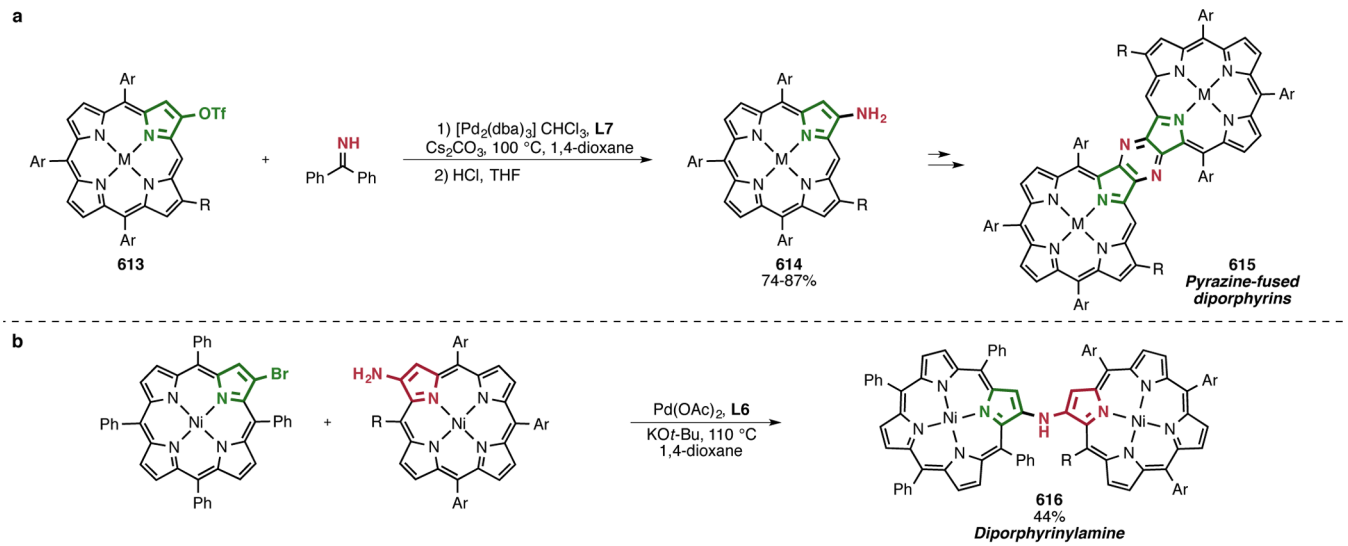
Scheme 146. N-Arylation of Five-Membered Heteroaryl Halides in the Synthesis of Organic Materials



phyrin **615**. Similarly, Ruppert produced a series of large π-conjugated diporphyrinylamines in order to explore their electronic properties (Scheme 147b, one example shown).[499] Target compound **616**, in which two nickel porphyrins are linked through their pyrrolic units, was obtained through a challenging aminopyrrole−halopyrrole C−N coupling. The reaction was hampered by the formation of undesired C−H activation products, which significantly decreased the reaction yield. Thus, an excess of the nucleophilic aminoporphyrin was added to increase the reaction yield from 18 to 44%.

A different application of the coupling of five-membered heterocyclic halides is the functionalization of imidazoles embedded in nucleosides.[500,501] Aiming to study UV-induced mutagenic DNA lesions, Carell and co-workers synthesized dinucleotide **617** by employing Pd-catalyzed cross-coupling (Scheme 148a).[502] The C−N bond between the C4-amino group of the cytosine base and the C8-position of the guanine base was generated using an **L6**-based catalyst with LHMDS as the base (33% yield). Prior protection of all reactive functional groups present in the coupling partners was required for the success of the reaction. Similarly, in order to study the carcinogenic activity of a dietary mutagen, Rizzo and co-workers prepared analogue **620** bearing a naphthalene unit in

