An Efficient Pd-Catalyzed Coupling of Hydrazine Derivatives with Aryl Halides

Fang-Fang Ma,[a] Zhi-Yong Peng,[a] Wan-Fang Li,[a] Xiao-Min Xie,[a] Zhaoguo Zhang*[a,b]

[a] School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. of China
Fax +86(21)54748925; E-mail: zhaoguo@sjtu.edu.cn

[b] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. of China

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Abstract: A convenient method for the intermolecular N-arylation of hydrazides with aryl halides in the presence of a palladium catalyst, a MOP-type ligand, and Cs_2CO_3 is reported. The reaction gives coupling products in good to excellent yields and has a high tolerance towards a wide spectrum of functional groups.

Key words: palladium, MOP ligands, aryl halide, *N*-aryl hydrazides, N-arylation

N-Aryl hydrazines have many important applications in organic synthesis and industry.[1] Particularly, they are versatile intermediates in the preparation of biologically active nitrogen-containing heterocyclic compounds, such as pyrazoles,[2] indoles,[3] indazoles,[4] pyridazines,[5] and carbazoles.[6]

N-Aryl hydrazines have traditionally been prepared either by stoichiometric oxidation of anilines to the corresponding diazonium salts and subsequent reduction,[7] or by electrophilic amination of highly electron-rich arenes,[8] aryllithium reagents,[9] aryl magnesium reagents,[9a] and arylzinc halides[10] with dialkyl azodicarboxylates. However, these methods often employ expensive reagents or starting materials and require multi-step syntheses and/or harsh conditions, which limits their tolerance towards functional groups. In the past few decades, novel preparations of aryl-substituted hydrazines using transition-metal catalysts have attracted growing attention. Copper acetate catalyzed reaction between di-*tert*-butyl hydrazine-1,2-dicarboxylate (BocNHNHBoc) and arylbismuth compounds was reported to afford aryl-substituted hydrazines.[11] Organoboronic acids reacting with *tert*-butyl carbazate[12] or azodicarboxylate[13] were also efficient methods for the preparation of aryl-substituted hydrazines. Pd- or Cu-catalyzed cross-coupling reactions between aryl halides and hydrazine derivatives also led to aryl hydrazines.[14] However, this reaction was case-dependent and high yields were obtained only when activated aryl bromides (*para*-substituted with electron-withdrawing groups), aryl iodides, or specific halogenated heterocycles were employed. Recently, a Pd-catalyzed coupling reaction of aryl chlorides and hydrazine has been reported.[15] Although hydrazine is an ideal substrate from an economic standpoint, it presents potential problems associated with the formation of byproducts such as arene and aniline, along with the desired products. In addition, the reaction conditions remain relatively harsh because of the required use of strong base, *t*-BuONa, which results in poor functional group tolerance. We have recently synthesized a series of bulky and electron-rich MOP-type ligands and applied them in Pd-catalyzed coupling reactions between unreactive aryl halides and amines.[16] To continue our interest in Pd-catalyzed C–N bond formation reactions, we decided to focus on the preparation of *N*-aryl hydrazides. Herein, we report a Pd-catalyzed coupling reaction of aryl halides and BocNHNHBoc using 2-di-*tert*-butylphosphino-2′-isopropoxy-1,1′-binaphthyl as the ligand to afford monoaryl-substituted hydrazines.

The *tert*-butyloxycarbonyl (Boc) group is a very convenient amine protecting group because it is easy to remove; this led us to test the coupling reaction of 1-bromo-4-methylbenzene (**1b**) and (NH_2NHBoc) with palladium and 2-di-*tert*-butylphosphino-2′-isopropoxy-1,1′-binaphthyl as the catalyst and Cs_2CO_3 as the base in 1,4-dioxane at 100 °C. Although the catalyst was very effective for the amination of aryl halides with primary amines,[16] it gave poor regioselectivity (Figure 1; **A/B** = 27:59). Fortunately, no diaryl-substituted hydrazides were formed in the reaction.

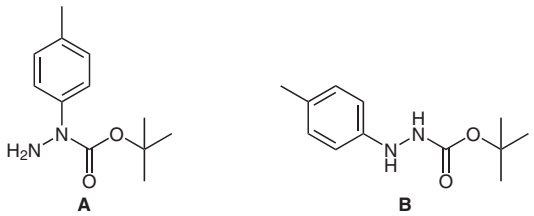

Figure 1

To solve the regioselectivity and purification problems, we investigated the Pd-catalyzed coupling reaction of 1-bromo-4-methylbenzene (**1b**) with BocNHNHBoc. A set of ligands **L1**–**L9** (Figure 2) were screened and the results are summarized in Table 1.

