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Employing Arynes in Transition-Metal-Free Monoarylation of Aromatic Tertiary Amines

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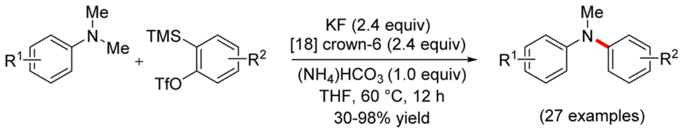
ABSTRACT



The highly monoselective N-arylation of aromatic tertiary amines using a transition-metal-free approach using arynes has been developed. The reaction afforded functionalized diaryl amines in moderate to excellent yield. High levels of functional group compatibility especially with halogen containing substrates, dyes and donor−acceptor systems, and high yields of products are the notable features of the present reaction.

Aromatic amines are ubiquitous in various natural products, pharmaceuticals, agrochemicals, dyes, and materials and are useful synthetic building blocks.[1] Traditionally, methods such as substitution on an aromatic system with nucleophilic amine functionality, installation of the nitro group on an aromatic ring followed by reduction, and arylation of the N-containing functional group using copper following the Ullmann−Goldberg protocol are the different ways of constructing the aromatic carbon−nitrogen bonds.[2] However, with the advent of transition-metal catalysis, the N-arylation of amines can be easily realized by the Buchwald−Hartwig coupling (coupling of aryl halides with primary or secondary amines in presence of Pd-catalyst), Ullmann-type coupling (reaction of aryl halides with amines in presence of Cu), and the Chan−Lam coupling (coupling of an organoboron reagent with N−H functionality) (Scheme 1).[3] Moreover, the synthetic utility of organometallic reagents derived from B, Mg, Zn, etc. in a transition-metal-catalyzed amination reaction with an electrophilic source of nitrogen, and C−H activation of (hetero)aromatic rings have been useful for the construction of C_{aryl}−N bonds.[4] Recently, transition-metal-free N-arylation reactions employing organoboronic acid derivatives represent an alternative methodology for the C_{aryl}−N bond-forming reactions.[5] Interestingly, however, whereas the transition-metal-catalyzed arylation of primary and secondary amines is well-established, the analogous C−N bond construction using aromatic tertiary amines, to the best of our knowledge, has not been reported. Herein, we report an efficient and facile transition-metal-free, monoselective N-arylation of aromatic tertiary amines using arynes as the aryl source. Notably, the present procedure is efficient for the selective monoarylation of the $-NMe_2$ group and the method is applicable to several donor−acceptor systems and dyes.

Arynes are extremely electron-poor reactive intermediates in organic chemistry, and they are widely used for the

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(4) (a) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Zhang, M.; Zhang, A. *Synthesis* **2012**, 1. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236.

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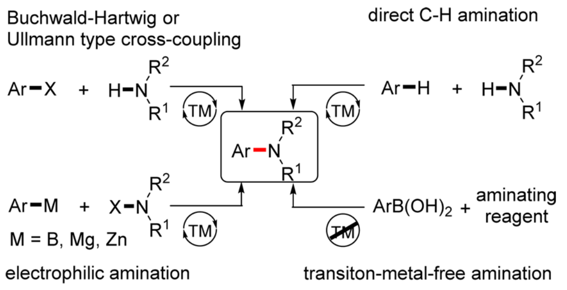
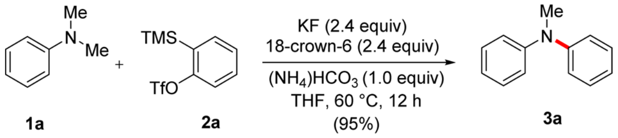
Scheme 1. Methods for Forming C_{aryl}−N Bonds



synthesis of several 1,2-disubstituted benzene derivatives of complex structure.[6] Due to the high electrophilicity and extremely strained carbon−carbon triple bond, arynes undergo facile insertion into element−element bonds leading to multisubstituted arenes of synthetic value.[7] In 2003, Larock et al. reported the insertion of arynes into the N−H bond of primary and secondary amines leading to the N-arylated products.[8] However, this method was not applicable for the arylation of tertiary amines. To address this issue based on our experience in aryne chemistry,[9] we initiated the present study by treating *N*,*N*-dimethyl aniline **1a** with the aryne generated in situ from 2-(trimethylsilyl)-aryl triflate **2a**[10] using KF and 18-crown-6 in the presence of ammonium bicarbonate as an additive. Interestingly, the reaction afforded the *N*-methyl-*N*-phenylaniline **3a** in 95% yield (Scheme 2).[11] The present method is highly monoselective, and no product derived from the C-arylation was observed.[12] The additive was found to be essential for better yields, as the reaction without the additive furnished the product in 33% yield.[11]

