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Transition-Metal-Free Diarylation of Isocyanates with Arynes

Woo Cheol Jang[†], Dong Wook Hwang[†], Jeong Hoon Seo and Haye Min Ko*

Department of Bio-Nano Chemistry, Wonkwang University, 460 Iksandae-ro, Iksan, Jeonbuk 54538, Republic of Korea

ARTICLE INFO * Corresponding author. e-mail: <u>hayeminko@wku.ac.kr</u>; Tel.:+82 63 850 6229

Article history: Received Received in revised form Accepted Available online A facile method for the transition-metal-free diarylation of isocyanates with arynes in the presence of cesium fluoride has been developed, which affords functionalized diaryl amines in moderate to excellent yields. This reaction has good functional group tolerance and provides excellent regioselectivity by utilizing a methoxy-substituted aryne precursor.

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Introduction

Diphenylamines are ubiquitous in natural products, pharmaceuticals, agrochemicals, dyes, and materials. In particular, the diphenylamine backbone is a key motif in materials science due to its promising optical and electrical properties as a good charge carrier with hole transport abilities. Accordingly, diphenylamine derivatives are widely used as the electron-donating moieties to trigger intramolecular charge transfer in electrochromic materials, dye-sensitized solar cells (DSSCs), organic field effect transistors, and organic lightemitting diodes (OLED).^{1a-d} Diphenylamine derivatives are also commonly in many pharmaceuticals. Numerous diphenylamine based compounds^{1e-n} are known to possess diverse bioactivities including anticancer, EGFR tyrosine kinase inhibition, and sirtuin-2-selective inhibition activities. For example, N-Bdimethylaminoethyl derivatives of diphenylamine have potent antihistamine activity.10 Thus, many research groups are still interested in the synthesis of diphenylamine derivatives. Most of these useful building blocks are prepared via transition-metal catalyzed C-N bond formation reactions. In this regard, palladium or copper catalyzed C-N coupling reactions are commonly employed. To construct the C-N bond of arylamines, Ullmann-type reactions² have been carried out using Cu, aryl halides, and amines. Although this reaction is convenient and airstable, high temperatures and a stoichiometric amount of catalysts are usually required. Another method for C-N bond formation is the Buchwald-Hartwig coupling reaction³ of an aryl halide with an amine in the presence of a palladium catalyst, which is effective and has high selectivity. In contrast, the first transition-metal free C-N bond coupling reaction utilizing arynes and amines was reported by Larock and co-workers.⁴ Several other groups have also reported transition-metal free C-N bond coupling reactions5-7 using acetanilides,5c tertiary amines,6 or isocyanates7 with benzynes. Despite the limited regioselectivity

resulting from benzynes, this method serves as a simple alternative route to furnish diarylamine derivatives. Thus, these results⁴⁻⁷ encouraged us to focus on the chemistry and reactivity of benzynes for the development of a new strategy under transition-metal free conditions. Herein, we report a facile *N*-diarylation reaction with isocyanates and benzynes, without using transition-metals, for the synthesis of diarylamine derivatives.

Results and Discussion

Based on previous results,^{7a} we carried out the diarylation reaction using model substrate **1a** and tosyl isocyanate **2a** (2.4 equiv.) in the presence of CsF (3 equiv.) in acetonitrile at 100 °C, and obtained the corresponding diarylation product **3a** in 45% yield (Table 1, entry 1). Thus, our initial attempts were directed toward identifying the optimal conditions for the *N*-diarylation of **2a**.

Gratifyingly, the desired product **3a** was obtained in excellent yield (88%) when the amount of **2a** (1.2 equiv.) was decreased, notwithstanding the formation of the mono *N*-arylation product **3a'** (Entry 2). The use of the K₂CO₃/18-crown-6 combination (3 equiv./ 3 equiv.) as the aryne generating reagent gave **3a** in 77% yield (Entry 13). Similarly, when **2a** (2.4 equiv.) was used with