Most ligands failed to give the desired product (Table 1, entries 1–8). Xantphos (**L1**) and DPPF (**L2**), which are efficient ligands for amidation reactions of iodide and bromide substrates,[14a,17] were ineffective for the amidation of 1-bromo-4-methylbenzene (**1b**) due to the fact that these

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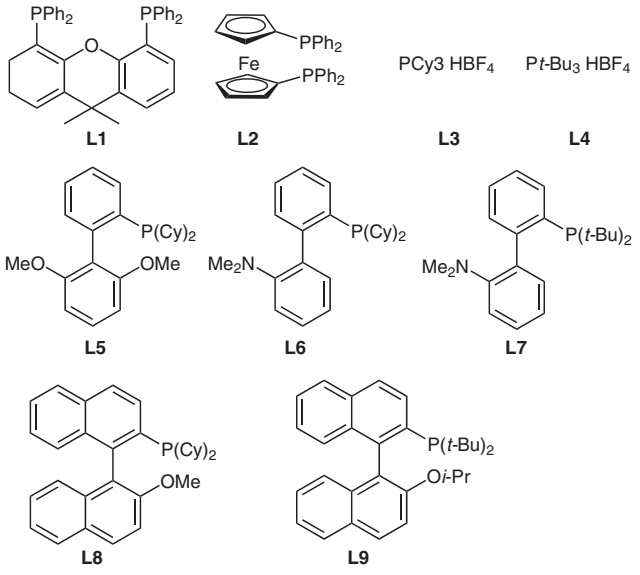


Figure 2 Structures of ligands **L1**–**L9**

ligands showed lower reactivity for oxidative addition of inactivated aryl halides. Although ligands **L3**–**L9** were shown to promote oxidative addition of some extremely hindered aryl chlorides,[16,18] only 2-di-*tert*-butylphosphino-2′-isopropoxy-1,1′-binaphthyl (**L9**) was found to be effective in the present reaction. Among the ligands tested, **L9** is the bulkiest and most electron-rich. It was found that greater ligand bulk facilitated reductive elimination and led to higher reactivity.

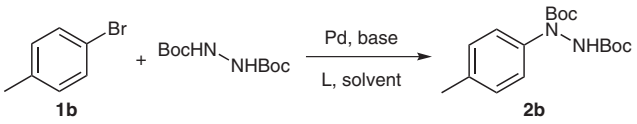
The effects of bases and solvents on the reaction were also investigated. Phosphate and carbonate bases were found to be more effective than stronger bases such as *t*-BuONa and KOH (Table 1, entries 9–13). Solvents seemed to be inconsequential for the reaction; good to excellent conversion was obtained in either 1,4-dioxane, *t*-BuOH, or toluene as solvents (Table 1, entries 9 and 14–15). When $Pd(OAc)_2$ was employed as the Pd source, the yield decreased drastically (Table 1, entry 17). Based on these results, the optimized reaction conditions were determined as follows: Cs_2CO_3 as the base, 1,4-dioxane as the solvent, and Pd(0)/**L9** as the catalyst combination (Table 1, entry 9).

The substrate scope was studied by employing various aryl bromides and chlorides. Under the optimized reaction conditions, a wide variety of substrates, including aryl, heteroaryl, and naphthalene halides, readily coupled with BocNHNHBoc to produce *N*-aryl hydrazides in moderate to high yields. The results are shown in Table 2.

Generally, aryl bromides substituted with electron-rich, electron-neutral, or electron-poor groups at the *para* or *meta* position worked equally well, providing the corresponding coupling products in high yields. Various functional groups, such as *tert*-butyl, methyl, methoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy, acetyl, and cyano were tolerated under these conditions. For a bromochloroarene substrate (Table 2, entry 7), the reaction occurred selectively at the C–Br bond. When 1-(4-bromophenyl)ethanone was employed as substrate, no competitive ketone arylation was observed (Table 2, entry 10). When electron-rich phenyl bromides, such as **1e**, **1i**, and **1m** were employed, 4 mol% catalyst loading was required for full conversion (Table 2, entries 5, 9, and 13). Moreover, for electron-neutral and electron-rich chlorobenzenes (Table 2, entries 16, 18, 19, and 21), higher catalyst loadings were necessary to obtain moderate to good yields. Meanwhile, the reaction was not limited to phenyl halides since naphthalene and heteroaromatic halides (Table 2, entries 12 and 15) also gave the desired products in moderate yields.

