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A Highly Versatile Catalyst System for the Cross-Coupling of Aryl Chlorides and Amines

Rylan J. Lundgren, Antonia Sappong-Kumankumah, and Mark Stradiotto*[a]

Abstract: The syntheses of 2-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline (**L1**, 71%) and 2-(di-1-adamantylphosphino)-*N*,*N*-dimethylaniline (**L2**, 74%), and their application in Buchwald–Hartwig amination, are reported. In combination with $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$, these structurally simple and air-stable P,N ligands enable the cross-coupling of aryl and heteroaryl chlorides, including those bearing as substituents enolizable ketones, ethers, esters, carboxylic acids, phenols, alcohols, olefins, amides, and halogens, to a diverse range of amine and related substrates that includes primary alkyl- and arylamines, cyclic and acyclic secondary amines, N–H imines, hydrazones, lithium amide, and ammonia. In many cases, the reactions can be performed at low catalyst loadings (0.5–0.02 mol% Pd) with excellent functional group tolerance and chemoselectivity. Examples of cross-coupling reactions involving 1,4-bromochlorobenzene and iodobenzene are also reported. Under similar conditions, inferior catalytic performance was achieved when using $Pd(OAc)_2$, $PdCl_2$, $[PdCl_2(cod)]$ (cod = 1,5-cyclooctadiene), $[PdCl_2(MeCN)_2]$, or $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) in combination with **L1** or **L2**, or by use of $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$ with variants of **L1** and **L2** bearing less basic or less sterically demanding substituents on phosphorus or lacking an *ortho*-dimethylamino fragment. Given current limitations associated with established ligand classes with regard to maintaining high activity across the diverse possible range of C–N coupling applications, **L1** and **L2** represent unusually versatile ligand systems for the cross-coupling of aryl chlorides and amines.

Keywords: amination · anilines · homogeneous catalysis · palladium · phosphanes

Introduction

The Pd-catalyzed cross-coupling of aryl halides and N–H-containing compounds (Buchwald–Hartwig coupling) has rapidly emerged as an indispensable method for the construction of C–N bonds in contemporary organic synthesis.[1–4] The high levels of selectivity, broad substrate scope, and excellent functional group tolerance displayed by state-of-the-art Pd-based catalysts have resulted in the widespread application of this reaction in the synthesis of pharmaceutical intermediates, natural products, and organic materials, both in industrial and academic settings.[5–7] Insights gained regarding the key mechanistic steps in Pd-catalyzed C–N coupling have enabled the development of several highly active classes of catalysts for the cross-coupling of less expensive and more abundant (compared to bromo and iodo compounds), but less reactive, aryl chloride substrates to amines at low catalyst loadings, with excellent yields and reasonable scope.[8] There now exist several ligand classes that promote such difficult C–N coupling reactions of aryl chlorides, including (Figure 1) bulky trialkylphosphanes,[9–12] *N*-heterocyclic carbenes,[13–15] biaryldialkylphosphanes[7] and chelating bisphosphanes,[16,17] as well as N- or O-heteroatom-functionalized phosphanes.[18–26] More recently, difficulties associated with particularly challenging classes of amine substrates have been addressed by the use of specialized 'task-specific' ligands in combination with a judiciously selected Pd precursor. These reactivity challenges include the selective monoarylation of small primary alkylamines (including methylamine),[19,27] the arylation of poorly nucleophilic[27–29] or heteroatom-functionalized anilines,[30–32] the coupling of base-sensitive substrates,[33] the arylation of lithium amide,[34,35] and the synthesis of anilines from ammonia.[35–38] However, the structural complexity that is introduced in order to address these specific reactivity challenges

[a] R. J. Lundgren, A. Sappong-Kumankumah, Prof. Dr. M. Stradiotto
Department of Chemistry
Dalhousie University
Nova Scotia B3H 4J3 (Canada)
E-mail: mark.stradiotto@dal.ca

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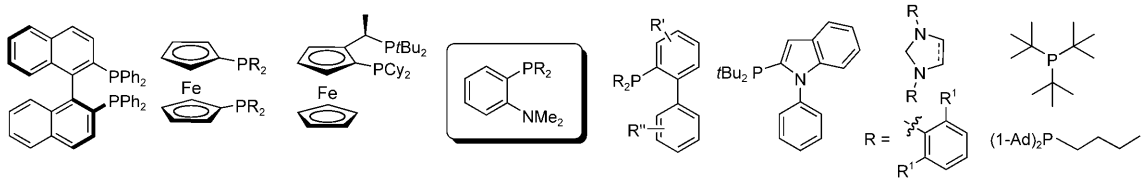


Figure 1. Selected examples within the evolution of ligands for Pd-catalyzed C–N cross-coupling reactions.

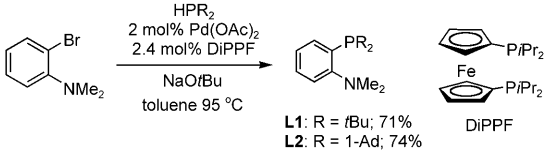
often limits the efficacy of the respective ligands with a wider range of amine substrate classes.

Despite significant research effort, a singular catalyst system that can couple the broad spectrum of potential amine partners with aryl chlorides at modest Pd loadings is not known. While certain ligand systems display high activity for selected substrates in Pd-mediated C–N coupling reactions, these ligands often fail when alternative amine classes are employed, or require substantially higher Pd/ligand loadings to achieve reasonable yields. For instance, Hartwig and co-workers have demonstrated that specific ligand variants within the Josiphos family display high activity and scope in the cross-coupling of aryl bromides and chlorides to primary amines; however, secondary amines proved to be rather poor partners.[16,17,35] Sterically demanding *N*-heterocyclic carbenes represent another well-explored ligand class for C–N coupling reactions, led primarily by the groups of Nolan and Organ.[13–15] While secondary amines are readily cross-coupled to aryl chlorides under mild conditions with low Pd loadings, adequate reactivity with smaller, nucleophilic primary amines has not been accomplished.[13–15] Finally, examples of Buchwald's family of biarylphosphane ligands[7] have shown broad activity for a number of challenging amination reactions, and these are perhaps the most versatile class of ancillary ligands for C–N coupling chemistry. However, these achievements have typically been accomplished through the use of specially designed, task-specific variants within the rather large biarylphosphane ligand family.[7] This has led to serious limitations with regard to the generality of Pd-catalyzed amine arylation, for which ideally a single catalyst system would be active towards all amine classes in addition to maintaining activity with a broad range of aryl halide partners.