Tetrahedron

Table 1. Optimization Studies.^a

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$\begin{array}{c c c c c c c } & variation from standard conditions & Yield 3a/3a' (\%)^b \\ \hline 1 & 2.4 equiv. 2a & 45/12 \\ 2 & none & 88/11 \\ 3 & 2.0 equiv. CsF & 35/40 \\ 4 & 80 ^{\circ}C, instead of 100 ^{\circ}C & 71 \\ 5 & 0.15 \ M \ CH_3 \ CN & 60 \\ 6 & 0.6 \ equiv. 2a, 2.0 \ equiv. \ CsF & 83 \\ 7 & T \ HF \ instead of \ CH_3 \ CN & 5 \\ 8 & D \ CM \ instead of \ CH_3 \ CN & No \ rex \\ 9 & T \ oluene \ instead \ of \ CH_3 \ CN & No \ rex \\ 10 & T \ BAT/T \ HF \ instead \ of \ CsF/\ CH_3 \ CN & No \ rex \\ 11 & T \ BAF/T \ HF \ instead \ of \ CsF/\ CH_3 \ CN & No \ rex \\ 12 & \ KF/18 \ crown-6 \ instead \ of \ CsF & 60 \\ 13 & \ K_2 \ CO_3/18 \ crown-6 \ instead \ of \ CsF & 50/4 \\ \hline \end{array}$	TMS 1a OTf	$ \begin{array}{c} T_{S} & C^{O} & C^{H_{3}} \\ \hline & 2a \ (1.2 \ equiv.) \\ \hline & 3.0 \ equiv. \ CsF \\ CH_{3}CN \ (0.1 \ M), \ 100 \ ^{\circ}C, \ 14h \end{array} \begin{array}{c} T_{S} & C^{H_{3}} \\ \hline & 3a \end{array} $	+ CH ₃ + HN\ 3a'
1 2.4 equiv. 2a 45/12 2 none 88/11 3 2.0 equiv. CsF 35/40 4 80 °C, instead of 100 °C 71 5 0.15 M CH ₃ CN 60 6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CSF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 50/4 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	Entry	variation from standard conditions	Yield 3a/3a' (%) ^b
2 none 88/11 3 2.0 equiv. CsF 35/40 4 80 °C, instead of 100 °C 71 5 0.15 M CH ₃ CN 60 6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 50/4 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	1	2.4 equiv. 2a	45/12
3 2.0 equiv. CsF 35/40 4 80 °C, instead of 100 °C 71 5 0.15 M CH ₃ CN 60 6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 50/4 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	2	none	88/11
4 80 °C, instead of 100 °C 71 5 0.15 M CH ₃ CN 60 6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 50/4 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	3	2.0 equiv. CsF	35/40
5 0.15 M CH ₃ CN 60 6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	4	80 °C, instead of 100 °C	71
6 0.6 equiv. 2a, 2.0 equiv. CsF 83 7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	5	0.15 M CH ₃ CN	60
7 THF instead of CH ₃ CN 5 8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CSF/CH ₃ CN trace 11 TBAF/THF instead of CSF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CSF 60 13 K ₂ CO ₃ /18-crown-6 instead of CSF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CSF 50/4	6	0.6 equiv. 2a , 2.0 equiv. CsF	83
8 DCM instead of CH ₃ CN No rex 9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	7	THF instead of CH ₃ CN	5
9 Toluene instead of CH ₃ CN No rex 10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	8	DCM instead of CH ₃ CN	No rex
10 TBAT/THF instead of CsF/CH ₃ CN trace 11 TBAF/THF instead of CsF/CH ₃ CN No rex 12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a, K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	9	Toluene instead of CH ₃ CN	No rex
TBAF/THF instead of CsF/CH3CN No rex KF/18-crown-6 instead of CsF 60 KF/18-crown-6 instead of CsF 77/10 K2CO3/18-crown-6 instead of CsF 50/4	10	TBAT/THF instead of CsF/CH ₃ CN	trace
12 KF/18-crown-6 instead of CsF 60 13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a , K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	11	TBAF/THF instead of CsF/CH ₃ CN	No rex
13 K ₂ CO ₃ /18-crown-6 instead of CsF 77/10 14 2.4 equiv. 2a , K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	12	KF/18-crown-6 instead of CsF	60
14 2.4 equiv. 2a , K ₂ CO ₃ /18-crown-6 instead of CsF 50/4	13	K ₂ CO ₃ /18-crown-6 instead of CsF	77/10
	14	2.4 equiv. 2a, $K_2CO_3/18$ -crown-6 instead of CsF	50/4

^aReagents and conditions: *o*-silyl aryl triflate **1a** (0.1 mmol), tosyl isocyanate **2a**, fluoride source, CH₃CN (0.1 M), 100 °C, 14 h. ^bIsolated yield.

Scheme 1. Substrate Scope of the Benzyne Precursors.



^{*a*}Regioisomeric mixture. ^{*b*}Tosyl isocyanate (0.6 equiv.).

K₂CO₃/18-crown-6 instead of CsF, 3a was formed in moderate yield (Entry 14). Using the KF/18-crown-6 combination, 3a was synthesized in 60% yield (Entry 12). However, the mono Narylation product 3a' was still formed, and the reaction did not proceed further. To avoid forming 3a', decreasing the fluoride source to 2 equiv., gave the desired product 3a in 35% yield (Entry 3). Additionally, a lower reaction temperature (80 °C) or increasing the concentration of the reaction solution (0.15M) did not improve the vield despite the absence of **3a'** (Entries 4-5). Various solvents were tested, and it was found that acetonitrile was the best solvent (Entries 7-9). When TBAF or TBAT were employed as the fluoride source with THF, the desired product 3a was not formed (Entries 10-11). Finally, when the reaction was performed using 0.6 equiv. of 2a, the desired product 3a was isolated in 83% yield without the formation of mono N-arylation product 3a' (Entry 6).