The reaction was significantly affected by steric factors. For aryl halides with a substituent at the *ortho* position, such as 2-methyl or 2-methoxy bromobenzenes, no desired coupling products were obtained, even when the less bulky ligand **L8** was employed. To prepare *ortho*-substituted aryl hydrazides, the coupling of NH_2NHBoc with

Table 1 Optimized Reaction Conditions for the Coupling of 1-Bromo-4-methylbenzene and Di-*tert*-butylhydrazine-1.2-dicarboxylate[a]



1b 2b

Entry	Ligand	Base	Solvent	Conversion (%)[b]
1	**L1**	Cs_2CO_3	1,4-dioxane	0.7
2	**L2**	Cs_2CO_3	1,4-dioxane	0.0
3	**L3**	Cs_2CO_3	1,4-dioxane	0.0
4	**L4**	Cs_2CO_3	1,4-dioxane	0.6
5	**L5**	Cs_2CO_3	1,4-dioxane	0.0
6	**L6**	Cs_2CO_3	1,4-dioxane	0.3
7	**L7**	Cs_2CO_3	1,4-dioxane	26.5
8	**L8**	Cs_2CO_3	1,4-dioxane	1.8
9	**L9**	Cs_2CO_3	1,4-dioxane	100.0
10	**L9**	K_3PO_4	1,4-dioxane	92.0
11	**L9**	K_2CO_3	1,4-dioxane	65.7
12	**L9**	KOH	1,4-dioxane	4.8
13	**L9**	*t*-BuONa	1,4-dioxane	0.6
14	**L9**	Cs_2CO_3	*t*-BuOH	93.1
15	**L9**	Cs_2CO_3	toluene	93.1
16	**L9**	K_3PO_4	toluene	81.3
17	**L9**	Cs_2CO_3	1,4-dioxane	17.5[c]

[a] *Reagents and conditions:* 1-Bromo-4-methylbenzene (1.0 mmol), di-*tert*-butylhydrazine-1.2-dicarboxylate (1.2 mmol), base (1.5 mmol), solvent (4.0 mL), $[Pd(dba)_2]$ (0.02 mmol), **L** (0.03 mmol), 100 °C, 20 h.
[b] Determined by GC analysis.
[c] $Pd(OAc)_2$ was used as Pd source.

Table 2 General Scope of Reaction with Di-*tert*-butyl Hydrazine-1,2-dicarboxylate using $[Pd(dba)_2]$ and **L9**[a]

Entry	Starting material	Ar	X	Product	Yield (%)[b]
1	**1a**	Ph	Br	**2a**	96
2	**1b**	4-MeC_6H_4	Br	**2b**	96
3	**1c**	4-*t*-BuC_6H_4	Br	**2c**	89[c]
4	**1d**	3,5-MeC_6H_3	Br	**2d**	91
5	**1e**	4-$MeOC_6H_4$	Br	**2e**	87[c]
6	**1f**	4-FC_6H_4	Br	**2f**	93
7	**1g**	4-ClC_6H_4	Br	**2g**	85
8	**1h**	4-$CF_3C_6H_4$	Br	**2h**	87
9	**1i**	4-$CF_3OC_6H_4$	Br	**2i**	95[c]
10	**1j**	4-$MeCOC_6H_4$	Br	**2j**	75
11	**1k**	4-CNC_6H_4	Br	**2k**	77
12	**1l**	2-$C_{10}H_{10}$	Br	**2l**	68
13	**1m**	3-$MeOC_6H_4$	Br	**2m**	89[c]
14	**1n**	3-$CF_3C_6H_4$	Br	**2n**	95
15	**1o**	3-pyridine	Br	**2o**	64[c]
16	**1a′**	Ph	Cl	**2a**	75[c]
17	**1h′**	4-$CF_3C_6H_4$	Cl	**2h**	88
18	**1b′**	4-MeC_6H_4	Cl	**2b**	75[c]
19	**1e′**	4-$MeOC_6H_4$	Cl	**2e**	58[c]
20	**1p**	4-$EtO_2CC_6H_4$	Cl	**2p**	73
21	**1m′**	3-$MeOC_6H_4$	Cl	**2m**	71[c]
22	**1q**	3-$EtO_2CC_6H_4$	Cl	**2q**	87

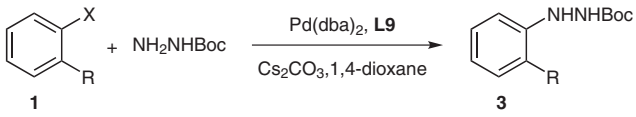
[a] *Reagents and conditions*: Aryl halide (1.0 mmol), di-*tert*-butylhydrazine-1,2-dicarboxylate (1.2 mmol), base (1.5 mmol), solvent (4.0 mL), $[Pd(dba)_2]$ (0.020 mmol), **L9** (0.030 mmol), 100 °C, 20 h.
[b] Isolated yield.
[c] $[Pd(dba)_2]$ (0.040 mmol), **L9** (0.060 mmol).

ortho-substituted aryl halides was examined; the results are detailed in Table 3.

