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Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines, and Aldehydes via Aryl–Aryl Amino Group Migration

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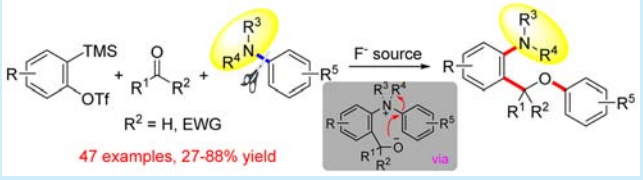
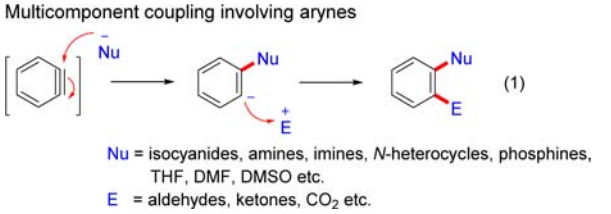
Supporting Information

ABSTRACT: The transition-metal-free multicomponent coupling of arynes, aromatic tertiary amines, and aldehydes proceeding via the aryl to aryl amino group migration has been demonstrated. This protocol allows rapid access to *ortho*-functionalized tertiary amines in moderate to good yields. Moreover, activated ketones can also be used as the aldehyde component in the present reaction. The similarity of the aryl–aryl tertiary amino group migration with the Smiles rearrangement is striking.

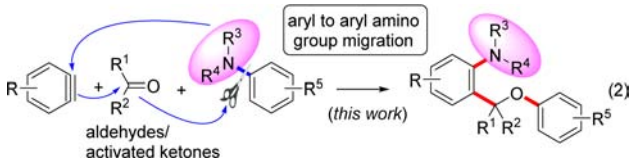


Transition-metal-free multicomponent coupling (MCC) involving arynes constitutes one of the convenient methods for the rapid access to 1,2-disubstituted benzene derivatives having complexity and diversity.[1,2] Traditionally, in aryne MCCs, a nucleophile (having no acidic hydrogen) adds to the aryne generating a transient aryl anion intermediate, which is subsequently trapped by an electrophile (third-component) to form the MCC product (eq 1). A wide variety of nucleophiles such as



isocyanides,[3] imines,[4] *N*-heterocycles (such as pyridine and isoquinoline),[5] phosphines,[6] and solvents (including THF,[7] DMF,[3c,8] and DMSO[9]) can trigger the aryne–nucleophile zwitterion generation. The electrophilic coupling partners are usually carbonyl compounds including CO_2.[10]

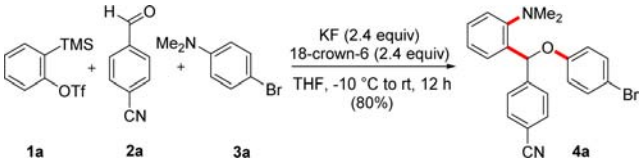
The use of amines as nucleophilic triggers in aryne MCCs has received only limited attention. This is primarily due to the spontaneous protonation of the aryl anion generated from amine and aryne resulting in arylation of amines.[11] In 2007, Yoshida and co-workers reported the aryne MCCs initiated by silyl-protected amines using aldehydes as the third-component leading to the synthesis of 2-aminobenzyl alcohols.[12] Apart from the work of Yoshida, the synthetic utility of tertiary amines as nucleophilic trigger in aryne MCCs remains underexplored.[13] Notably, the use of tertiary allylamines was utilized in an aryne aza-Claisen rearrangement by Greaney and co-workers.[14] We have recently reported the transition-metal-free *N*-arylation of tertiary amines using arynes as the aryl source.[15] Herein, we report the three-component coupling of arynes, aromatic tertiary amines, and aldehydes leading to the synthesis of *ortho*-functionalized tertiary amines (eq 2). Activated ketones can also be used as the third component in this reaction. Mechanistically, this reaction



proceeds via a unique aryl to aryl tertiary amino group migration and is analogous to Smiles rearrangement.[16]

