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# Facial and practical synthesis of benzimidazole-based N-heterocyclic carbenes

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#### ARTICLE INFO

#### ABSTRACT

ing from aryldiamine and aryl halides.

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#### Introduction

N-heterocyclic carbene (NHC) is an important class of ligands used in organometallic chemistry. Many NHCs are based on an imidazole central core, due to its convenient preparation from glyoxal and primary amines. However, for NHCs that contain fused rings as central cores, such as a benzimidazole, the synthetic route would be different. Such synthesis often requires first the preparation of N,N'-substituted o-phenylenediamine, followed by ring formation reactions. Therefore, efficient synthesis of N,N'disubstituted o-phenylenediamine is of great interest, and can often be achieved based on aromatic C-N coupling reactions. Such C-N coupling was explored under Ullmann coupling conditions,<sup>1,2</sup> which is usually used for C-C couplings of aryl halides. There has also been significant progress in Pd catalyzed C-N coupling in the past few decades. Boger<sup>3</sup> reported Pd catalyzed intermolecular C-N coupling in 1984, followed by more advanced protocol from Hartwig<sup>4</sup> and Buchwald.<sup>5,6</sup> One of the initial and also the most widely used catalytic system is based on Pd<sub>2</sub>dba<sub>3</sub>/BINAP in the presence of a base. This system can catalyze many different couplings of primary or secondary amines with aryl halides. Additional catalytic systems are based on a variety of ligands, such as Xantphos<sup>7</sup> and DPEphos.<sup>7,8</sup> With respect to the synthesis of o-phenylenediamine or analogs for NHC precursors with a benzimidazole core, Huang<sup>9</sup> used Ullmann coupling to prepare N,N-diphenyl-ophenylenediamine. However, the yield of Ullmann coupling was only around 30% and required long reaction time. Wenderski<sup>10</sup> and Hao<sup>11</sup> used Buchwald reaction to prepare N,N'-diaryl-o-phenylenediamines with 37-60% yields. Other reported syntheses of © 2013 Elsevier Ltd. All rights reserved.

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### **Result & discussion**

An efficient synthesis of benzimidazole-based N-heterocyclic carbenes has been developed. The key step

in this synthetic methodology was a one-pot protocol for the synthesis of N,N'-diarylaryldiamines start-

As shown in Scheme 1, we used the synthesis of compound **1** as a model reaction to screen for optimal C–N coupling conditions.

The challenge involved chemoselective preparation of *N*,*N*'-diphenyl-o-phenylenediamine form two secondary amine moieties in a one-pot reaction and to minimize the formation of tertiary amine byproducts. The results are summarized in Table 1. For the reactions conducted in toluene with sodium *tert*-butoxide as a base (entries 1–4), the classical Pd<sub>2</sub>dba<sub>3</sub>/BINAP (entry 4) proved to be the best. Not only the yield of the desired product such as tertiary amines. Entries 5–7 explored additional solvents and bases for the Pd<sub>2</sub>dba<sub>3</sub>/BINAP catalyzed amination reaction. Overall, so-dium *t*-butoxide turned out to be the optimal base for the reaction, even though Cs<sub>2</sub>CO<sub>3</sub> is easier to handle and may serve as a good alternative with slightly longer reaction time.



Scheme 1. Synthesis of N,N'-diphenyl-o-phenylenediamine.



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such compounds are limited to the reactions of 1,2-dibromobenzene and a primary amine with a catalytic system using monophosphine ligands.<sup>12,13</sup> Reports are also rare on the selectivity of tertiary amine formation versus the desired di-secondary amine. In this Letter, we show that N,N'-diaryl-o-phenylenediamines or analogs can be efficiently prepared from aryldiamine and aryl bromides in high yields with high chemoselectivity.

 Table 1

 N,N'-Diphenyl-1,2-diaminobenzene formation using various Pd/ligands and bases (cf. Scheme 1)

