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Substrate-Controlled Selectivity Switch in the Three-Component Coupling Involving Arynes, Aromatic Tertiary Amines, and CO_2

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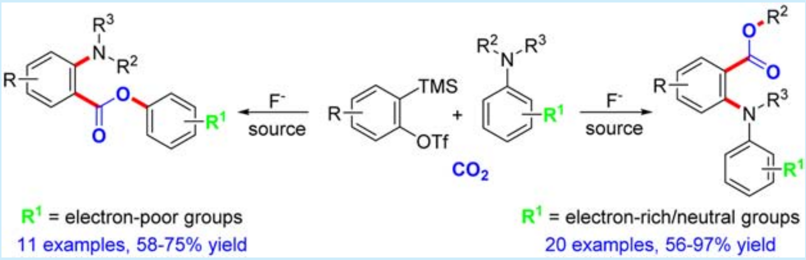
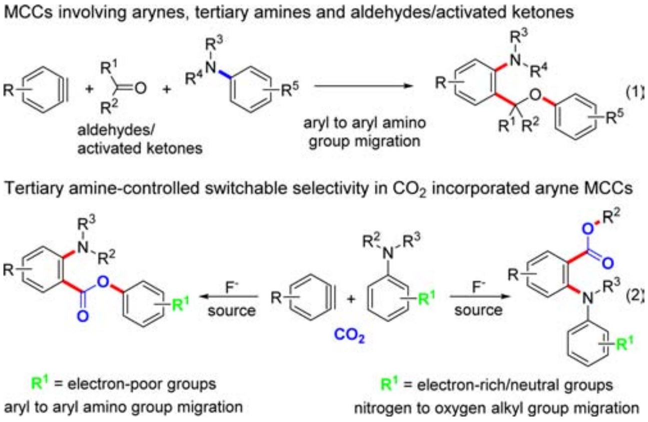
Supporting Information



ABSTRACT: The transition-metal-free multicomponent coupling involving arynes, aromatic tertiary amines, and CO_2 is reported. The reaction exhibits switchable selectivity depending on the electronic nature of the aromatic amines used. With amines bearing electron-releasing/neutral groups as the nucleophilic trigger, the reaction afforded 2-arylamino benzoates via a nitrogen to oxygen alkyl group migration. Employing electron-deficient amines in the reaction furnished 2-aminoaryl benzoates proceeding via the aryl to aryl amino group migration resembling a Smiles rearrangement.

The efficient utilization of CO_2 as a one-carbon feedstock is one of the safest and most inexpensive methods for the synthesis of value-added products, as CO_2 is a cheap and readily available gas.[1] However, employing CO_2 as a C1 source in organic chemistry is limited mainly because of its high thermodynamic stability and kinetic inertness.[2] One way to explore the synthetic transformations using CO_2 involves the use of CO_2 along with high energy substrates/reactive intermediates.[3] In this regard, employing CO_2 in reactions using highly electrophilic aryne intermediates constitutes a convenient method to install the CO_2 moiety directly to the aromatic ring.[4] In 2006, Yoshida, Kunai and co-workers demonstrated, for the first time, the incorporation of CO_2 in aryne multicomponent coupling (MCC)[5] triggered by imines for the straightforward synthesis of benzoxazinones.[6] Subsequently, the same group uncovered the synthesis of anthranilic acids by the MCC involving arynes, secondary amines, and CO_2.[7] We have reported the incorporation of CO_2 in aryne MCCs triggered by isocyanides for the practical synthesis of phthalimides.[8] Moreover, Kobayashi and co-workers disclosed the Cu-catalyzed aryne MCCs involving terminal alkynes and CO_2 for the synthesis of isocoumarin derivatives.[9] Apart from these works, the incorporation of CO_2 in aryne reactions remains underexplored.