Herein, we report a structurally simple and air-stable P,N ligand system that allows the Pd-catalyzed cross-coupling of aryl and heteroaryl chlorides to a diverse range of amine and related substrates, including primary alkyl- and arylamines, cyclic and acyclic secondary amines, N–H imines, hydrazones, lithium amide, and ammonia. In many cases, the loading of Pd required is low (0.5–0.02 mol%), establishing these easily prepared, air-stable P,N ligands as a versatile solution for many challenging C–N cross-coupling applications.

Results and Discussion

We recently initiated a research program aimed at exploring the utility of simple P,N-substituted phenylene ligands in transition metal catalysis[39] and postulated that variants of such ligands possessing a basic and sterically demanding phosphane donor in addition to a weakly coordinating secondary donor might promote highly effective catalysis in Pd-mediated C–N coupling reactions. Indeed, while simple alkylphosphane ligands have found success in amine arylation chemistry, catalyzed reactions conducted using low Pd loadings or transformations involving difficult substrates often require ligand systems that feature additional donor groups to promote catalyst stability or activity.[7,16] Ligand **L1** was prepared in 71% yield (after recrystallization) by a catalytic P–C coupling reaction of 2-Br-*N*,*N*-dimethylaniline and tBu$_2$PH employing Pd(OAc)$_2$ and DiPPF (1,1′-bis(diisopropylphosphino)ferrocene); the related 1-adamantyl (1-Ad)-substituted ligand **L2** was prepared in an analogous fashion in 74% yield (Scheme 1). The use of the robust and



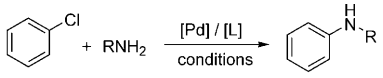
Scheme 1. Synthesis of ligands **L1** and **L2** by P–C cross-coupling.

air-stable secondary phosphane (1-Ad)$_2$PH in the preparation of **L2** circumvents the use of highly oxygen- and moisture-sensitive and/or pyrophoric reagents, which are commonly required for the synthesis of bulky alkylphosphane ligands for use in Pd-catalyzed C–N coupling reactions. Both **L1** and **L2** were found to be stable (by ^{1}H and ^{31}P NMR) in the solid state for at least two months when stored under air. The ease with which **L1** and **L2** can be synthesized is in contrast to the situation for some of the most widely used ligands for challenging Pd-catalyzed C–N coupling reactions, which commonly require multistep syntheses from less readily available and/or costly reagents.

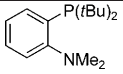
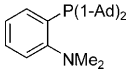
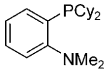
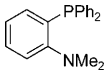
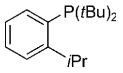
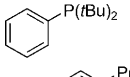
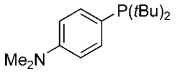
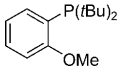
The reaction of chlorobenzene and aniline using 0.5 mol% Pd at 100°C in toluene was selected to assess the catalytic utility of **L1** and related P,N ligands in Pd-catalyzed C–N coupling. Under these screening conditions, most of the commonly employed Pd starting materials, including Pd-

$(OAc)_2$, $PdCl_2$, $[PdCl_2(cod)]$, $[PdCl_2(MeCN)_2]$, and $[Pd_2(dba)_3]$, gave only modest conversions after 4 h. However, we discovered that $[Pd(allyl)Cl]_2$ and **L1** afforded an active catalyst system, providing 91% isolated yield of diphenylamine in 4 h, with no significant amount of diarylation product (triphenylamine) being formed. The use of $[Pd(cinnamyl)Cl]_2$ provided even better catalytic activity (92% yield in 2.5 h; Table 1, entry 1), while the use of **L2** with $[Pd(cinnamyl)Cl]_2$ gave high yields (87%) under similar conditions (Table 1, entry 3). The use of two equivalents of **L1** or **L2** was found to be ideal under these conditions and toluene was identified as the solvent of choice, although 1,4-dioxane or dimethoxyethane could also be employed. The influence of the position and nature of the substituents on both the P- and N-donor fragments was explored by testing a series of related ligands under the conditions that proved favorable for **L1** and **L2**. Ligands possessing less basic or less sterically demanding substituents on phosphorus (**L3** and **L4**, Table 1, entries 5 and 7) were found to be largely ineffective for the cross-coupling of chlorobenzene and aniline, each giving less than 10% conversion on the basis of gas chromatographic (GC) data. The importance of the nitrogen donor group was evidenced by the failure of mixtures of $[Pd(cinnamyl)Cl]_2$ and ligands **L5** or **L6** to provide the desired cross-coupling product in appreciable yield after 2.5 h. The failure of the structurally similar ligands **L7** and **L8** to provide significant yields of diphenylamine under our standard conditions was surprising; **L7** has been demonstrated to be an excellent ligand for Suzuki–Miyaura reactions of heteroaryl chlorides.[40] Collectively, these results provide compelling evidence in support of the concept that both the basic and sterically demanding phosphane donor and the *ortho*-situated dimethylamino group in **L1** and **L2** are necessary for achieving high activity in this particular Pd-catalyzed C–N coupling application.