Scheme 2. Monoselective N-Arylation of *N*,*N*-Dimethylaniline



With the optimized reaction conditions in hand, we then examined the substrate scope of this transition-metal-free N-arylation reaction (Scheme 3). A variety of *N*,*N*-dimethyl anilines having an electron-donating or -withdrawing group at the 4-position of the aromatic ring were well tolerated, furnishing the diarylamine derivatives in good to excellent yields (**3b**−**f**). Electron-rich aldehydes usually insert into arynes in a [2 + 2] fashion.[13] However, 4-dimethylamino benzaldehyde derivative **1g** still afforded the desired product in 30% yield. Moreover, substitution at the 3- and 2-position of the aromatic ring of **1** and the disubstitution resulted in smooth conversion to the product (**3h**−**k**). It is noteworthy, that halides, which are very unlikely to survive under transition-metal-catalyzed reaction conditions,[3] are well tolerated under the present N-arylation protocol (**3c**, **3d**, **3i**). Gratifyingly, *N*,*N*-dimethyl aniline derivatives bearing a phosphonate group, double bond, and triple bond on the aromatic ring readily underwent efficient N-arylation thereby further expanding the scope of this reaction (**3l**−**3n**). The naphthyl substituted amine furnished the corresponding product **3o** in 98% yield, and even more interesting is that the dansyl chloride afforded the product **3p** in 61% yield. Interestingly, challenging substrates such as Leucomalachite green underwent efficient N-arylation leading to the formation of desired product **3q** in 78% yield. Delightfully, *N*,*N*-dimethyl anilines derived from donor−acceptor systems resulted in a smooth N-arylation reaction affording the desired products signifying the versatility of the present reaction (**3r**−**t**).[14]

Next, we evaluated the effect of varying the substituents on the aryne precursor **2** (Table 1). Electronically different 4,5-disubstituted symmetrical aryne precursors **2b**−**d** readily afforded the diphenylamine derivatives **3u**−**w** in excellent yields (entries 1−3). Moreover, the 3,6-dimethyl substituted symmetrical aryne precursor **2e** worked well to afford the product **3x** in 64% yield (entry 4). Additionally, 3-methoxy benzyne generated from **2f** and the naphthalyne

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(6) For recent reviews on aryne chemistry, see: (a) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (b) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (d) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (e) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (f) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (g) Okuma, K. *Heterocycles* **2012**, *85*, 515. (h) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (i) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199.

(7) For a recent account on aryne insertions, see: (a) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725. For selected recent reports, see: (b) Stephens, D.; Zhang, Y.; Cormier, M.; Chavez, G.; Arman, H.; Larionov, O. V. *Chem. Commun.* **2013**, *49*, 6558. (c) Kim, J.; Stoltz, B. M. *Tetrahedron Lett.* **2012**, *53*, 4994. (d) Fang, Y.; Rogness, D. C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 6262. (e) Okuma, K.; Itoyama, R.; Sou, A.; Nagahora, N.; Shioj, K. *Chem. Commun.* **2012**, *48*, 11145. (f) Rodríguez-Lojo, D.; Cobas, A.; Peña, D.; Pérez, D.; Guitián, E. *Org. Lett.* **2012**, *14*, 1363. (g) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686. (h) Dhokale, R. A.; Mhaske, S. B. *Org. Lett.* **2013**, *15*, 2218. (i) Hendrick, C. E.; McDonald, S. L.; Wang, Q. *Org. Lett.* **2013**, *15*, 3444. (j) Yoshida, H.; Yoshida, R.; Takaki, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8629. For a highlight, see: (k) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

(8) (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. It may be noted that Larock et al. observed the arylation of in situ generated *N*,*N*-dimethyl aniline in the reaction of ketone-derived hydrazones with arynes. For details, see: (c) Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 11232.

