

Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine**

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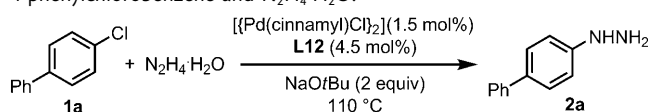
Aryl hydrazines are highly valuable intermediates in the synthesis of a number of important nitrogen-containing heterocyclic frameworks such as indoles (through the Fischer indole synthesis),^[1] indazoles, aryl pyrazoles, and aryl triazoles.^[2] In some cases, hydrazine reacts with haloarenes directly in nucleophilic aromatic substitution reactions; however, such reactions typically occur at high temperatures, and/or only with highly electron-deficient haloarenes, or at selected positions of halogenated heterocycles.^[3,4] The prevailing method for the preparation of aryl hydrazines relies on the stoichiometric oxidation of anilines to their corresponding diazonium salts and subsequent reduction.^[5] The transition-metal-catalyzed cross-coupling of aryl halides and hydrazine represents an attractive alternative to the traditional synthesis of aryl hydrazines. However, despite the tremendous progress made in the field of Buchwald–Hartwig amination reactions over the past decade,^[6] no such reaction has been reported.

Hydrazine presents a number of potential problems in palladium-catalyzed cross-coupling reactions. First, hydrazine is an aggressive reductant of both organic and inorganic substrates,^[7] and could reduce key Pd^{II}Ar(X) species, thereby promoting the generation of catalytically inactive Pd⁰ aggregates, as well as reducing aryl halide substrates by hydrodehalogenation. Second, aryl hydrazines can undergo metal-mediated N–N bond cleavage,^[8] thus resulting in the formation of undesired aniline by-products. Finally, and most importantly, the product aryl hydrazines still possess three reactive N–H bonds that can undergo further C–N cross-coupling, thus leading to polyarylated products. Some of these challenges have been circumvented by the use of hydrazine surrogates with attenuated reactivity such as benzophenone hydrazone^[9] or protected hydrazides,^[10] although such strategies are not ideal from efficiency or economic standpoints. In addition, aryl- or alkyl-substituted hydrazines, which are less prone to undergo some of the above described detrimental side reactions, have been employed as substrates.^[11] Herein, we report on a palladium catalyst system and reaction conditions that allow, for the first time, the cross-coupling of aryl chlorides and tosylates with hydrazine. The reactions

proceed rapidly under relatively mild conditions with excellent monoarylation selectivity, thus providing direct access to aryl hydrazines.

We began by screening a variety of ligands (Scheme 1) and reaction conditions (Table 1) in the hope of effecting the cross-coupling of 4-phenylchlorobenzene with readily avail-

Table 1: Optimization of the palladium-catalyzed cross-coupling of 4-phenylchlorobenzene and N₂H₄·H₂O.^[a]



Entry	Variation from standard conditions	Conv. [%]	Yield [%]
1	none	> 99	73
2	9 mol % of L12	> 99	61
3	toluene instead of 1,4-dioxane	> 99	79
4	DMA instead of 1,4-dioxane	< 10	0
5	DCE instead of 1,4-dioxane	0	0
6	0.3 M of ArCl instead of 0.1 M	65	35
7	4 equiv of hydrazine instead of 2 equiv	51	24
8	3 equiv of NaOtBu instead of 2 equiv	90	66
9	KOH instead of NaOtBu	45	24
10	Cs ₂ CO ₃ instead of NaOtBu	65	14
11	ArBr instead of ArCl	95	45
12 ^[b]	N ₂ H ₄ ·HCl instead of N ₂ H ₄ ·H ₂ O	> 99	80
13 ^[b]	N ₂ H ₄ ·HCl instead of N ₂ H ₄ ·H ₂ O, 65 °C	99	76
14 ^[b,c]	[PdCl ₂ (MeCN) ₂] instead of [{Pd(cinnamyl)Cl} ₂]	> 99	69
15 ^[b,c]	[Pd(dba) ₂] instead of [{Pd(cinnamyl)Cl} ₂]	99	60
16	no [Pd], no ligand	< 10	0