The present study commenced by the treatment of aryne generated in situ from 2-(trimethylsilyl)aryl triflate **1a**[17] (using KF and 18-crown-6) with 4-cyanobenzaldehyde **2a** and 4-bromo *N*,*N*-dimethylaniline **3a**. Interestingly, under these conditions, a facile reaction occurred resulting in the formation of *O*-arylated 2-(dimethylamino)benzhydrol **4a** in 80% yield (Scheme 1).[18] The

Scheme 1. MCC Involving Aryne, 4-Cyanobenzaldehyde, and 4-Bromo-*N*,*N*-dimethylaniline



product formation took place via the migration of NMe_2 group from the amino aryl moiety of **3a** to the aryl part of aryne. Notably, from a product perspective, *ortho*-functionalization of aromatic tertiary amines is difficult to realize compared to the *para*-derivatization.[19]

With the reaction conditions for the synthesis of *ortho*-functionalized tertiary amines in hand, we then examined the

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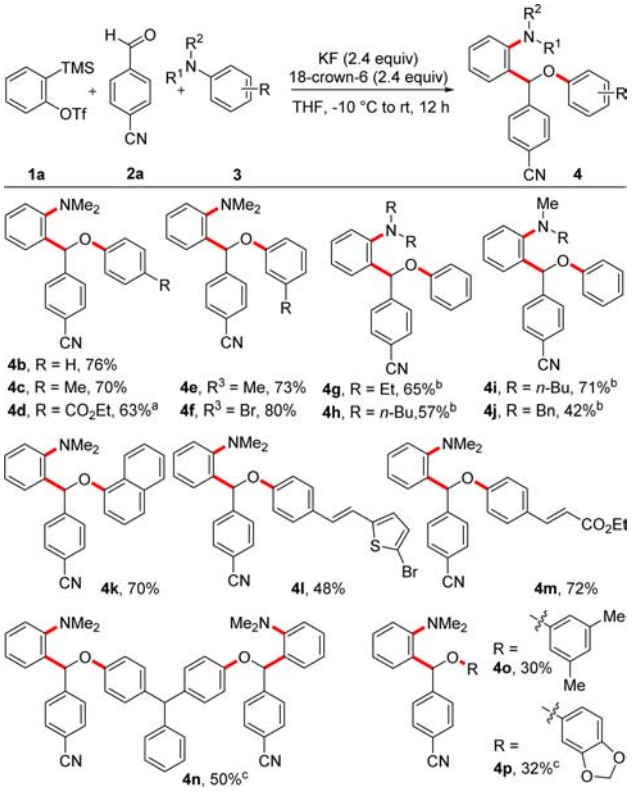
Scheme 2. MCCs Involving Arynes, Aldehydes, and Tertiary Amines: Scope of Tertiary Amines*