(9) (a) Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 4620. (b) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040. (c) Kaicharla, T.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 6238. (d) Bhojgude, S. S.; Kaicharla, T.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2012**, *14*, 4098.

(10) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. For a modified procedure for the synthesis of the triflate, see: (b) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

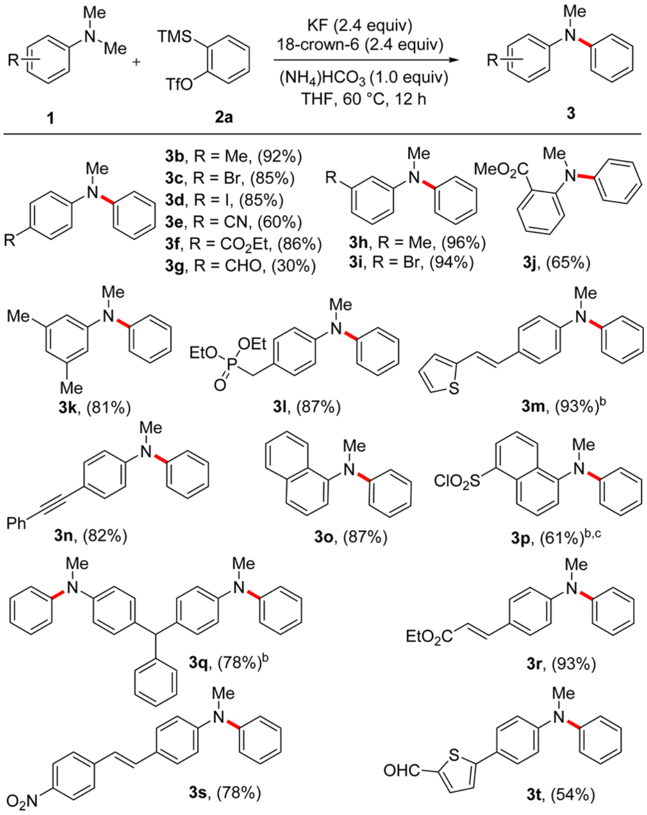
(11) For details, see the Supporting Information.

(12) (a) Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006. See also: (b) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199.

(13) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.

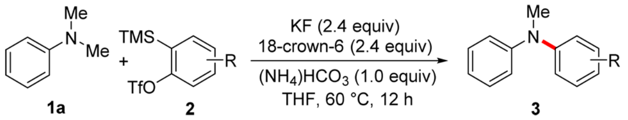
(14) It may be noted that aliphatic tertiary amines such as *N*,*N*-dimethyloctylamine and sterically hindered aromatic amines such as *N*,*N*,2,4,6-pentamethylaniline did not afford the N-arylated product under the optimized conditions.

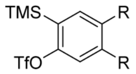
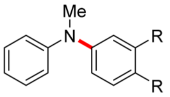
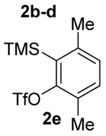
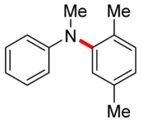
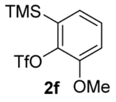
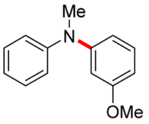
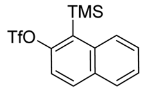
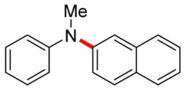
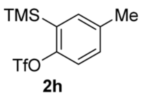
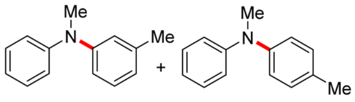
Scheme 3. Substrate Scope of the N-Arylation Reaction: Variation of the Tertiary Amines[a]



[a] General conditions: **1** (0.50 mmol), **2a** (0.60 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (2.0 mL), 60 °C and 12 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale. [c] The reaction was carried out using 2.0 equiv of **2a** and 4.0 equiv each of KF and 18-crown-6.