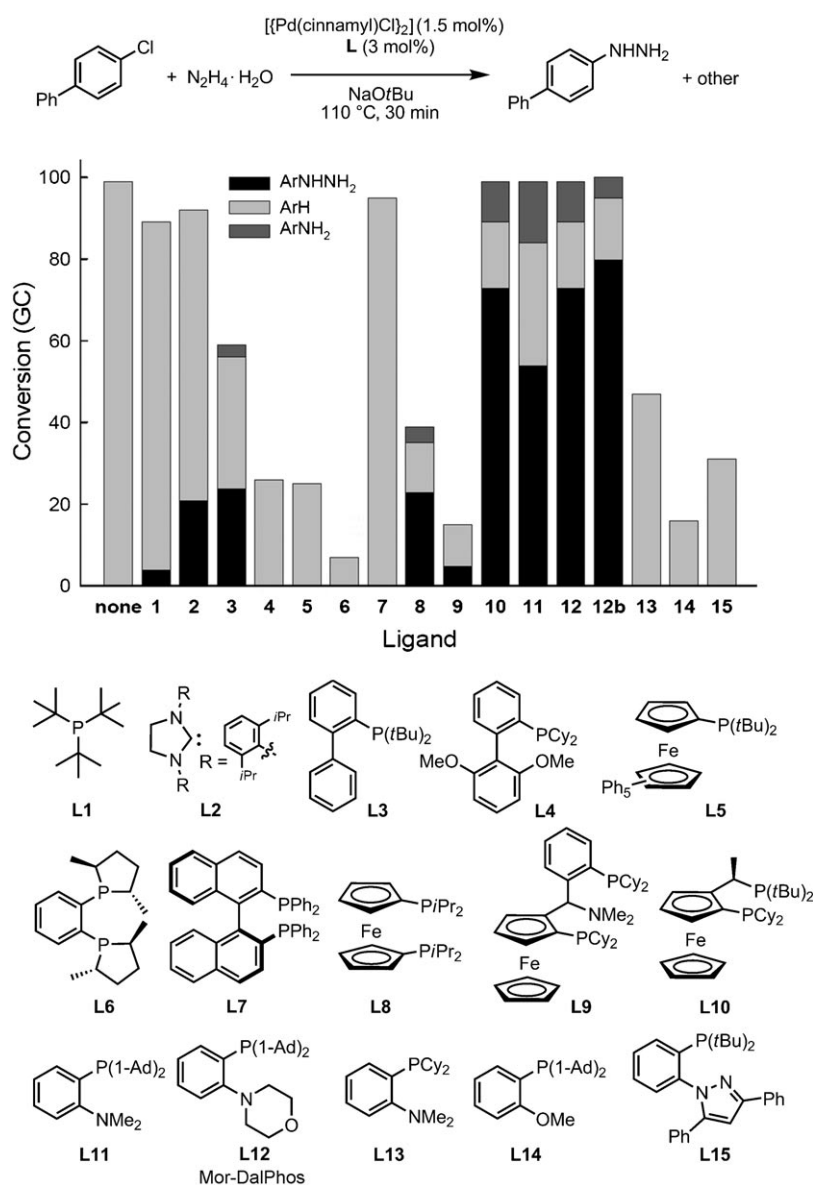
[a] Standard reaction conditions: reactions were carried out on a 0.2 mmol scale, [Pd]/L = 1:1.5, N₂H₄·H₂O (2 equiv), and NaOtBu (2 equiv), 110 °C, in 1,4-dioxane (0.1 M in substrate). Conversions and yields were determined by GC analysis. [b] Employing N₂H₄·HCl and NaOtBu (3.5 equiv). [c] At 90 °C. dba = *trans,trans*-dibenzylideneacetone.

able hydrazine sources. A series of structurally diverse phosphane and N-heterocyclic carbene ligands were tested employing [{Pd(cinnamyl)Cl}₂] (1.5 mol%) and the ligand (3 mol%) at 110 °C in 1,4-dioxane with 2 equivalents of hydrazine hydrate and NaOtBu. Electron-rich monophosphanes or carbenes including P(*t*Bu)₃ (**L1**), IPr (**L2**), *t*Bu-JohnPhos (**L3**), SPhos (**L4**), Q-Phos (**L5**), as well as bisphosphanes DuPhos (**L6**), binap (**L7**), DiPPF (**L8**), and Taniaphos (**L9**) all gave poor results: either resulting in low conversions of the starting aryl chloride, or providing mainly the hydrodehalogenated product. The electron-rich bisphosphine ligand Josiphos (**L10**)^[6b,10a] or DalPhos P,N ligands (**L11** and **L12**)^[6l,m] provided a breakthrough in reactivity: high