Table 1. Ligand screening in the cross-coupling of aniline or ammonia to chlorobenzene.[a]



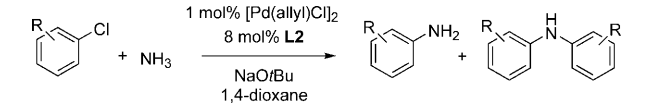
Condition A: amine = $PhNH_2$ Condition B: amine = NH_3

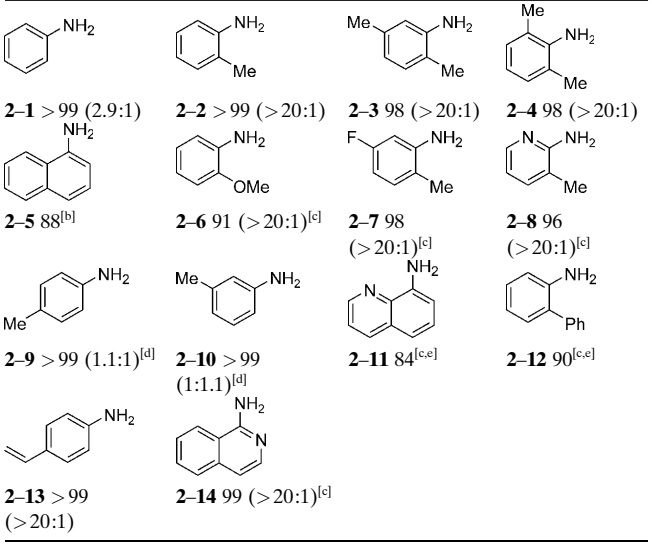
Entry	[L]		Conditions	Yield [%]
1			**A**	92
2	**L1**		**B**	77 (1:1.3)
3			**A**	87
4	**L2**		**B**	>99 (2.9:1)
5			**A**	<10
6	**L3**		**B**	13 (1:6)
7			**A**	<10
8	**L4**		**B**	n.d.
9			**A**	<10
10	**L5**		**B**	n.d.
11			**A**	<10
12	**L6**		**B**	56 (1:16)
13			**A**	17
14	**L7**		**B**	67 (<1:20)
15			**A**	<10
16	**L8**		**B**	49 (<1:20)

[a] Conditions A: ArCl/aniline/NaO*t*Bu 1:1.2:1.4, 1.0 mmol scale in 2 mL toluene at 100°C, 2.5 h, 0.25 mol% $[Pd(cinnamyl)Cl]_2$, and Pd/L 1:2. Yields of isolated product. Conditions B: ArCl/NH_3/NaO*t*Bu 1:10:1.4–1.6, [ArCl] = 0.025 M, 1 mol% $[Pd(allyl)Cl]_2$, Pd/L 1:4, 20 h at 110°C in 1,4-dioxane. Conversions determined by consumption of chlorobenzene, with $PhNH_2$:Ph_2NH indicated in parentheses as determined on the basis of calibrated GC data. Data represents an average of two runs. n.d. = not determined.

Having established **L1** and **L2** as superior ligands for a relatively facile C–N coupling process, we sought to explore their utility in a considerably more difficult transformation. Although the high abundance and low cost of ammonia make it an ideal nitrogen source in amine synthesis, the small and highly nucleophilic, deactivating nature of this substrate present considerable challenges with respect to its efficient utilization in metal-catalyzed C–N coupling reactions. While cross-couplings of ammonia with aryl bromides and iodides have been reported using catalysts based on Pd[35–38] and Cu,[41–44] the selective monoarylation of ammonia with aryl chlorides represents a challenging reaction, one that has only started to be addressed very recently by the use of specially designed ancillary ligands. Furthermore, selective monoarylation of ammonia employing deactivated aryl chlorides lacking *ortho*-substituents represents a particular challenge; transformations of this type are limited to examples by Buchwald and co-workers[36] and a very recent report by Hartwig.[35b] After a brief optimization campaign, it was discovered that employing **L2** with $[Pd(allyl)Cl]_2$ (2 mol% Pd; Pd/L 1:4) at 110°C in 1,4-dioxane resulted in the complete conversion of chlorobenzene to a mixture of aniline and diphenylamine after 20 h (Table 1, entry 4); selectivity in favor of the monoarylation product was achieved ($PhNH_2$:Ph_2NH = 2.9:1) and the reaction was conveniently conducted by employing ammonia as a commercially available 0.5 M stock solution in 1,4-dioxane. We found the structural features of **L2** to be prerequisites for obtaining high activity and selectivity, as other related ligands afforded lower conversions and favored the formation of diphenylamine, the undesired diarylation product (Table 1). The range of anilines that could be prepared by monoarylation of ammonia employing aryl or heteroaryl chlorides with $[Pd(allyl)Cl]_2$ and **L2** was found to be good (Table 2).[35,36,38] The use of *ortho*-substituted aryl or heteroaryl chlorides resulted in very high selectivities in favor of monoarylation (generally >20:1), while maintaining high levels of conversion. Although the use of the deactivated aryl chloride substrates 3- and 4-chlorotoluene still gave complete conversion at 4 mol% Pd, the selectivity in favor of the monoarylation product was substantially reduced (ca. 1:1); in this instance, it appears that the use of a chelating bisphosphine ligand can provide better selectivity with electron-rich aryl chlori-

Table 2. Cross-coupling of aryl and heteroaryl chlorides with ammonia.[a]





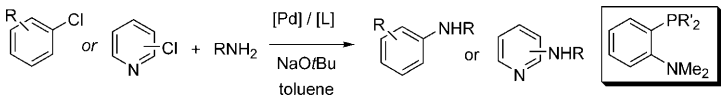
[a] ArCl/NH_3/NaO*t*Bu 1:10:1.4–1.6, [ArCl] = 0.025–0.04 M, conversions determined by consumption of ArCl, with $ArNH_2$/Ar_2NH indicated in parentheses as determined on the basis of calibrated GC data, 16–20 h, 110–120 °C in 1,4-dioxane. [b] From ca. 90% pure 1-chloronaphthalene. [c] Using Pd/L 1:2. [d] Using 4 mol% Pd. [e] Isolated yield.

des.[35b] The activated substrate 4-chlorostyrene provided high conversions (>99%) and excellent selectivities in favor of monoarylation (>20:1), suggesting that both the steric profile and nucleophilicity of the product aniline are factors in determining mono- versus diarylation ratios when employing ammonia as a nitrogen source.