Entry	o-Phenylenediamine & bromobenzene	Pd/ligand	Base	Solvent	T (°C)	<i>t</i> (h)	Yield (%)
1	Amine (1 equiv) & bromobenzene (2 equiv)	5%Pd(OAc) <sub>2</sub> /10%PPh <sub>3</sub>	NaOtBu(3 equiv)	Tol	110	11	Trace
2	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd(OAc) <sub>2</sub> /10%dppf	NaOtBu(3 equiv)	Tol	110	14	23
3	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd(OAc) <sub>2</sub> /10%NHC <sup>a</sup>	NaOtBu(3 equiv)	Tol	110	14	28
4	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd <sub>2</sub> dba <sub>3</sub> /7.5%BINAP	NaOtBu(3 equiv)	Tol	110	16	82
5	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd <sub>2</sub> dba <sub>3</sub> /7.5%BINAP	NaOtBu(3 equiv)	DME	110	16	80
6	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd <sub>2</sub> dba <sub>3</sub> /7.5%BINAP	Cs <sub>2</sub> CO <sub>3</sub> (3 equiv)	Tol	110	20	68
7	Amine(1 equiv) & bromobenzene (2 equiv)	5%Pd2dba3/7.5%BINAP	K <sub>2</sub> CO <sub>3</sub> (3 equiv)	Tol	110	20	55

<sup>a</sup> NHC = *N*,*N*'-diphenylbenzimidazolium chloride.



Figure 1. Prediction of tertiary amine products.

# Table 2Results of tertiary amine products

Entry	Equiv of bromobenzene	<i>T</i> (°C)	<i>t</i> (h)	(1a or 1b) Yield (%)
1	2	110	16	Trace
2	2.4	110	16	Trace
3	3	110	18	Trace
4	4	110	24	Trace

In order to confirm the selectivity of BINAP system for completing the C–N coupling at the secondary amine stage, we increased the amount of bromobenzene and/or prolonged the reaction time (Fig. 1 and Table 2) to see if the relative amount of tertiary amine products such as **1a** or **1b** would increase or not.

LC–MS analysis of the crude reaction mixtures showed that only a trace amount of mono- or di-tertiary amine was formed even with an increased amount of halides or prolonged reaction times (Table 2). Therefore, Pd<sub>2</sub>dba<sub>3</sub>/BINAP catalytic system appears to be ideal for preparing di-secondary amine intermediates. Based

 $N-R_2$ 

 $I-R_2$ 

12,88%



5%Pd<sub>2</sub>dba<sub>3</sub>/7.5% BINAP, 3 equiv NaOtBu

toluene

100°C

11, 52%

<sup>a</sup>Use Cs<sub>2</sub>CO<sub>3</sub> instead of NaOtBu.

9,81%

Table 3

Synthesis of di-secondary amine intermediates





<sup>a</sup> The reaction conditions: *N*,*N*'-diarylaryldiamine was distilled in trimethyl orthoformate. Then concd HCl and formic acid were added to the solution. The mixture was heated to 80 °C. After 2 h, the mixture was cooled to room temp and concentrated. The product was purified by silica flash column chromatography.

on the above optimized conditions, we extended the one-pot synthetic procedure to other aryldiamines and arylbromides. The results are summarized in Table 3.

As shown in Table 3, a series of N,N'-diarylaryldiamines were successfully prepared in high yields. When sodium t-butoxide was used as the base (entries 1, 2, 5, 6, 8–12), high yields were obtained in relatively short reaction time. On the other hand, when aryl halides were not compatible with sodium t-butoxide (entries 3, 4, and 7), Cs<sub>2</sub>CO<sub>3</sub> served as a fairly good alternative offering yields in 71–84% range in 24 h of reaction time. One limitation for our protocol is that strongly electron deficient aryldiamines such as 4-nitro-1,2-diaminobenzene or 2,3-diaminopyridine could not afford the corresponding desired products. In addition, due to the relatively high reaction temperature, small amounts of Ullmann homocoupling products were formed from aryl halides. Additional work to address these two issues is currently underway.

With a series of *N*,*N*'-diarylaryldiamines in hand, we proceeded to prepare the corresponding NHC precursors through cyclization with trimethylorthoformate and HCl. The results are summarized in Table 4. While the cyclization worked well for 8 of the 12 cases, diamines with strong electron withdrawing substitutions did not work (entries 4, 7, and 10), nor did the 7-member ring system (entry 12).

In summary, using the classical  $Pd_2dba_3/BINAP$  catalytic system for C–N coupling, we developed a one-pot protocol for the synthesis of *N*,*N*'-diarylaryldiamines starting from aryldiamine and aryl bromides. The synthetic procedure has excellent selectivity for producing the desired di-secondary amine products while minimizing the formation of tertiary amine byproducts. With dif-

ferent bases used in the reaction, one can also tune the reaction to be useful for wider ranges of functional groups in the starting materials. In most cases, further reactions with trimethyl orthoformate afforded the corresponding NHC precursors in good to high yields.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02. 006.

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