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Scheme 1. Ligand screening for the palladium-catalyzed cross-coupling of 4-phenylchlorobenzene and $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$. Reaction conditions: reactions were carried out on a 0.15 mmol scale, 110 °C, in 1,4-dioxane (0.1 M in substrate). Conversions were determined by GC analysis. **12b** = 6 mol % of **L12** employed. Ad = adamantyl, Cy = cyclohexyl.

conversions with lower amounts of arene side product were achieved. Other related P-phenyl ligands (**L13–15**), as well as cataCXium ligands A, PICy, POMetB (see the Supporting Information) were ineffective, thus demonstrating the extreme sensitivity of the reaction to the structure of the ligand.

The coupling of 4-phenylchlorobenzene proved to be sensitive to the reaction conditions. When **L12** (Mor-DalPhos) was employed, toluene (Table 1, entry 3) or 1,4-dioxane could be used interchangeably, but the use of *N,N*-dimethylacetamide (DMA) or 1,2-dichloroethane (DCE) inhibited the transformation (Table 1, entries 4 and 5). The use of excess $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ or NaOtBu both resulted in diminished conversions and yields (Table 1, entries 7 and 8). Other bases such as

KOH and Cs_2CO_3 were inferior to NaOtBu (Table 1, entries 9 and 10). Interestingly, aryl chlorides appear to be superior substrates compared to aryl bromides, where incomplete conversion of 4-phenylbromobenzene and 45 % yield of the desired product was observed (Table 1, entry 11).^[12] Conveniently, solid $\text{N}_2\text{H}_4\cdot\text{HCl}$ could also be employed with additional base (Table 1, entries 12 and 13). The palladium source proved less important, with $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ only slightly outperforming $[\text{PdCl}_2(\text{MeCN})_2]$ or $[\text{Pd}(\text{dba})_2]$ (Table 1, entries 14 and 15).

After having defined a catalyst system and the reaction conditions for the cross-coupling of aryl chlorides and hydrazine, we sought to explore the scope of the reaction (Table 2). To simplify isolation and purification, the product aryl hydrazines were isolated as their corresponding hydrazone derivatives after treatment with benzaldehyde.^[13] Cross-coupling of electron-neutral aryl chlorides proceeded with good yields by employing 5 mol % of [Pd] at 90 °C. Substrates included biaryl derivatives with ether and CF_3 substituents (Table 2, entries 4 and 5), as well as heterocycles such as pyrrole and pyridine (Table 2, entries 6 and 8). Electron-poor substrates like 4-trifluoromethylchlorobenzene (Table 2, entry 7) gave poorer yields because of increased hydrodehalogenation, while the electron-rich substrate 4-chloroanisole (Table 2, entry 9) reacted slowly. 4-Fluorochlorobenzene could be employed as a substrate with moderate success when the reaction was conducted in 1,4-dioxane (49 % yield, Table 2, entry 10); in toluene, a significant amount of defluorinated product was observed. Other examples of aryl chlorides substituted at the 3-position with alkyl, oxygen, sulfur, or fluoro groups resulted in good yields (72–88 %; Table 2, entries 11–13). *ortho*-Substitution was also tolerated;

Table 2: Scope of the palladium-catalyzed cross-coupling of aryl chlorides and hydrazine.^[a]

$\text{Aryl}-\text{Cl}$ or $\text{HetAryl}-\text{Cl}$ 1		$\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$		$\xrightarrow[2) \text{ PhCHO, MeOH}]{1) [\text{Pd}] / \text{L12, NaOtBu}}$		$\text{Aryl}-\text{NHNHPh}$ or $\text{HetAryl}-\text{NHNHPh}$ 2	
Entry	ArCl	[Pd] [mol %]	T [°C]	t [h]	Prod., yield [%] ^[b]		
1		5	90	1	2b , 86		
2		5	90	1	2c , 93		

Table 2: (Continued)