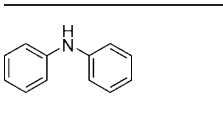
Encouraged by the successful demonstration that **L1** and **L2** represent highly effective ligands for Pd-catalyzed couplings of chlorobenzene with aniline and ammonia, we sought to explore further the scope of this catalyst system with primary and secondary amines (Tables 3 and 4, respectively). Throughout these catalytic studies, we observed that in combination with either **L1** or **L2**, the complexes [Pd(cinnamyl)Cl]$_2$ and [Pd(allyl)Cl]$_2$ could be used interchangeably. An initial survey of various aryl or heteroaryl chlorides and anilines revealed this catalyst system to be generally insensitive to the nature of the coupling partners. Good to excellent yields were obtained for the coupling of a series of substituted aryl chlorides to anilines, including 2-aminopyridine and 8-aminoquinoline, as well as some electron-poor anilines that are often difficult substrates in C–N coupling reactions (Table 3). Lithium amide ($LiNH_2$) could be used as an alternative nitrogen source, providing high yields of the corresponding symmetrical diarylamine under appropriate conditions. Electronically neutral or deactivated aryl chlorides could be coupled with simple primary alkylamines such as octylamine, benzylamine, and cyclohexylamine in high yields at catalyst loadings of 0.1–0.05 mol% Pd. It is worthy of mention that while Guram and co-workers[45] have disclosed the use of PR_2-substituted phenylene ligands conceptually related to **L1** and **L2** in Pd-catalyzed C–N coupling reactions, their optimal ligand configuration required 2 mol% Pd and 6 mol% ligand to achieve a 92% yield of *N*-(2,5-dimethylphenyl)octylamine; in comparison, an 87% isolated yield was achieved using our catalyst system with one-twentieth of this Pd loading (0.1 mol%). Aryl chlorides substituted at the *ortho*, *meta*, or *para* position each proved to be compatible substrates under our standard conditions, with negligible diarylation being observed. Couplings of 2- or 3-pyridyl and related *N*-heteroaryl chlorides to primary amines proceeded with high efficiency, allowing catalyst loadings as low as 0.02 mol% Pd to be employed. The broad scope of this reactivity is exemplified by the fact that both the sterically demanding substrate *tert*-butylamine, as well as the unhindered methylamine, could each be cross-coupled in high yield with no significant diarylation. Furthermore, other classes of N–H-containing substrates, including imines and benzophenone hydrazone, could also be cross-coupled in good yields. The cross-coupling of aryl and pyridyl chlorides with amines bearing pendant olefin groups also proved to be feasible. In these cases, good to excellent yields of the *N*-aryl aminoalkene could be achieved without competing isomerization or Heck chemistry at the olefin position.[46]

Having established **L1** and **L2** as excellent ligands for cross-couplings of aryl chlorides with ammonia as well as a wide range of primary alkyl- and arylamines, we sought to explore the reactivity profile of this system with secondary amine substrates. Given that most catalyst systems tend to drastically favor either primary or secondary amine substrates with respect to their productivity, we were pleased to discover that **L1** or **L2** in combination with [Pd(allyl)Cl]$_2$ or [Pd(cinnamyl)Cl]$_2$ could also couple secondary amines, such as morpholine, piperidine, and *N*-methylpiperazine, to a diverse set of electronically activated, deactivated, and neutral aryl chlorides, as well as to *N*-heteroaryl chlorides, at low catalyst loadings (0.5–0.05 mol% Pd; Table 4). *N*,*N*-Dimethylanilines were also successfully prepared by employing dimethylamine as the substrate. The use of dimethylamine as a 2.0 M solution in THF required the reactions to be performed at 65 °C (instead of 100–110 °C); nonetheless, high isolated yields were obtained by using 0.2–2 mol% Pd. The use of dimethylamine as a coupling partner is very uncommon,[7,47,48] and the results presented herein represent rare examples in which ubiquitous *N*,*N*-dimethylanilines have been prepared by cross-coupling of aryl chlorides.[48] While secondary *N*-methylanilines represented more challenging substrates for our catalyst system, good yields of the corresponding diarylalkylamines were obtained by modifying our standard conditions (Pd/L 1:0.9 in 1,4-dioxane; Table 4).[49] In this manner, a series of unsymmetrical diarylmethylamines could be prepared, a process that corresponds to a selective two-step diarylation starting from H_2NMe (Table 3). The sterically demanding, acyclic secondary amine *N*-methylisopropylamine could also be employed as a substrate. In this case, *para*-, *meta*-, and even challenging *ortho*-substitut-

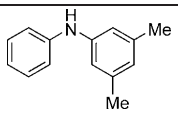
Table 3. Cross-coupling of aryl and heteroaryl chlorides with primary amines.[a]



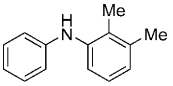
L1: R' = *t*Bu
L2: R' = 1-Ad



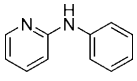
3–1 91 (0.2); 89 (1)[b]



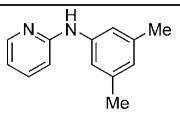
3–2 99 (0.5)



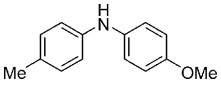
3–3 93 (0.5)



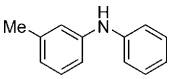
3–4 92 (0.2)



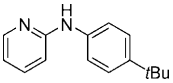
3–5 99 (0.2)



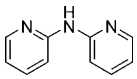
3–6 88 (0.2)



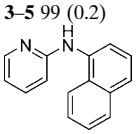
3–7 98 (0.5)



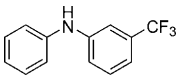
3–8 99 (0.2)



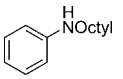
3–9 97 (0.5); 99 (0.5)[b]



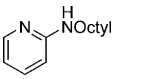
3–10 83 (0.2)



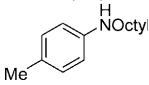
3–11 94 (1.0)



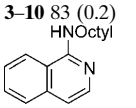
3–12 98 (0.05)



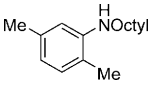
3–13 94 (0.02)



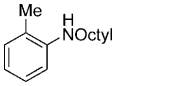
3–14 94 (0.05)



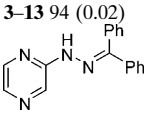
3–15 90 (0.02)



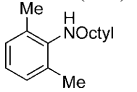
3–16 87 (0.1)