Table 1. Variation of the Aryne Moiety[a]



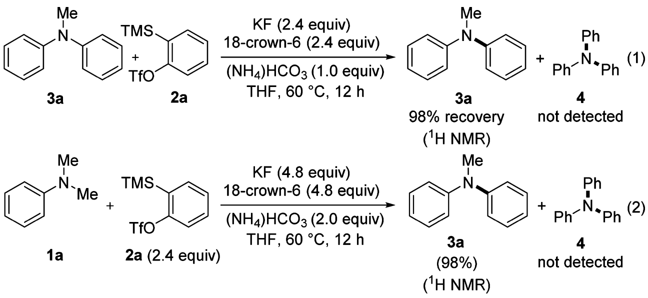
entry	aryne precursor	product(s), yield (%)
1 2 3	 **2b-d**	 **3u**, R = Me, (93%) **3v**, R = O(CH$_2$)O, (94%) **3w**, R = F, (88%)
4		 **3x**, (64%)
5		 **3y**, (94%)
6		 **3z**, (96%)
7		 **3aa** [1.3:1][b], (93%) **3aa′**

[a] General conditions: **1a** (0.50 mmol), **2** (0.60 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (2.0 mL), 60 °C and 12 h. Yields of the isolated products are given. [b] The regioisomer ratio was determined by ^{1}H NMR analysis.

derived from **2g** furnished single regioisomers **3y** and **3z** in excellent yield (entries 5, 6). Finally, the unsymmetrical benzyne derived from **2h** underwent efficient N-arylation to deliver an inseparable mixture of regioisomers **3aa** and **3aa′** in 93% overall yield (entry 7).

We carried out a series of experiments to probe the mechanism of this unique N-arylation reaction. To gain insight into the nature of the arylation reaction and the stability of product **3a** under the reaction conditions, **3a** was treated with aryne precursor **2a** under the optimized reaction conditions (Scheme 4, eq 1). This reaction returned **3a** quantitatively without the formation of any detectable amount of diarylated product **4**. Moreover, when **1a** was treated with an excess of **2a**, KF, and [18] crown-6, the reaction delivered only **3a** and **4** was not detected (eq 2).[11] These observations tend to indicate that the present arylation reaction is highly monoselective under the optimized conditions.[15]

Scheme 4. Experiments to Illustrate Selective Monoarylation



The mechanistic rationale for this transition-metal-free transformation is shown in Scheme 5. The reaction is likely initiated by the generation of aryne by the fluoride induced 1,2-elimination of **2a**. The nucleophilic addition of *N*,*N*-dimethylaniline **1a** to the aryne generates the zwitterionic intermediate **5**, which was protonated to form the dimethyl diphenyl ammonium salt **6**. Demethylation induced by the fluoride ion or the basic reaction medium furnishes the final product **3a**.[16,17]

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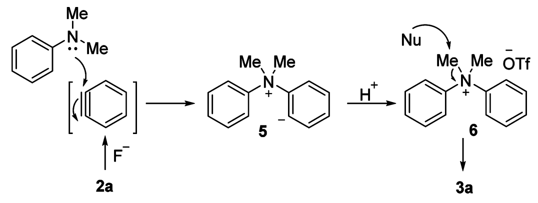
(15) Possibly, the lone pair of electrons on nitrogen in **1a** is more available for nucleophilic attack on aryne. However, in the case of **3a**, since the lone pair of electrons on nitrogen is delocalized between two benzene rings, it may not be available for nucleophilic attack on aryne.

(16) For a related demethylation of quaternary ammonium salt in the presence of nucleophilic fluoride media, see ref 8c.

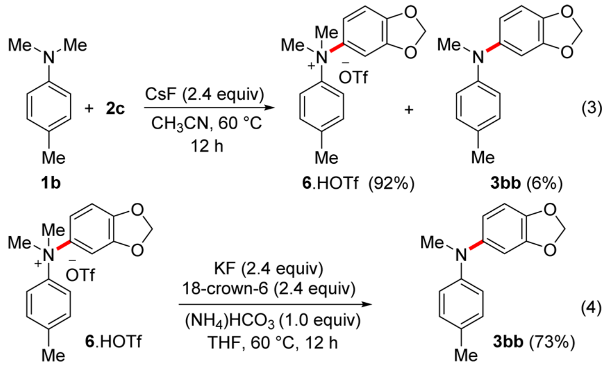
(17) For experiments indicating the role of fluoride ion or base in the demethylation step, see the Supporting Information.