Scheme 1. Aryne MCCs Triggered by Aromatic Tertiary Amines



In the context of our interest in developing transition-metal-free MCCs involving arynes,[4a,10] we have recently reported the aryne MCCs triggered by aromatic tertiary amines using aldehydes/activated ketones as the third component (Scheme 1, eq 1).[11,12] The reaction afforded *ortho*-functionalized tertiary amines proceeding via the aryl to aryl amino group migration similar to the Smiles rearrangement.[13] Inspired by this finding, we envisaged the use of CO_2 in aryne MCCs triggered by aromatic tertiary amines. When the reaction was performed using electron-releasing/neutral tertiary amines as the nucleophilic trigger, 2-arylamino benzoates are formed via a unique nitrogen to oxygen alkyl group migration (eq 2). Interestingly, with electron-deficient tertiary amines, the reaction afforded 2-

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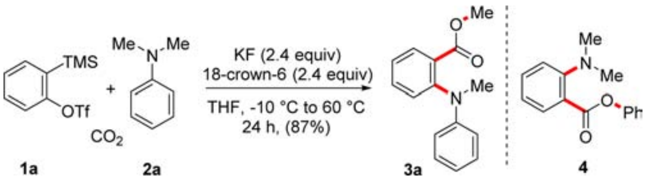
aminoaryl benzoates via an aryl to aryl amino group migration (mechanistically similar to Smiles rearrangement).[14] Herein, we report this substrate-controlled switchable selectivity observed in the aryne MCCs involving CO_2 and aromatic tertiary amines. Notably, related anthranilic acid derivatives are endowed with interesting biological properties.[15]

Our present study commenced with the treatment of an aryne generated in situ from 2-(trimethylsilyl) aryl triflate **1a**[16] (using KF and 18-crown-6) with *N*,*N*-dimethyl aniline **2a** in THF under an atmosphere of CO_2 (balloon). Under these conditions, we expected the 2-aminoaryl benzoate derivative **4** formed by the aryl to aryl NMe_2 migration.[11a] But delightfully, the 2-arylamino benzoate **3a** was isolated in 87% yield (Scheme 2). The product **3a** was formed by the *N*-arylation of **2a** followed by quenching of the aryl anion using CO_2 and a subsequent nitrogen to oxygen methyl group migration.[17] The reactions performed using other common fluoride sources such as CsF and tetrabutylammonium fluoride (TBAF) resulted in a reduced yield of **3a**.

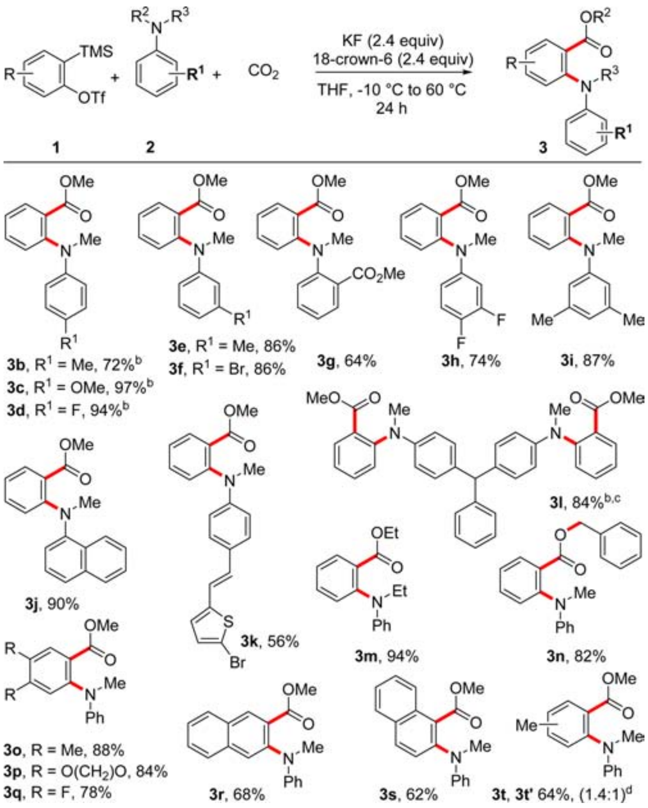
Scheme 2. MCC Involving Aryne, *N*,*N*-Dimethylaniline, and CO_2