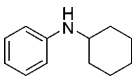
3–17 79 (0.05)



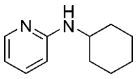
3–18 91 (0.2)



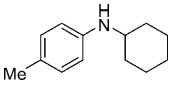
3–19 84 (0.1)



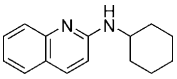
3–20 87 (0.05)



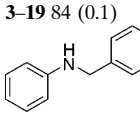
3–21 77 (0.02)



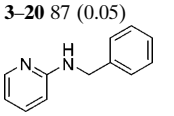
3–22 70 (0.05)



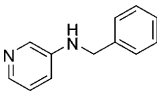
3–23 97 (0.05)



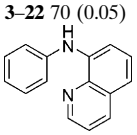
3–24 91 (0.05)



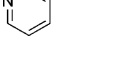
3–25 99 (0.02)



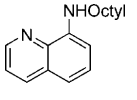
3–26 85 (0.4)



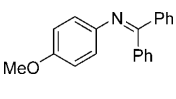
3–27 68 (0.5)



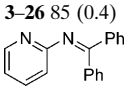
3–28 83 (0.3)



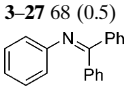
3–29 99 (0.2)



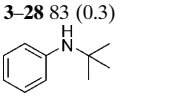
3–30 80 (1)



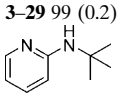
3–31 97 (0.5)



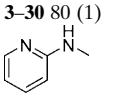
3–32 98 (0.5)



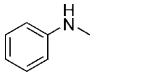
3–33 83 (1.5)



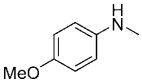
3–34 95 (1)



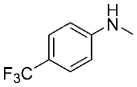
3–35 97 (1)[c]



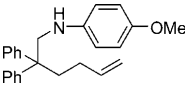
3–36 > 99 (2)[c,d]



3–37 (2)[e]



3–38 97 (2)[c,d]



3–39 78 (0.5)[f]

3–40 95 (0.5)[f]

3–41 97 (0.5)[f]

3–42 94 (0.5)[f]

3–43 68 (0.5)[f]

3–44 90 (0.2)[f]

3–45 73 (0.5)[f]

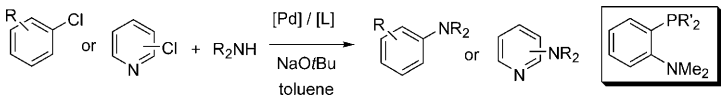
3–46 98 (0.5)[f]

[a] ArCl/amine/NaO*t*Bu 1:1.2:1.4, 1.0 mmol scale, 3–48 h (reaction times not optimized; see the Supporting Information). Isolated yields are an average of two runs, mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd/L 1:2). [b] Using 10 equiv of $LiNH_2$, [ArCl] = 0.2 M. [c] Using 4 equiv H_2NMe at 65 °C. [d] Percent conversion determined on the basis of GC data; where ambiguous, the left portion of the product is derived from the aryl chloride. [e] Using 4 equiv of H_2NMe at 85 °C. [f] Using 1.05 equiv of amine.

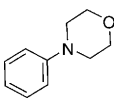
ed, deactivated aryl chloride substrates could be employed, delivering the product amine in acceptable yields. These catalytic reactions involving secondary amines are particularly impressive in view of the ability of **L1** and **L2** to also promote the arylation of much smaller nitrogen substrates such as ammonia and methylamine.

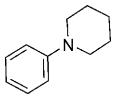
While for convenience most of the experiments documented herein were conducted under inert conditions with exclusion of oxygen and moisture by employing an inert-atmosphere glovebox, the stability of our catalyst system allowed the reactions to be run under less rigorous conditions. For example, in the coupling of chlorobenzene with octylamine at 0.1 mol% Pd, >99% conversion was achieved after 20 h by following a protocol in which the catalyst components (Pd source and **L1** or **L2**) were weighed out on the benchtop and combined with NaO*t*Bu in anhydrous toluene, and only then was the reaction vial placed under an atmosphere of dinitrogen. When the coupling of chlorobenzene and piperidine at 0.2 mol% Pd was conducted in air employing toluene that had not been purified to remove water

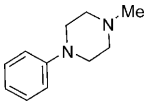
Table 4. Cross-coupling of aryl and heteroaryl chlorides with secondary amines.[a]

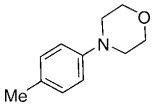


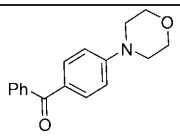
L1: R' = *t*Bu
L2: R' = 1-Ad

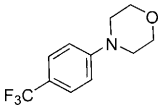

4–1 99 (0.2)

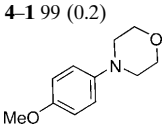

4–2 88 (0.2)

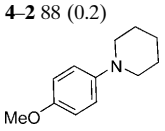

4–3 86 (0.2)

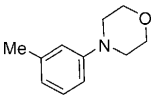

4–4 81 (0.2)

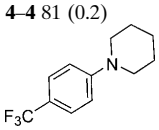

4–5 89 (0.2)

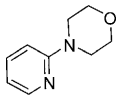

4–6 84 (0.2)

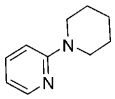

4–7 83 (0.2)

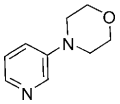

4–8 94 (0.2)

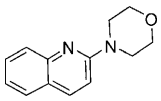

4–9 94 (0.2)

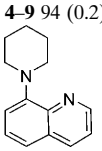

4–10 98 (0.2)

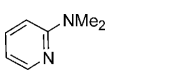

4–11 80 (0.05)

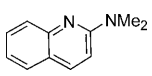

4–12 92 (0.2)

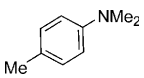

4–13 95 (0.5)

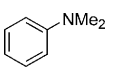

4–14 96 (0.1)

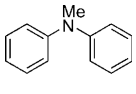

4–15 94 (0.2)

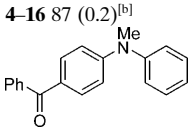

4–16 87 (0.2)[b]