Entry	ArCl	[Pd] [mol %]	T [°C]	t [h]	Prod., yield [%] ^[b]
3	R = Ph	3	90	1	2a , 86
4	R = 4-OMeC ₆ H ₄	5	90	0.5	2d , 82
5 ^[c]	R = 4-CF ₃ C ₆ H ₄	3	90	0.5	2e , 83
6	R = N-pyrrole	5	90	1	2f , 78
7	R = CF ₃	5	90	1	2g , 50 (44) ^[d]
8	R = 3-pyridine	5	65	2	2h , 97
9 ^[c]	R = OMe	10	110	1	2i , 27
10 ^[c,e]	R = F	5	90	0.33	2j , 49
11		5	90	1	2k , 88
12 ^[c,f]		5	90	0.5	2l , 83
13		10	110	0.5	2m , 95
14		5	90	1	2n , 72
15		5	90	1	2o , 77
16		5	90	0.5	2p , 75
17		5	65	1	2q , 83
18 ^[c]		10	90	1	2r , 71
19		5	65	1.5	2s , 69
20 ^[f]		3	65	1	2t , 81
21		5	90	0.5	2u , 75
22		5	90	0.5	2v , 58

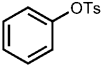
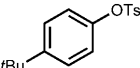
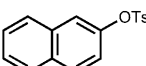
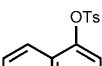
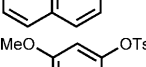
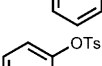
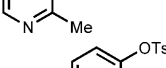
[a] Reaction conditions: ArCl/N₂H₄·H₂O/NaOtBu = 1:2:2–1.8, [Pd] = [{Pd(cinnamyl)Cl}₂], [Pd]/**L12** = 1:1.5, in toluene (0.1 M in substrate). [b] Yield of isolated product. [c] Employing N₂H₄·HCl and NaOtBu (3.5 equiv). [d] > 95 % conversion of ArCl, yield at 2.5 mol % of [Pd] in brackets. [e] In 1,4-dioxane. [f] Isolated aryl hydrazine. TBDMS = *tert*-butyldimethylsilyl.

2-chloro-*p*-xylene was cross-coupled cleanly and gave the desired product in 88 % yield after derivatization (Table 2, entry 11), while the bulky substrate 2-phenylchlorobenzene could be employed with success using 10 mol % of [Pd] (Table 2, entry 18). Chloropyridine and quinoline substrates such as 3-chloropyridine and 6-chloroquinoline were also suitable substrates (Table 2, entries 19 and 20). Importantly, unlike 2- or 4-halopyridines, such chloro-substituted heterocycles are not amenable to nucleophilic aromatic substitution with hydrazine, thus indicating that such cross-coupling

strategies are complementary to established methods that employ hydrazine. Aminoaryl chloride substrates were also readily cross-coupled in moderate to good yields without significant interference from the pendant NH functionality (Table 2, entries 21 and 22). This protocol is also suitable for larger-scale reactions; for example, 92 % yield (2.09 g) of **2p** was obtained when the reactions were conducted on a 10 mmol scale.

Aryl tosylates, which are readily available and easily prepared from phenols, could also be employed in the present reaction by using a similar catalytic protocol (Table 3).

Table 3: Scope of the palladium-catalyzed cross-coupling of aryl tosylates and hydrazine.^[a]

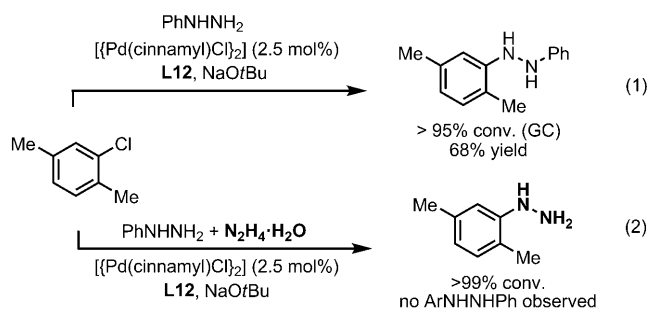
$\begin{array}{c} \text{Aryl}-\text{OTs} \\ \text{or} \\ \text{HetAryl}-\text{OTs} \\ \mathbf{3} \end{array} + \text{N}_2\text{H}_4\cdot\text{H}_2\text{O} \xrightarrow[2) \text{PhCHO, MeOH}]{1) [\text{Pd}] / \text{L}\mathbf{12}, \text{NaOtBu}}$					$\begin{array}{c} \text{Aryl}-\text{N}(\text{H})-\text{N}=\text{CH}-\text{Ph} \\ \text{or} \\ \text{HetAryl}-\text{N}(\text{H})-\text{N}=\text{CH}-\text{Ph} \\ \mathbf{4} \end{array}$
Entry	ArOTs	[Pd] [mol %]	T [°C]	t [h]	Prod., yield [%] ^{1b}
1 ^[c]		5	65	1	2a , 64
2 ^[c]		5	65	1	4a , 73
3		5	65	0.5	4b , 67
4 ^[d]		5	65	0.5	4c , 97
5		5	65	0.5	4d , 51
6		5	50	0.5	4e , 79
7		5	65	0.5	2f , 59

[a] Reaction conditions: identical to Table 2. [b] Yield of isolated product. [c] Employing N₂H₄·HCl and NaOtBu (3.5 equiv). [d] Isolated aryl hydrazine. Ts = 4-toluenesulfonyl.