With optimized conditions in hand, we then examined the substrate scope with respect to the aryne and aniline substrates (Scheme 3). A series of *N*,*N*-dimethyl anilines with differently substituted electron-releasing/neutral/moderately electron-poor groups are tolerated under the reaction conditions furnishing the 2-arylamino benzoate derivatives in good yields (**3b**−**j**). Moreover, the NMe_2 moiety present in donor−acceptor system **2k** furnished the MCC product in 56% yield (**3k**) and leuco-malachite green underwent efficient twofold MCC with a methyl group transfer leading to the formation of desired product **3l** in 84% yield. Additionally, this alkyl group migration reaction is not limited to *N*,*N*-dimethyl aniline derivatives; delightfully, *N*,*N*-diethyl aniline **2m** and *N*-benzyl-*N*-methyl aniline **2n** resulted in the ethyl and benzyl group migration respectively to afford the target products in high yields (**3m**, **3n**) thus demonstrating the versatility of the present method. Furthermore, electronically diverse 4,5-disubstituted symmetrical arynes generated from their precursors readily afforded the 1,2-disubstituted arene derivatives in good yields (**3o**−**q**). It is noteworthy that both symmetrical and unsymmetrical naphthalyne worked well and the corresponding MCC products are formed in good yields (**3r**, **3s**). Finally, the reaction of **2a** and CO_2 with 4-methylbenzyne generated from the triflate precursor resulted in the formation of an inseparable mixture of regioisomers (**3t** and **3t′**) in 64% yield and 1.4:1 selectivity.

Interestingly, treatment of 4-carboethoxy *N*,*N*-dimethyl aniline with aryne generated from **1a** (using KF and 18-crown-6) under an atmosphere of CO_2 (balloon) −10 °C afforded the *ortho*-functionalized tertiary amine **4a** in 75% yield (Scheme 4). The product formation took place via the aryl to aryl migration of the NMe_2 group and is analogous to the Smiles rearrangement. This rearrangement reaction worked well with various electron-poor aromatic tertiary amines, and in all cases, the desired product was formed in moderate to good yields (**4b**−**e**). In the case of 4-trifluoromethyl derivative **4b**, the structure was confirmed by single-crystal X-ray analysis.[18] In addition, this MCC worked well with electronically different symmetrically substituted aryne precursors, and the expected Smiles rearrangement products were isolated in good yields (**4f**−**i**). Notably, the unsymmetrical naphthalyne generated from the triflate precursor afforded a single regioisomer **4j** in 62% yield. Besides, attempted CO_2 incorporation MCC with 4-methylbenzyne furnished an inseparable mixture of regioisomers (**4k** and **4k′**) in 61% yield with 1.7:1 selectivity.

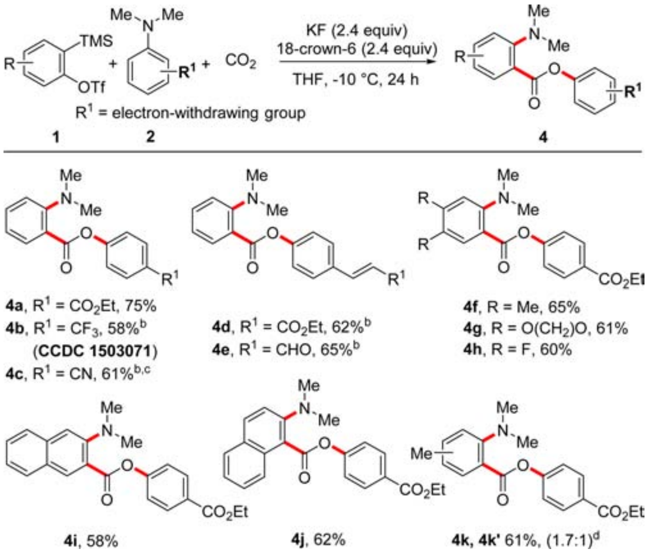
Scheme 3. Scope of Aryne MCCs for the Synthesis of 2-Arylamino Benzoates[a]



[a]General conditions: **1** (0.6 mmol), **2** (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), under an atmosphere of CO_2 (balloon), −10 °C to rt, 12 h, then stirred at 60 °C for 12 h. Yields of the isolated products are given. [b]Reaction stirred at 100 °C for 12 h instead of 60 °C. [c]Run on 0.25 mmol scale. [d]The regioisomer ratio was determined by ^1H NMR analysis.