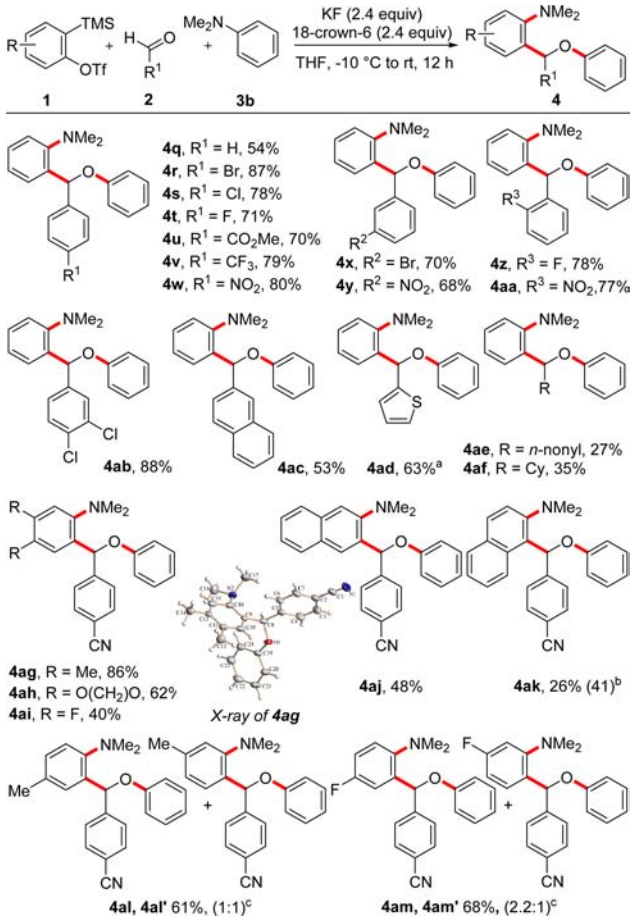


*General conditions: **1a** (0.6 mmol), **2a** (1.0 mmol), **3** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), −10 °C to rt, 12 h. Yields of the isolated products are given. [a]23% of *N*-arylated product was also isolated. [b]Reaction run at 60 °C for 12 h. [c]Run on 0.25 mmol scale.

substrate scope of this reaction. First, the variation of tertiary amine was evaluated (Scheme 2). A series of aromatic tertiary amines with different substituents on the aromatic ring were well-tolerated to furnish the 2-aminobenzhydrol derivatives in moderate to good yields (**4a**−**f**).[20] Moreover, variations at the NMe_2 moiety in **3** were possible, and these substrates afforded the desired products when the reaction was performed at 60 °C (**4g**−**j**). The naphthyl substrate and the donor−acceptor tertiary amines also underwent smooth aryne MCCs with aryl−aryl NMe_2 migration (**4k**−**m**). Interestingly, the commonly used dye leuco-malachite green afforded 2-fold MCC upon treatment with **1a** and **2a** forming the product **4n** in 50% yield. Notably, tertiary amines with electron-releasing groups on the aryl ring furnished only moderate yields of the target compounds (**4o**,**p**) under the present conditions.[21]

Next, we examined the scope of the aryne MCC with various aldehydes and differently substituted arynes (Scheme 3). A series of aromatic aldehydes with electron-releasing and -withdrawing substituents at the 4-position of the ring are well-tolerated, affording the 1,2-disubstituted arenes in good yields (**4q**−**w**).[22] Moreover, 3-substituted and 2-substituted aldehydes underwent smooth aryne MCCs to deliver the desired products in good yields (**4x**−**aa**). 3,4-Dichloro, naphthyl, and furyl substitution did not affect the outcome of the reaction (**4ab**−**ad**). Notably, linear and branched aliphatic aldehydes resulted in a relatively low yield of the product under the present conditions (**4ae**−**af**). In addition, electronically different 4,5-disubstituted arynes

Scheme 3. Scope of Aldehydes and Arynes*



*General conditions: **1** (0.6 mmol), **2** (1.0 mmol), **3a** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), −10 °C to rt, 12 h. Yields of the isolated products are given. [a]Given is ^{1}H NMR yield. [b]Yield of *N*-arylated product. [c]The regioisomer ratio was determined by ^{1}H NMR analysis.

generated from the corresponding precursors afforded the functionalized tertiary amines in moderate to good yields (**4ag**−**ai**). In the case of the dimethyl derivative **4ag**, the structure was confirmed by X-ray analysis.[23] In addition, the symmetrical and unsymmetrical naphthalynes furnished the desired products in moderate yields (**4aj**,**ak**). In the case of unsymmetrical naphthalyne, the corresponding *N*-arylated product was also observed 41% yield.[15] Furthermore, the reaction of **2a** and **3a** with unsymmetrical arynes (4-methyl- and 4-fluoroarynes) resulted in the formation of a regioisomeric mixture of MCC products in good yields (**4al**,**am**).

Gratifyingly, this aryne MCC is not limited to aldehydes as the third component but instead worked well with cyclic and acyclic activated ketones. For instance, reaction of aryne generated from **1a** with *N*-methylisatin **5a** and **3b** resulted in the formation of the oxindole derivative **6a** in 72% yield (Scheme 4, eq 3). *N*-Substitution as well as substitution at the carbocyclic ring of isatin are well tolerated under the present conditions to furnish the desired products in moderate to good yields (**6b**−**e**). The structure of the oxindole derivative **6d** was confirmed by X-ray analysis.[23] Moreover, the reaction using trifluoroacetophenone **7** as the carbonyl surrogate afforded the MCC product **8** in 62% yield upon treatment with **3b** and aryne generated from **1a** (eq 4), thereby further expanding the scope of the present reaction.