Moderate to excellent yields (51–97 %) for a range of aryl tosylate substrates were obtained, including *ortho*-, *meta*-, and *para*-substituted derivatives (Table 3, entries 2 and 5–7).^[14] Heteroaromatic substrates such as 2-methyl-3-pyridyl tosylate were also suitable reaction partners (Table 3, entry 6).

Diarylation of hydrazine was anticipated to be a potential challenge to overcome; however, throughout both screening experiments and the substrate scope studies, no significant amount of material arising from multiple arylation of hydrazine was observed. This observation is interesting in light of the fact that [{Pd(cinnamyl)Cl}₂]/**L12** is a highly capable catalyst for the cross-coupling of aryl hydrazines. For example, 2-chloro-*p*-xylene could be coupled to phenylhy-

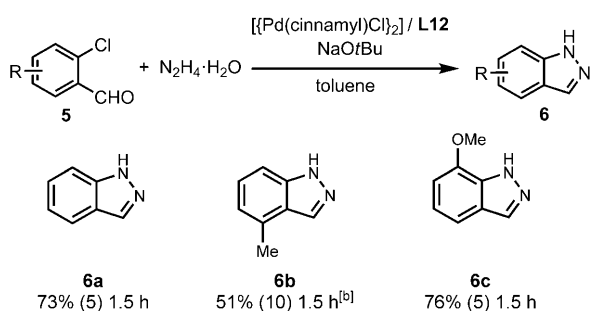
drazine in 68% yield under our standard reaction conditions [Scheme 2, Eq. (1)]. However, in the presence of $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ the only product that was observed was 2,5-dimethylphenyl-



Scheme 2. Palladium-catalyzed cross-coupling of PhNHNH_2 and $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$. Reaction conditions: RNHNH_2 (1.2 equiv), NaOtBu (1.3 equiv), **L12** (0.075 equiv), toluene (0.1 M in substrate), 90°C , 30 min.

hydrazine [Scheme 2, Eq. (2)]. Given the similar steric environment of hydrazine and phenylhydrazine at the terminal nitrogen atom, we postulate that the origin of the high chemoselectivity observed with $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2/\text{L12}$ is primarily electronic in nature—with the more nucleophilic hydrazine substrate reacting preferentially.^[15]

Finally, we exploited our newly developed method to prepare 1-*H*-indazoles directly from 2-chlorobenzaldehydes and hydrazine (Scheme 3).^[16] While there exist many metal-



Scheme 3. Reaction conditions: $\text{ArCl}/\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}/\text{NaOtBu} = 1:2:2$, $[\text{Pd}]/\text{L} = 1:1.5$, $[\text{ArCl}] = 0.20\text{ M}$ in toluene at 65°C , mol % of $[\text{Pd}]$ employed is indicated in brackets. [b] Employing $\text{N}_2\text{H}_4\cdot\text{HCl}$ and NaOtBu (3.5 equiv) at 90°C .

catalyzed tandem indazole syntheses, our protocol allows for the generation of substituted NH-indazoles, which are attractive substrates for further elaboration. Moderate to good yields were observed in short reaction times (1–1.5 h) and under relatively mild reaction conditions ($65\text{--}90^\circ\text{C}$).^[17]

In conclusion, we have developed the first palladium-catalyzed cross-coupling of aryl chlorides and tosylates with hydrazine. The reaction relies on the use of appropriately designed ligands to overcome the difficulties associated with the use of hydrazine, and proceeds rapidly under mild conditions with excellent chemoselectivity. Given the readily available nature of aryl chlorides and tosylates, and the importance of aryl hydrazines in heterocycle synthesis, we

believe that this method will find widespread application. Studies directed to the further development of the scope and utility of this and related challenging C–N cross-coupling reactions are ongoing.

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