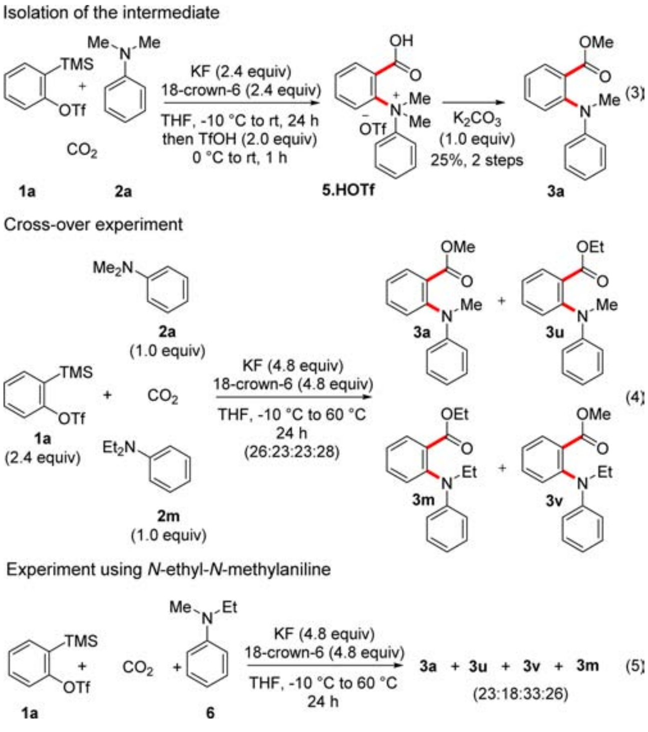
To probe the mechanism of the alkyl group migration, a series of experiments were performed. The reaction of **2a** with the aryne generated from **1a** and CO_2 followed by quenching the reaction mixture with TfOH resulted in formation of the ammonium salt **5.HOTf** (Scheme 5, eq 3). Treatment of **5.HOTf** with K_2CO_3 afforded the methyl ester **3a** in 25% yield (two steps). This indicates the intermediacy of the ammonium salt in the reaction. To gain insight into the nature of the alkyl group migration, we performed several mechanistic experiments.[17] The reaction of the aryne generated from **1a** and CO_2 with **2a** and **2m** afforded a mixture of four products (**3a**, **3m**, **3u**, and **3v**) in the ratio 26:23:23:28 (eq 4). The products **3a** and **3m** could be formed by the intramolecular alkyl group migration. Interestingly, the formation of **3u** and **3v** clearly

Scheme 4. Scope of Aryne MCCs Involving CO_2 and Electron-Poor Tertiary Amines[a]



[a] General conditions: 1 (0.6 mmol), 2 (0.5 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), under an atmosphere of CO_2 (balloon), −10 °C, 24 h. Yields of the isolated products are given. [b] Reaction run at −10 °C to rt for 12 h. [c] Given is ^1H NMR yield. [d] The regioisomer ratio was determined by ^1H NMR analysis.