Scheme 5. Plausible Reaction Mechanism



A strong indication for the presence of **6** comes from the fact that the reaction of tertiary amine **1b** with aryne precursor **2c** in the presence of CsF resulted in smooth formation of the quaternary ammonium salt **6**·HOTf[18] in 92% along with 6% of the arylated product **3bb** (Scheme 6, eq 3).

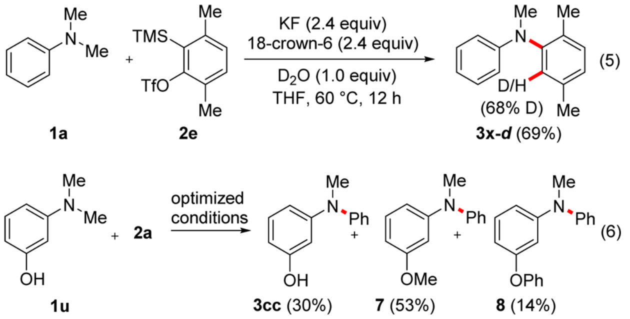
Scheme 6. Experiments to Confirm **6**·HOTf as the Intermediate



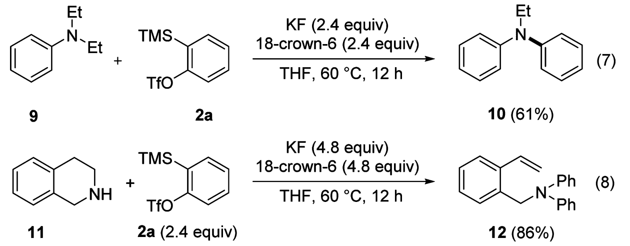
Moreover, subjecting the salt **6**·HOTf under the optimized reaction conditions resulted in the formation of the desired arylated product **3bb** in 73% yield (eq 4).

To shed light on protonation of the zwitterionic intermediate **5**, an experiment using D_2O as the additive was performed. Treatment of **1a** with **2e** in the presence of a fluoride source and D_2O afforded the desired product **3x-*d*** in 69% yield with 68% deuterium incorporation at the 2-position (Scheme 7, eq 5). This indicates the role of additive in protonating the zwitterionic intermediate **5**. Moreover, to test the possibility of the competing O-arylation under the reaction conditions, the amine **1u** was treated with **2a** under the optimized conditions (eq 6). The reaction afforded the N-arylated product **3cc** in 30% yield along with the O-methylated product **7** in 53% yield, which is likely formed by the demethylation of intermediate **6** by the phenol **3cc**. In addition, the product **8** derived from the O-arylation of **3cc** was observed in 14% yield.

Scheme 7. Mechanistic Experiments



Scheme 8. Arylation of *N*,*N*-Diethyl Aniline and Tetrahydroisoquinoline



Furthermore, this novel arylation reaction is not limited to *N*,*N*-dimethyl aniline derivatives. Interestingly, *N*,*N*-diethyl aniline **9** resulted in the formation of N-arylated product **10** in 61% yield presumably by the elimination of a molecule of ethylene (Scheme 8, eq 7). Moreover, tetrahydroisoquinoline **11** underwent efficient cascade arylation involving the initial N−H insertion of aryne followed by the arylation of the resultant N-arylamine leading to the styrene derivative **12** in 86% yield (eq 8).

In conclusion, we have developed a transition-metal-free and highly monoselective N-arylation of aromatic tertiary amines using arynes. A broad substrate scope, high levels of functional group compatibility especially with halogen containing substrates, dyes, and donor−acceptor systems, and high yields of products are the notable features of the present reaction.

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Supporting Information Available. Detailed experimental procedures, mechanistic experiments, and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[18] For a report on the synthesis of a similar adduct using arynes, see: Okuma, K.; Nojima, A.; Nakamura, Y.; Matsunaga, N.; Nagahora, N.; Shioji, K. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 328.