



# Transition-metal-free synthesis of aromatic amines *via* the reaction of benzyne with isocyanates

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## ABSTRACT

An unexpected reaction between benzyne and isocyanates to generate aromatic amines has been developed under transition-metal-free conditions. The *in situ* prepared anions formed through cleavage of the N–C bond in isocyanates, reacted with aryne precursors to afford various aniline derivatives in moderate to excellent yield and tolerated various substituents on the *o*-silyl aryl triflate and the isocyanate.

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## Introduction

Aromatic amines are important motifs in natural products, materials, pharmaceuticals and dyes.<sup>1</sup> Therefore, efficient and concise synthetic strategies towards this class of compounds is of significant interest. Traditional methods to access these useful building blocks typically proceed *via* the formation of carbon–nitrogen bonds. In particular, the palladium-catalyzed carbon–nitrogen bond formation reaction (Buchwald–Hartwig amination), Ullmann reaction, and Chan–Lam coupling reaction in the presence of Cu are well represented in the literature.<sup>2</sup> An amination reaction using carbon–hydrogen activation has been reported as an alternative methodology to construct C<sub>aryl</sub>–N bonds.<sup>3</sup> Despite several advantages, the requirement for expensive transition metals and directing groups is an obstacle for the utility of these reactions.

Over the past decades, benzyne chemistry has been extremely well developed. The reactivity of benzyne intermediates is attributed to a lowered LUMO arising from a strained  $\pi$ -bond, which facilitates several coupling reactions with neutral nucleophiles such as ureas<sup>4</sup> and imines.<sup>5</sup> The *in situ* generated benzyne intermediates formed from *o*-silyl aryl triflates under the action of fluoride reported by Kobayashi and co-workers<sup>6</sup> have allowed functionalization at the 1- and 2-positions of benzene.

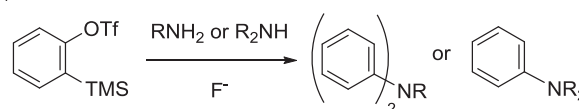
Such mild reaction conditions help overcome the limitations of transition metal catalyzed cross-coupling amination reactions,

such as the use of strong bases or high temperature. Interestingly, with respect to benzyne, mono *N*-arylation<sup>7</sup> has not been studied in detail.

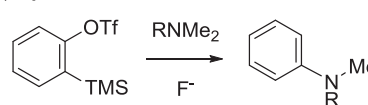
A representative mono *N*-arylation reaction utilizing primary or secondary amines has been demonstrated by Larock and co-workers.<sup>7d</sup> Due to the difficulty in reacting tertiary amines with arynes according to the formation of an ammonium salt, only one successful reaction has been reported by Biju and co-workers

### Previous work

#### a) Larock and co-workers<sup>7d</sup>



#### b) Biju and co-workers<sup>7a</sup>



#### c) This work

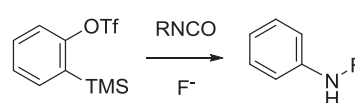


Fig. 1. Synthetic Methods for Constructing C<sub>aryl</sub>–N Bonds utilizing benzyne.

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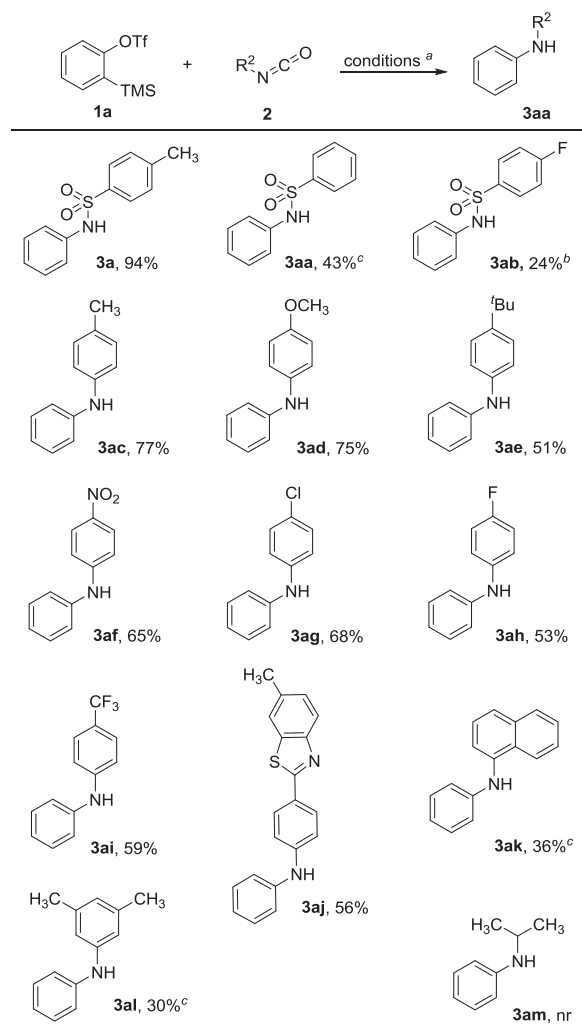
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(Fig. 1).<sup>7a</sup> To the best of our knowledge, the use of substituted isocyanates as a coupling partner for mono *N*-arylation employing benzyne precursors has not been reported. Herein, we report an efficient transition-metal free mono *N*-arylation reaction between benzyne and various isocyanates.