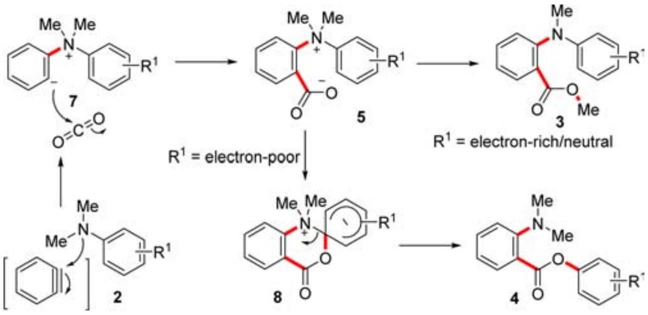
Scheme 5. Mechanistic Experiments



indicates the possibility of the intermolecular alkyl group migration in the present reaction. Moreover, performing the reaction using *N*-ethyl *N*-methyl aniline **6** under the present reaction conditions furnished four products (**3a**, **3u**, **3v**, and **3m**) in the ratio 23:18:33:26 shedding further light on the possibility of the intermolecular nature of the present alkyl group migration (eq 5).

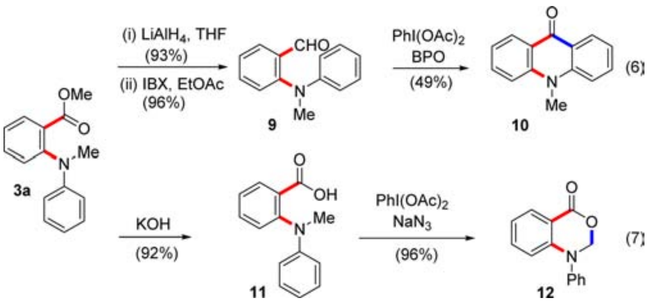
The mechanism of this substrate-controlled switchable selectivity in aryne MCCs can be elucidated as follows (Scheme 6). The initial addition of aromatic tertiary amine **2** to the aryne formed from **1** generates the 1,3-zwitterionic intermediate **7**. In the absence of a proton source, the aryl anion intermediate **7** adds to CO_2 generating the key dimethyl phenyl ammonium benzoate intermediate **5**. With electron-rich/-neutral amines, the intermediate **5** could undergo a methyl group transfer to furnish the 2-arylamino benzoate **3**. However, in the case of tertiary amines having an electron-poor group attached, the intermediate **5** could undergo an intramolecular nucleophilic aromatic substitution reaction (S_NAr) resulting in the aryl to aryl NMe_2 group migration leading to the formation of 2-aminoaryl benzoate **4** via the σ-complex **8**.

Scheme 6. Tentative Mechanism of the Substrate-Controlled Switchable MCCs



Furthermore, the synthetic utility of the present alkyl group migration MCC has been demonstrated in the transition-metal-free synthesis of biologically important acridones and benzoxazinones. 2-Arylaminobenzoate **3a** was converted to 2-arylamino benzaldehyde **9** by a reduction−oxidation sequence. Direct aryl-aldehyde Csp^2−Csp^2 bond formation via $PhI(OAc)_2$-mediated intramolecular cross-dehydrogenative coupling of **9** furnished the acridone **10** in 49% yield (Scheme 7, eq 6).[19] In addition, benzoate **3a** was hydrolyzed to acid **11** under basic conditions followed by intramolecular Csp^3−O bond formation has been accomplished in the presence of $PhI(OAc)_2/NaN_3$ leading to the formation of benzoxazinone **12** in 96% yield (eq 7).[20]

Scheme 7. Synthetic Utility of 2-Arylamino Benzoates



In conclusion, we have demonstrated switchable selectivity in the aryne MCCs involving aromatic tertiary amines and CO_2. The selectivity depends on the electronic nature of the aromatic amine used. The reaction of aromatic amines bearing electron-releasing/-neutral groups, arynes, and CO_2 furnished 2-arylamino benzoates via a nitrogen to oxygen alkyl group migration. Interestingly, the selectivity was switched to the formation of 2-aminoaryl benzoates (via an aryl to aryl amino group migration) employing electron-deficient amines as nucleophiles in aryne MCCs using CO_2 as the third component. A reasonable mechanism for the switchable reactions is provided. Further studies on related aryne MCCs using CO_2 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.6b02845.

Details on experimental procedures, characterization data of all compounds (PDF)
X-ray data for **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) For details, see the Supporting Information.

(18) CCDC 1503071 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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