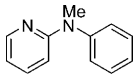

4–17 93 (0.2)[b]

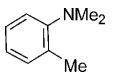

4–18 89 (0.5)[b]

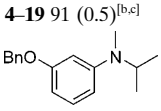

4–19 91 (0.5)[b,c]

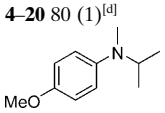

4–20 80 (1)[d]

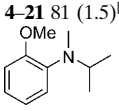

4–22 76 (1)[d]


4–23 87 (1)


4–24 83 (2)[b,c]


4–25 87 (2.0)


4–26 72 (2.5)


4–27 65 (4.0)

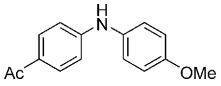
[a] ArCl/amine/NaO*t*Bu 1:1.2:1.4, 1.0 mmol scale, 3–48 h (reaction times not optimized; see the Supporting Information). Isolated yields are an average of two runs, mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd/L 1:2). [b] ArCl/$HNMe_2$ 1:2, at 65°C in toluene/THF 1:1. [c] Percent conversion determined on the basis of GC data; where ambiguous, the left portion of the product is derived from the aryl chloride. [d] Pd/L 1:0.9 in 1,4-dioxane.

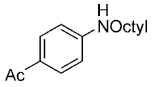
or oxygen, quantitative conversion to *N*-phenylpiperidine was still achieved after 24 h.

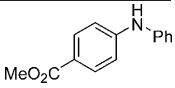
The use of Pd–allyl-type starting materials presents a potential drawback, namely the requirement for a strongly nucleophilic base for the in situ generation of a Pd(0) catalyst.[50] However, we found that base-sensitive compounds could be employed as substrates by using a *catalytic* amount of NaO*t*Bu to activate the Pd(allyl)-type precatalyst, and a stoichiometric amount of a more appropriate base such as Cs_2CO_3 or $LiN(SiMe_3)_2$ to facilitate the cross-coupling chemistry. This technique allowed the cross-coupling of aryl chloride substrates containing enolizable ketone, ester, carboxylic acid, phenol, alcohol, and amide groups with primary or secondary amines (Table 5).

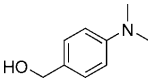
Chemoselectivity in Pd-catalyzed C–N cross-coupling reactions remains a relatively unexplored challenge.[51] Despite the high activity displayed by our catalyst system for a wide range of amine substrates, intermolecular C–N couplings proceeded chemoselectively. For example, when one equivalent of chlorobenzene was reacted with 1.05 equivalent each of octylamine and morpholine in the presence of 0.125 mol% $[Pd(cinnamyl)Cl]_2$ and **L2** at 95°C, 88% conversion of the aryl chloride was observed (on the basis of GC data), with formation of the octylamine cross-coupling product being favored over that of the morpholine-derived product by a factor of 18:1 (Scheme 2). Competition experi-

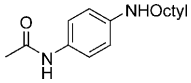
Table 5. Cross-coupling of base-sensitive substrates.[a]

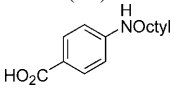

5–1 96 (0.5)[b]

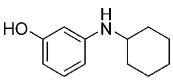

5–2 74 (0.5)[b]

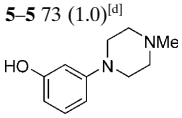

5–3 96 (0.5)[c]

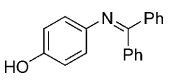

5–4 82 (2.0)[c]

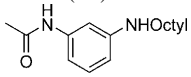

5–5 73 (1.0)[d]


5–6 72 (0.5)[d]

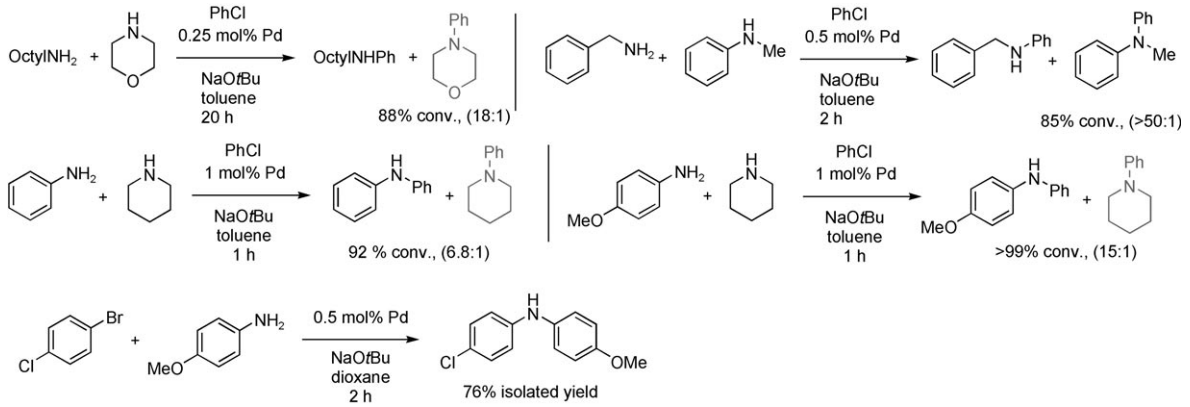

5–7 80 (0.5)[d]


5–8 70 (0.5)[d]


5–9 67 (1.5)[d]


5–10 98 (1.0)[d]

[a] ArCl/amine/base 1:1.2:2.2, 0.5–1.0 mmol scale, 2–4 mol% NaO*t*Bu, 2–48 h (reaction times not optimized; see the Supporting Information), 110°C; mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd/L 1:2). [b] Using Cs_2CO_3 in 1,4-dioxane. [c] Using LiHMDS in THF/dioxane at 65°C. [d] Using LiHMDS in toluene.