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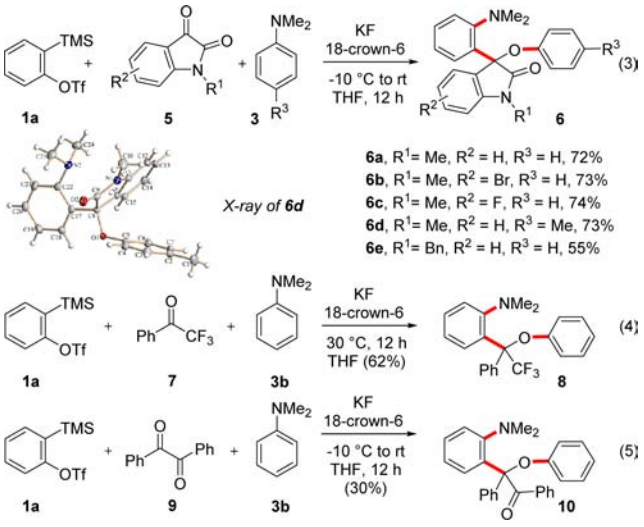
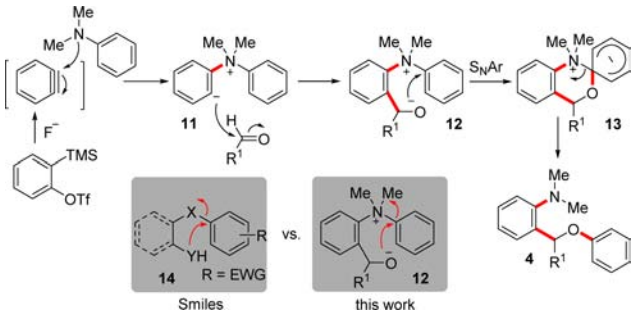
Scheme 4. Aryne MCCs Employing Activated Ketones



Notably, the use of benzil **9** as the third-component returned the MCC product **10** in 30% yield (eq 5).

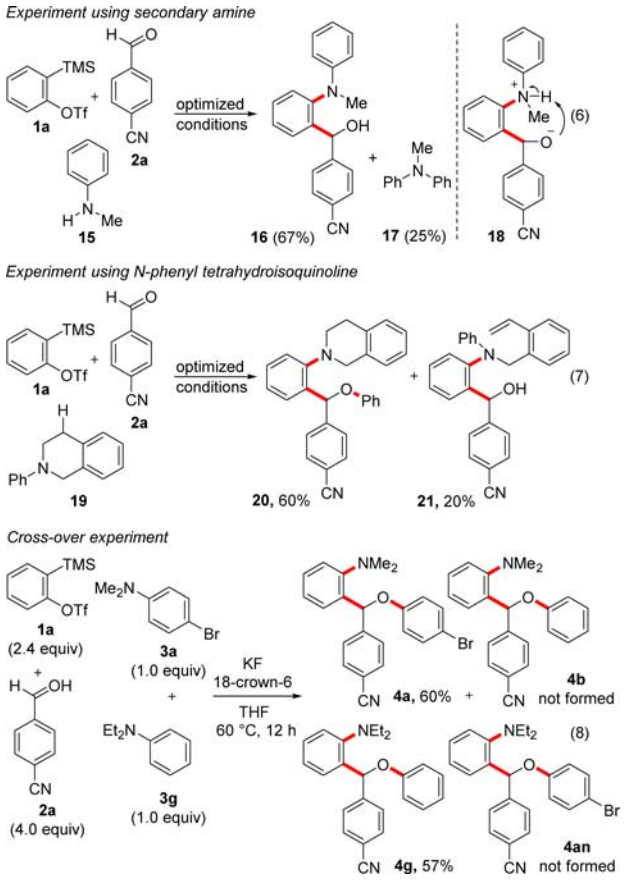
The mechanism of this aryl−aryl amino group migration can be delineated as follows (Scheme 5). The initial nucleophilic