Scheme 147. Modification of Porphyrins via C−N Coupling



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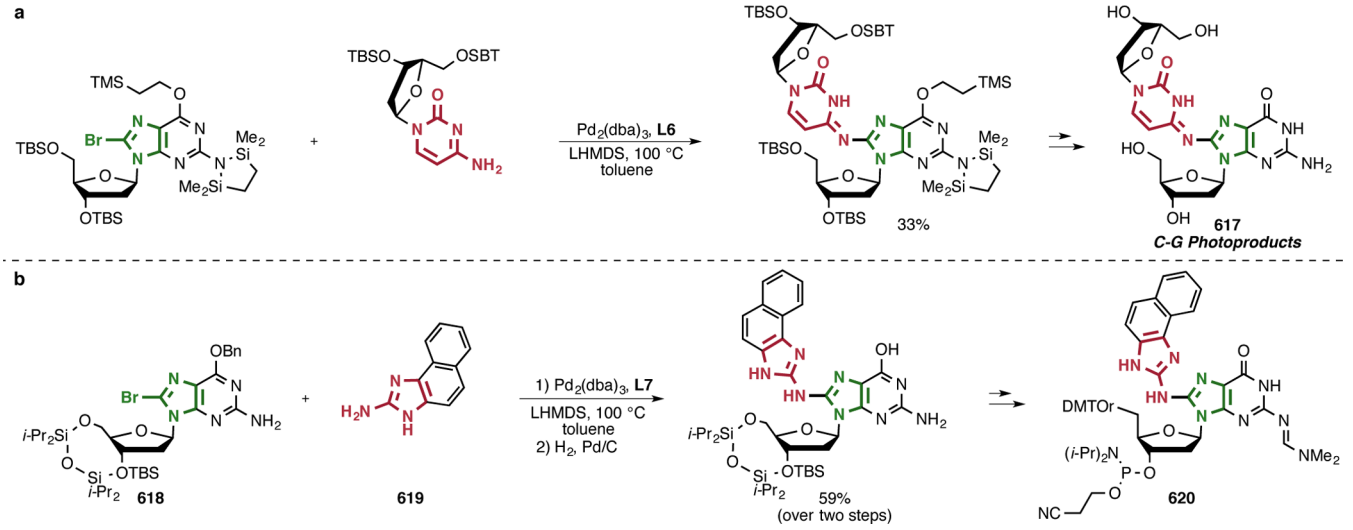
Scheme 148. Modification of Nucleosides via N-Arylation

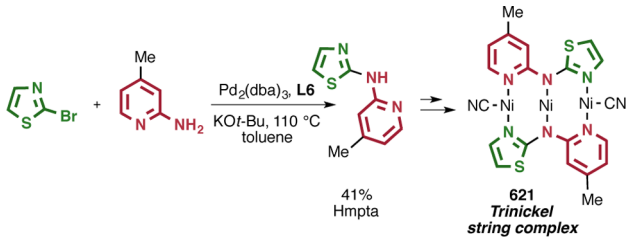


its backbone (Scheme 148b).[503] The two imidazole-based species, **618** and **619**, were successfully coupled in the presence of a $Pd_2(dba)_3$/**L7** complex and LHMDS as the base.

10.5. Applications of the Coupling of Five-Membered Heteroaryl Halides in the Synthesis of Ligands

Given the importance of 1D metal string complexes as molecular wires, Peng and co-workers synthesized and studied a new class of linear trinickel compounds **621** (Scheme 149).[504]

Scheme 149. Synthesis of Hmpta Ligand via the Coupling of 2-Bromothiazole



The chelating ligand present in this complex, 4-methylpyridylthiazolylamine (Hmpta), was accessed by coupling 2-bromothiazole and 2-amino-4-methylpyridine using an **L6**-based catalyst (41% yield). Together with cyanide ligands, the resulting tridentate structures were successfully combined with a nickel source to yield air- and moisture-stable complexes.

11. CONCLUSIONS

Over the past few decades, the high demand for nitrogen-containing compounds has prompted the development of Pd-catalyzed reactions for the synthesis of amines through C−N bond formation. These methods have become increasingly versatile as a result of innovations in catalyst design and improvements in reaction conditions. In addition, the commercial availability of Pd-based precatalysts and the evolution of reaction conditions toward operational simplicity have both been key factors in the rapid adoption of Pd-catalyzed N-arylation reactions by the synthetic community. Reflecting these trends, this review is focused on work published in the past 8 years that has demonstrated the exceptional utility of Pd-catalyzed C−N cross-coupling reactions for the preparation of anilines and aniline derivatives in industrial and academic settings. In particular, we have presented the N-arylation of nine classes of nitrogen-based coupling partners in the context of the synthesis of heterocycles, medicinally relevant compounds, natural products, organic materials, and catalysts. The wide range of research areas in which Pd-catalyzed C−N cross-coupling is encountered in the current literature highlights the extensive applicability of this transformation in the field of chemistry.

We anticipate that this review will serve as an up-to-date summary of recent applications of Pd-catalyzed C−N cross-coupling. It is our hope that the modern precatalysts and ligands presented herein will encourage chemists to utilize improved N-arylation conditions developed in recent years and apply them in increasingly challenging synthetic transformations. Finally, the limitations of current methods described in this review should serve as an impetus for continued development of superior C−N coupling methods.

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Notes

The authors declare no competing financial interest.

Biographies

Paula Ruiz-Castillo studied chemistry at Universidad Complutense de Madrid (Madrid, Spain) in 2010 and spent 1 year at Utrecht University (Utrecht, The Netherlands) working under the supervision of Prof. Bert Klein Gebbink. She then joined Prof. Stephen Buchwald for her Ph.D. studies and graduated in 2016 after working on Pd-catalyzed cross-coupling reactions to form C−N and C−O bonds.

Stephen L. Buchwald is the Camille Dreyfus Professor and the associate head of the Department of Chemistry at the Massachusetts Institute of Technology (Cambridge, MA), where he has been a faculty member since 1984. He has had a long-standing interest in metal-catalyzed transformations for use in organic synthesis. He has been the recipient of many awards, including the Arthur C. Cope Award, the BBVA Frontiers of Knowledge Award in Basic Sciences, and the Gustavus J. Esselen Award for Chemistry in the Public Interest.

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