Scheme 2. Chemoselective C–N cross-coupling reactions. All reactions employ [Pd(cinnamyl)Cl]$_2$ and **L2** (Pd/L 1:2), with conversions and product ratios determined on the basis of GC data unless indicated.

ments between benzylamine and *N*-methylaniline also demonstrated high selectivity for arylation of the primary amine, giving 85% conversion to *N*-benzylaniline after 2 h (accompanied by only a trace amount of Ph_2NMe) when employing 0.5 mol% Pd. Anilines can also be chemoselectively coupled to chlorobenzene in the presence of a secondary amine (e.g., piperidine), with excellent conversions and good selectivities over the course of 1 h, by employing 1 mol% Pd. Finally, while our current study has focused on the cross-coupling of more challenging aryl chloride substrates, aryl iodides and bromides can also be employed with excellent results. Iodobenzene and octylamine could be coupled with >99% conversion by employing 0.05 mol% Pd under standard conditions.[52] Chemoselective amination (100°C; 0.5 mol% Pd) at the bromide position of 1,4-bromochlorobenzene with 4-anisidine was obtained by using [Pd(cinnamyl)Cl]$_2$ and **L2** to afford the chloro-functionalized diarylamine in 76% isolated yield. The powerful combination of high catalytic activity, broad substrate scope, and excellent chemoselectivity displayed by Pd catalysts featuring **L1** or **L2** suggests that these catalyst systems should be of widespread utility in the construction of complex molecular frameworks by the use of C–N coupling techniques.

Conclusion

In summary, the results presented herein reveal the structurally simple and air-stable ligands **L1** and **L2** to be broadly useful for the Pd-catalyzed cross-coupling of aryl and heteroaryl chlorides with amines and related substrates. Good to excellent yields can be obtained using a wide range of amine partners, including primary aryl- and alkylamines, cyclic and acyclic secondary amines, lithium amide, N–H imines, hydrazones, and ammonia. In many cases, the reactions can be performed at low catalyst loadings with excellent functional group tolerance and chemoselectivity. Given current limitations associated with established ligand classes with regard to maintaining high activity across the diverse possible range of C–N coupling applications, **L1** and **L2** represent an unusually versatile ligand system for the cross-coupling of aryl chlorides and amines and an important contribution towards the development of more general catalysts for Pd-catalyzed C–N coupling reactions. Studies aimed at examining the utility of **L1** and **L2** in other challenging Pd-catalyzed cross-coupling reactions, as well as mechanistic studies concerning the origin of the broad scope and high activity in the catalysis featured herein, are ongoing.

Experimental Section

General considerations: Unless noted otherwise, all reactions were set up inside a dinitrogen-filled inert atmosphere glovebox. Toluene was deoxygenated by sparging with dinitrogen and then passed through a double-column solvent purification system purchased from mBraun Inc. 1,4-Dioxane (Aldrich) was dried over Na/benzophenone and then distilled under an atmosphere of dinitrogen. 1,2-Dimethoxyethane was deoxygenated by sparging with dinitrogen gas and then stored over activated 4 Å molecular sieves for 48 h prior to use. Chloroform-d_1 (Cambridge Isotopes) was used as received. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Aniline was distilled under reduced pressure prior to use. [Pd(cinnamyl)Cl]$_2$,[53] diphenyl-2-dimethylaminophenylphosphane (**L4**),[54] di(*tert*-butyl)-(2-isopropylphenyl)phosphane (**L5**),[55,56] di(*tert*-butyl)phenylphosphane (**L6**),[55,56] di-1-adamantylphosphane,[57] and amino alkene substrates[58] were prepared according to literature procedures. Di(*tert*-butyl)-(2-methoxyphenyl)phosphane (**L8**) was prepared in a similar manner to **L2**, and the spectroscopic features of the isolated complex matched those reported previously.[59] Pd starting materials, as well as NaO*t*Bu and Cs_2CO_3, were desiccated under reduced pressure for 24 h prior to use and stored under an inert atmosphere in a glove box. All other reagents were used as received from commercial sources. Conversions in the arylation of aniline and ammonia based on gas chromatography data were determined by calibration with chlorobenzene, aniline, or diphenylamine as standards; product identity was confirmed on the basis of ^{1}H NMR and GC-MS data and/or by comparison with authentic samples. ^{1}H, ^{13}C, and ^{31}P NMR spectra were acquired at 300 K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz, respectively, with chemical shifts reported in parts per million downfield of the signals of $SiMe_4$ for ^{1}H and ^{13}C, and of 85% H_3PO_4 in D_2O for ^{31}P.

Improved synthesis of 2-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline (L1): In an analogous manner to the synthesis of **L2** (see below), the title compound was prepared by Pd-catalyzed cross-coupling of *t*Bu$_2$PH and 2-bromo-*N*,*N*-dimethylaniline. The product was isolated in 71% yield

after recrystallization from hexane at −35 °C. Its spectral properties were consistent with those reported previously.[39]

Synthesis of 2-(di-1-adamantylphosphino)-*N*,*N*-dimethylaniline (L2): $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) was placed in a glass vial and dissolved in toluene (2 mL). This solution was then transferred to a vial containing DiPPF (1,1′-bis(diisopropylphosphino)ferrocene; 14.2 mg, 0.034 mmol) and the mixture was stirred for 10 min. A separate glass vial was first charged with NaO*t*Bu (192 mg, 2.0 mmol), and then a solution of $(1\text{-adamantyl})_2PH$ (410 mg, 1.36 mmol) in toluene (2 mL) was added. 2-Bromo-*N*,*N*-dimethylaniline (230 μL, 1.4 mmol) and the above $Pd(OAc)_2$/DiPPF solution were then added and the vial was sealed with a cap containing a PTFE septum. The mixture was stirred for 20 h at 110 °C, at which point the reaction was deemed complete on the basis of ^{31}P NMR data obtained from a withdrawn aliquot. The reaction mixture was then allowed to cool and passed through a plug of silica, and the plug was then washed with CH_2Cl_2 (40 mL). The combined eluent was collected and the solvent was removed in vacuo. The resulting pale-orange solid was washed with cold hexanes (2×4 mL). Removal of volatile materials in vacuo yielded the product as an off-white powder (0.424 g, 1.01 mmol; 74%). ^1H NMR ($CDCl_3$): $\delta = 7.71$ (m, 1H; Ar-H), 7.32 (m, 1H; Ar-H), 7.20 (m, 1H; Ar-H), 7.05 (m, 1H; Ar-H), 2.71 (s, 6H; $N(CH_3)_2$), 2.01–1.89 (m, 18H; 1-Ad), 1.67 ppm (s, 12H; 1-Ad); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 161.6$ (d, $J_{PC} = 21.6$ Hz; C_{quat}), 137.4 (d, $J_{PC} = 3.3$ Hz), 131.1 (d, $J_{PC} = 22.9$ Hz; C_{quat}), 129.6, 122.2, 120.6 (d, $J_{PC} = 3.9$ Hz), 46.1 (d, $J_{PC} = 4.2$ Hz; $N(CH_3)_2$), 41.8 (d, $J_{PC} = 13.0$ Hz; CH_2), 37.1 (CH_2), 29.0 ppm (d, $J_{PC} = 8.6$ Hz; CH); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 20.1$ ppm; HRMS (ESI): calcd for $C_{28}H_{40}N_1P_1$ ($[M+H]^+$): 422.2971; found: 422.2978; elemental analysis calcd (%) for $C_{28}H_{40}P_1N_1$: C 79.77, H 9.56, N 3.32; found: C 79.47, H 9.46, N 3.31.