As shown in Table 3, we obtained the products in high yields and excellent regioselectivity for all *ortho*-substituent substrates. Regardless of whether the *ortho*-substituent was methyl or methoxy, the corresponding amination products were isolated with good yields. The two regioisomers were clearly distinguished from each other in the ^1H NMR spectra, since the amination products contained two distinct exchangeable NH signals.

The reaction was also applicable to other dicarboxylate hydrazine derivatives, such as diethyl hydrazine-1,2-dicarboxylate. In this case, phenylhydrazide was obtained in quantitative yields by the reaction of **1a**.

Table 3 *ortho*-Substituted Aryl Halides Coupling with *tert*-Butyl hydrazinecarboxylate using $[Pd(dba)_2]$ and **L9**[a]

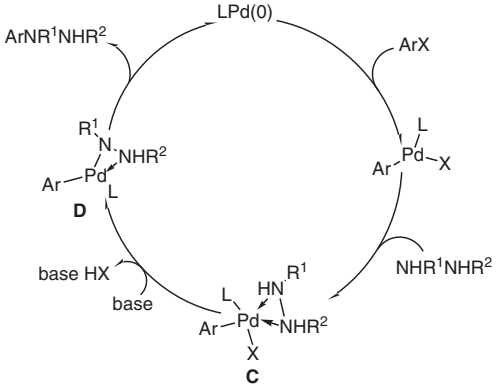


1 3

Entry	Substrate	R	X	Product	Yield (%)[b]
1	**1r**	CH_3	Br	**3r**	94[c]
2	**1s**	OCH_3	Br	**3s**	88
3	**1r′**	CH_3	Cl	**3r**	94
4	**1s′**	OCH_3	Cl	**3s**	81

[a] *Reagents and conditions:* Aryl halide (1.0 mmol), *tert*-butyl hydrazinecarboxylate (1.2 mmol), base (1.5 mmol), solvent (4.0 mL), $[Pd(dba)_2]$ (0.040 mmol), **L9** (0.060 mmol), 100 °C, 20 h.
[b] Isolated yield.
[c] $[Pd(dba)_2]$ (0.020 mmol), **L9** (0.030 mmol) were used.

On the basis of these observations, we proposed the following catalytic cycle (Scheme 1). Initially, the hydrazides coordinate to ArPdX (II), which arises from oxidative addition of Pd(0) to the aryl bromide. With the two nitrogen atoms, the five-coordinate complex **C** is formed, and subsequent abstraction of HBr by the base and intramolecular rearrangement affords complex **D**. Finally, reductive elimination of the monoarylated hydrazide forms the amidato complex **D** to give the product and regenerate the Pd(0) complex. When *ortho*-substituted aryl halides and BocNHNHBoc were employed as substrates, it was more difficult to form complex **C** due to steric hindrance, thus no products were observed. Although it seemed that the Pd-catalyzed C–N bond forming reaction occurs upon deprotonation of the more acidic N*H*Boc proton, steric factors are important and free NH_2 is more nucleophilic. Therefore, *ortho*-substituted aryl halides coupled with NH_2NHBoc under the optimized reaction conditions to give desired products with excellent regioselectivity.



Scheme 1 Proposed reaction mechanism

In summary, we have employed 2-di-*tert*-butylphosphino-2′-isopropoxy-1,1′-binaphthyl as a ligand for the synthesis of aryl hydrazines by the Pd-catalyzed coupling of

unreactive aryl halides bearing *meta*- and *para*-substituted groups with BocNHNHBoc in high efficiency.[19] For *ortho* substituted aryl halides, similar reactions can be realized by replacing BocNHNHBoc with NH_2NHBoc as the nucleophile, in which case good to excellent yields were also obtained. The reaction provides a useful method for preparation of aryl-substituted hydrazides with good functionality tolerance.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **General Procedure:** An oven-dried Schlenk tube was evacuated and backfilled with nitrogen. The Schlenk tube was charged with $[Pd(dba)_2]$ (11.4 mg, 2.0 mmol%), ligand (3.0 mmol%), mono- or di(*t*-butoxycarbonyl)hydrazine (1.2 mmol), and base (1.5 mmol), and capped with a rubber septum. The Schlenk tube was evacuated and backfilled with nitrogen three times. To the Schlenk tube were added aryl halide (1.0 mmol) and solvent (4.0 mL). The septum was replaced with a Teflon screw-cap and the mixture was heated to 100 °C with stirring for 20 h. Then reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (ethyl acetate–hexanes, 1:1→1:20)