With the optimized reaction conditions in hand, we next examined the scope of the benzyne substrates that can react with 2a (Scheme 1). N-Diarylation reactions with a methoxy or dimethoxy aryne precursor proceeded smoothly to give 3b4a and 3c in excellent yields (80%). Dimethyl benzyne and benzyne precursors gave the expected products 3d and 3e^{4b} in 69% and 92% yield, respectively. The reactions with difluoro and bromomethyl substituted (trimethylsilyl)phenyl triflates afforded the desired products 3i and 3j in moderate yields of 40% and 30%, respectively. In some cases, a mixture of regioisomers was formed, and the regioisomeric ratio was measured by ¹H NMR spectroscopy. Substrates with electron-withdrawing groups such as fluoride or chloride gave mixtures of regioisomeric products 3g, 3h in good to moderate yields. Similarly, tert-butyl substituted 2-(trimethylsilyl)phenyl triflate and polyaromatic systems were tolerated under the reaction conditions, and gave 3f and 3k in 51% and 25% yield, respectively.

Initially, when exploring the scope of the isocyanates, 2methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate was used as the coupling partner to avoid the formation of a complex mixture of regioisomers. Based on distortion model,^{8a-b} frontier contribution analysis.^{8c} molecular orbital and orbital electronegativity.8d *meta*-position of methoxy-benzyne the formed from 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate was determined as the preferred site of nucleophilic addition. The reactions with *p*methylbenzenesulfonyl, benzenesulfonyl, and **p**fluorobenzenesulfonyl isocyanates gave the corresponding products 4a,4a 4b, 4c in excellent yields (80%, 91% and 95%, respectively), while products 4d and 4e were formed from pmethoxyphenyl and p-fluorophenyl isocyanates in good yields (71%). The reactions utilizing phenyl isocyanates bearing methyl, dimethyl and trifluoromethyl groups provided the desired products 4f, 4g, and 4h in moderate yields (28-55%). All of these products were afforded as single regioisomers as confirmed by ¹H and ¹³C NMR spectroscopy. Similarly, the corresponding products 4i⁹ and 4j¹⁰ which come from (trimethylsilyl)phenyl trifluoromethanesulfonate 1e were isolated as single regioisomers in 98% and 82% yields, respectively. The reactions of phenyl isocyanates containing dimethyl, methoxy, tert-butyl and methyl groups with benzyne precursor le gave 4k,¹¹ 4l,¹² 4m¹³ and 4n¹² in 87%, 46%, 43% and 40% yields, respectively. The reaction of fluorophenyl isocyanate led to the formation of a single isomer 40^{12} in good yield (88%). When chloro or trifluoromethylphenyl isocyanates were subjected to the diarylation conditions, 4p12 and 4q¹⁴ were formed in 28% and 15% yields, respectively.





Scheme 3. Proposed Reaction Mechanism.



However, the use of aliphatic or polyaromatic isocyanates led to complex mixtures of the products 4p and 4r.

On the basis of these results, we proposed a plausible pathway for the formation of **3a**, as illustrated in Scheme 3. Hydrolysis of the isocyanate gives intermediate **5a**, which then reacts with the *in situ* generated aryne to furnish the *N*-arylation product **5b**. Then, **5b** is transformed into the desired product in the presence of CsF, followed by C-N bond coupling with another aryne. In the reaction of tosyl isocyanate and 2-(trimethylsilyl)phenyl triflate, tosyl amine 5a was formed first *via* hydrogen abstraction under the diarylation conditions.

Conclusion

In conclusion, we describe a facile, transition-metal free strategy to prepare diarylamine derivatives *via* the coupling of arynes with isocyanates. This work demonstrates that isocyanates are appropriate coupling partners for this transformation, and a diverse range of functional groups on the benzynes and isocyanates are tolerated under the present reaction conditions. The exemplified diversity of C-N bond formation *via* diarylation provides a new route to access potential materials and bioactive compounds. Further investigations to develop effective, efficient coupling partners for this diarylation are in progress.

Author information

[†]W.C.J. and D.W.H. contributed equally.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Transition-metal-free and ligand-free reaction Facile approach to synthesize diarylamines utilizing aryne precursors and isocyanates Unexpected cleavage of N-C bond in isocyanates