Synthesis of 2-(dicyclohexylphosphino)-*N*,*N*-dimethylaniline (L3): *n*BuLi (759 μL, 2.2 mmol) was added to a precooled (−35 °C) solution of 2-bromo-*N*,*N*-dimethylaniline (288 μL, 2.0 mmol) in Et_2O (3 mL) in a glass vial. After 30 min at −35 °C and an additional 15 min at room temperature, the yellow precipitate obtained was isolated by removing the supernatant by means of a pipette, washing the remaining solid with cold hexanes (3×2 mL), and removing the volatile materials in vacuo. The resulting solid was dissolved in Et_2O (6 mL) and then $ClPCy_2$ (440 μL, 2.0 mmol) was added dropwise and the mixture was stirred magnetically at room temperature for 48 h. The solvent and volatile materials were then removed in vacuo. The residue was redissolved in CH_2Cl_2 and this solution was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and water (10 mL). The organic layer was collected, dried in vacuo, and passed through a plug of silica eluting with pentane. Removal of the solvents in vacuo yielded the product as a white solid (0.162 g, 0.51 mmol, 25%). ^1H NMR ($CDCl_3$): $\delta = 7.35$ (d of t, $J = 7.6$, 1.9 Hz, 1H), 7.28 (m, 1H), 7.13 (d of d of d, $J = 8.0$, 4.3, 1.2 Hz, 1H), 7.05 (d of t, $J = 7.4$, 1.3 Hz, 1H), 2.72 (s, 6H), 1.90–1.74 (m, 12H), 1.30–0.99 ppm (m, 10H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 160.8$, 133.8 (d, $J = 2.7$ Hz), 132.0, 129.8, 123.6, 120.2 (d, $J = 2.9$ Hz), 46.4 (d, $J = 5.0$ Hz), 34.2 (d, $J = 14.3$), 30.8 (d, $J = 16.6$ Hz), 29.6 (d, $J = 8.9$ Hz), 27.8 (d, $J = 11.6$ Hz), 27.7 (d, $J = 7.6$ Hz), 27.0 ppm; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = -12.7$ ppm.

Synthesis of 4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline (L7):[60] The title compound was prepared according to a procedure similar to that described by Guram et al.,[60] but using 4-iodo-*N*,*N*-dimethylaniline instead of 4-bromo-*N*,*N*-dimethylaniline. This ligand is commercially available from Aldrich; however, its spectroscopic data have not hitherto been disclosed. ^1H NMR ($CDCl_3$): $\delta = 7.54$ (m, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 2.98 (s, 6H), 1.20 ppm (d, $J = 11.2$ Hz, 18H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 150.9$, 129.3 (d, $J = 101.7$ Hz), 122.0 (d, $J = 15.5$ Hz), 111.4 (d, $J = 9.1$ Hz), 40.3, 32.1 (d, $J = 19.3$ Hz), 30.7 ppm (d, $J = 14.2$ Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 36.7$ ppm.

Representative procedure for the coupling of primary or secondary amines with aryl chlorides: In an inert atmosphere glovebox, $[Pd(cinnamyl)Cl]_2$ (0.67 mg, 0.0013 mmol, from a stock solution in toluene) and **L2** (2.2 mg, 0.0052 mmol) were mixed in toluene (2.000 mL in total) for 10 min. An aliquot of this stock solution (383 μL) was added to a vial containing NaO*t*Bu (135 mg, 1.4 mmol), followed by additional toluene (600 μL). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. Chlorobenzene (103 μL, 1.0 mmol) and octylamine (200 μL, 1.2 mmol) were added by means of a microlitre syringe. The reaction mixture was heated at 110 °C and periodically monitored by TLC or gas chromatography. Upon completion of the reaction, the mixture was worked-up by column chromatography on silica (hexane/EtOAc, 20:1) and the product was isolated as a colorless oil (0.203 g, 99%). Alternatively, the appropriate amounts of $[Pd(cinnamyl)Cl]_2$, ligand, and NaO*t*Bu stored under N_2 could be weighed out on the benchtop into a vial. Following the addition of chlorobenzene, octylamine, and anhydrous toluene, the vial was sealed with a cap containing a PTFE septum, purged with N_2, and heated at 110 °C. The results were similar to those obtained from reactions conducted in a glovebox (99% conversion on the basis of GC data at 0.1 mol% Pd).

Representative procedure for the coupling of ammonia with aryl chlorides: In an inert atmosphere glovebox, $[Pd(allyl)Cl]_2$ (2.2 mg, 0.006 mmol) and **L2** (10.1 mg, 0.024 mmol) were vigorously mixed in dioxane (4 mL) for 10 min. An aliquot (1.000 mL) of this stock solution was withdrawn and added to a vial containing NaO*t*Bu (20 mg). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. 2-Chloro-3-methylpyridine (16 μL, 0.15 mmol) was added by means of a microlitre syringe, followed by a 0.5 M solution of NH_3 in 1,4-dioxane (3 mL). The mixture was stirred at 110 °C and the progress of the reaction was monitored by gas chromatography.

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