Scheme 5. Tentative Mechanism for the MCC



attack of tertiary amine on aryne generates the zwitterionic intermediate **11**, which adds to aldehyde forming the key tetrahedral intermediate **12**. The intermediate **12** in the absence of proton source could undergo an intramolecular nucleophilic aromatic substitution reaction (S_NAr) resulting in the formation of the desired product **4** via the σ-complex **13**. It is interesting to note the mechanistic similarity of the present amino group migration with the Smiles rearrangement. The key intermediate in the Smiles rearrangement is **14**, and the rearrangement depends on the electron deficiency of the ring (to facilitate S_NAr), leaving group ability of X, and nucleophilicity of Y.[16] Usually, this reaction proceeds via a five-membered intermediate but in rare cases proceeds via six-membered intermediates.[24] In our tertiary amine triggered aryne MCC, the key intermediate is the zwitterion **12**. The presence of the quaternary ammonium salt in **12** may be crucial for the aryl to aryl amino group migration, and the reaction proceeds via the six-membered intermediate **13**.[25,26] In addition, the electronic nature of the tertiary amine is also important as the substrates with electron-releasing groups furnished moderate yield of the product (Scheme 2, **4o,p**).

To gain insight into the aryl−aryl amino group migration, we have carried out mechanistic experiments. When the reaction was performed using the secondary amine **15**, the benzhydrol derivative **16** was formed in 67% yield and the *N*-arylated



product **17** was formed in 25% yield (eq 6). In this case, the aryl−aryl amino group migration was not observed. Possibly, the initially formed amine−aryne zwitterion adds to the aldehyde to generate the intermediate **18**, which undergoes an intramolecular proton transfer (in preference to aryl−aryl amino migration) to afford **16**. Moreover, the reaction using **19** as the amine source afforded the rearranged product **20** in 60% yield and the styrene derivative **21** in 20% yield (eq 7). The styrene **21** was formed by an intramolecular proton transfer of the initial amine−aryne−aldehyde adduct without the amino group migration. In addition, crossover experiments carried out using amines **3a** and **3g** afforded the products **4a** (60%) and **4g** (57%). The crossover products **4b** and **4an** were not formed under the reaction conditions (eq 8). This clearly indicates that the present aryl−aryl amino group migration is intramolecular in nature.

In conclusion, we have developed a three-component coupling of arynes, aldehydes, and aromatic tertiary amines allowing the rapid synthesis of 2-functionalized tertiary amines. The reaction proceeds via the aryl−aryl amino group migration, which is mechanistically similar to the Smiles rearrangement. Moreover, activated ketones can also be used as the aldehyde component in this reaction. Further studies in related aryne MCCs are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03319.

Details on experimental procedures and characterization data of all compounds (PDF)
X-ray data for **4ag** (CIF)
X-ray data for **6d** (CIF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated with best regards to Dr. Vijay Nair on the occasion of his 75th birthday.

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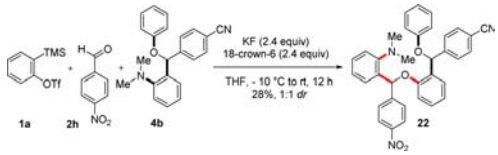
(20) 2-Substituted *N*,*N*-dimethylanilines furnished low yields of the MCC products. For instance, the attempted aryne MCC using methyl 2-(dimethylamino)benzoate afforded 25% yield of the desired MCC product.

(21) The NMe_2 moiety in **4b** can be engaged in another MCC with aryne generated from **1a** and aldehyde **2h** leading to the formation of the functionalized tertiary amine **22** in 28% yield and 1:1 dr.



(22) Notably, the use of 4-methoxybenzaldehyde as the aldehyde component afforded the expected MCC product in 23% yield.

(23) CCDC 1427513 (**4ag**) and CCDC 1427514 (**6d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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