## Results and discussion

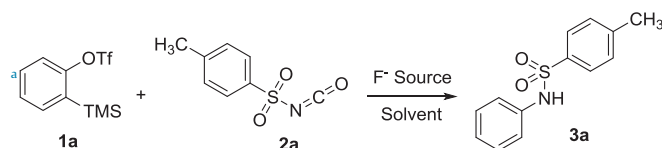
Initially, we investigated the reaction employing the model substrate **1a** and the commercially available tosyl isocyanate **2a** (1.2 equiv.) in presence of CsF in acetonitrile at room temperature (Table 1). Unexpectedly, the tosyl protected aniline **3a** was obtained in 28% yield (Entry 1). Encouraged by this result, the temperature was increased to 100 °C, which improved the yield to 48% (Entry 2). Interestingly, when the amount of tosyl isocyanate **2a** (2.4 equiv.) was increased, product **3a** was isolated in excellent yield 94% (Entry 3). Decreasing the fluoride source amount or using THF instead of acetonitrile, resulted in a diminished yield for **3a** (Entry 4). To examine the effect of additives, 18-crown-6, methanol and isopropyl alcohol were examined (Entries 5–7). Unfortunately, the crown ether or alcohol provided lower yield. Additionally, the use of TBAF failed to give product **3a** (Entries 8–9). Upon using KF/18-crown-6 or K<sub>2</sub>CO<sub>3</sub>/18-crown-6 as the benzyne triggering reagent, **3a** was observed in 28% or trace amounts, respectively (Entries 10–12). Finally, the use of tosyl isocyanate **2a** (2.4 equiv.) in presence of CsF (3.0 equiv.) in acetonitrile at 100 °C was selected as the best reaction conditions.

With the optimized conditions in hand, the scope of benzyne precursors was examined (Scheme 1). Both electron-donating and electron-withdrawing functional groups on the benzyne precursors were tolerated in this reaction. Alkyl groups such as *tert*-butyl, methyl, and dimethyl afforded the products (**3b**, **3d**, **3e**) in good to high yield, whereas methoxy groups gave **3c** and **3f** in 71% and 54% yields, respectively. In some cases involving *tert*-butyl, methoxy, dimethoxy groups, a regioisomeric mixture was observed (approximately 1:2 for **3b**, **3f** and 4:3 for **3e**). However, only one regioisomer was detected for the desired products (**3c**, **3g**, **3i**, **3k**). Polyaromatic **3g** and compounds **3h**, **3i**, **3j** were obtained in moderate yields.



**Scheme 2.** Substrate Scope of Different Isocyanates. <sup>a</sup>Reagents and conditions: *o*-silyl aryl triflate (0.1 mmol), tosyl isocyanate (0.24 mmol), CsF (0.3 mmol), acetonitrile (0.1 M), 100 °C, 14 h. <sup>b</sup>Tosyl isocyanate (0.12 mmol), CsF (0.2 mmol). <sup>c</sup>Tosyl isocyanate (0.3 mmol), CsF (0.4 mmol).

**Table 1**  
Optimization studies.



Entry	F <sup>-</sup> source	Solvent	Additive (1 equiv)	Yield <b>3a</b> (%) <sup>b</sup>
1 <sup>c,e</sup>	CsF	Acetonitrile		28%
2 <sup>c</sup>	CsF	Acetonitrile		48%
3	CsF	Acetonitrile		94%
4	CsF	THF		0%
5	CsF	Acetonitrile	18-crown-6 <sup>f</sup>	60%
6	CsF	Acetonitrile	MeOH	76%
7	CsF	Acetonitrile	<i>i</i> PrOH	48%
8 <sup>d</sup>	TBAF	THF		0%
9 <sup>d</sup>	TBAF	THF	MeOH	0%
10	KF	Acetonitrile	18-crown-6	28%
11 <sup>g</sup>	K <sub>2</sub> CO <sub>3</sub>	Acetonitrile	18-crown-6	5%
12	K <sub>2</sub> CO <sub>3</sub>	Acetonitrile	18-crown-6	4%

<sup>a</sup> Reagents and conditions: *o*-silyl aryl triflate (0.1 mmol), tosyl isocyanate (0.24 mmol), fluoride source (0.3 mmol), solvent (0.1 M), 100 °C, 14 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Tosyl isocyanate (0.12 mmol).

<sup>d</sup> Fluoride source (0.12 mmol).

<sup>e</sup> Room Temperature.

<sup>f</sup> Additive (3 equiv.).

<sup>g</sup> Potassium carbonate (0.24 mmol).

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