Synthesis of Imides, Amidines, Imidates, and Amides by Intercepting Aryne-Isocyanide Adduct with Weak Nucleophiles

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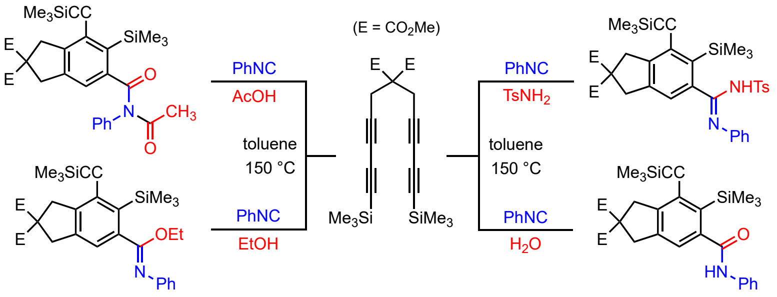
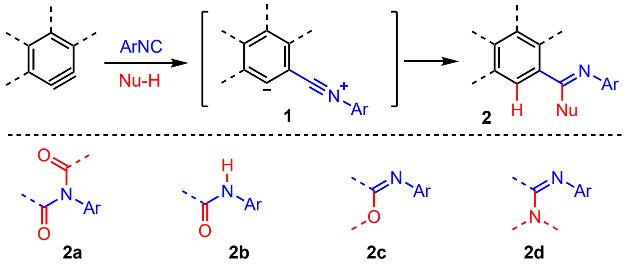


ABSTRACT: New aryne-based multicomponent coupling reactions for the formation of functionalized aromatic compounds have been developed. Arynes generated from triynes or tetraynes through hexadehydro Diels-Alder reaction (HDDA) readily react with isocyanide to generate nitrilium intermediate. Intercepting this nitrilium species with various weak nucleophile including carboxylic acids, alcohols, sulfonamides, or water, generated the corresponding imides, imidates, amidines or amides. The high regioselectivity of these transformations was mainly controlled by the substituents of the arynes.

Diversity-oriented synthesis (DOS) embraces various strategies[1] to effectively builds complex and diverse small molecules from relatively simple and readily available starting materials. In DOS, the chemical space can be populated with functional, skeletal and stereochemical diversities. While the functional group diversity is usually achieved by employing different starting materials skeletal and stereochemical diversities are realized by changing the connectivity and topology. In general, multicomponent coupling reactions (MCRs) are considered to be one of the most effective protocols in diversity-oriented synthesis that provides the highest degree of step and atom economy[2]. In light of the utility of MCRs, we envision that the characteristic hierarchy of reactivity of arynes toward weak nucleophiles can be exploited for MCR reactions, and herein we describe aryne-based DOS to generate cyclopentane-fused functionalized arenes containing an imide, imidate, amidine or amide functionality (Scheme 1).

Aryne is a versatile intermediate that can be transformed into numerous functionalized aromatic compounds[3]. In addition to the classical methods to generate benzyne[4], hexadehydro Diels–Alder reaction (HDDA) of multiynes[5] allows for the formation of highly functionalized arynes through a formal intramolecular [4+2] cycloaddition. The HDDA reaction of tri- and tetraynes pioneered by Johnson and Ueda[6] and subsequently by Hoye, Lee and others[7] has resulted in a significant expansion of the scope of aryne chemistry. Being formed under neutral reaction condition at varying range of temperature depending on the structural characteristics[8], the HDDA-derived arynes display reactivity profiles somewhat different from those arynes generated from base- or fluoride-mediated 1,2-elimination processes. After noticing the reactivity difference of arynes derived from different precursors, we intrigued by the possibility of modulating the reactivity of arynes toward isocyanide with transition metal catalysts. The reactions of arynes with isocyanide have been extensively exploited for heterocycle-fused arene synthesis[9]. The groups of Yoshida[9a,9c], Stolz[9e] and Nishihara[9g,9j] independently reported the formation of benzoannulated iminofurans through three-component coupling of aryne, isocyanide and aldehyde/ester/cyanoformates. Later in 2004, Yoshida demonstrated that 2-iminoisoindoline could

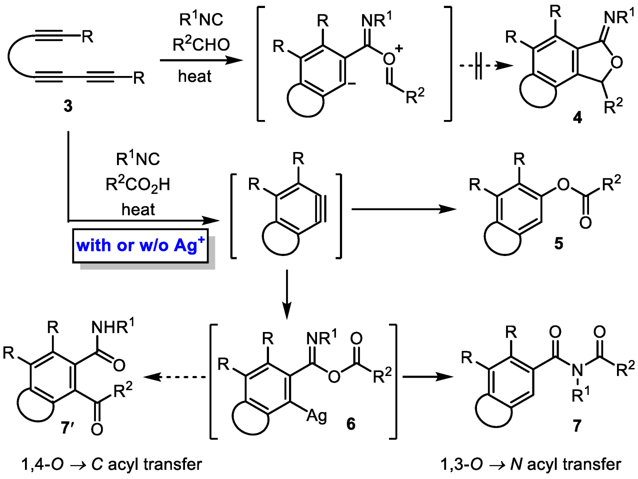
Scheme 1. Aromatic functionalization through MCR



be prepared from aryne, isocyanide, and N-tosylaldimines[9b]. Using CO_2 as a replacement for the carbonyl component in these reactions, Biju and his coworkers accomplished the synthesis of *N*-substituted phthalimide[9i]. By this protocol but replacing the carbonyl component with a terminal alkyne, Sha also demonstrated the synthesis of pyridine derivatives[9d,9f,9h].

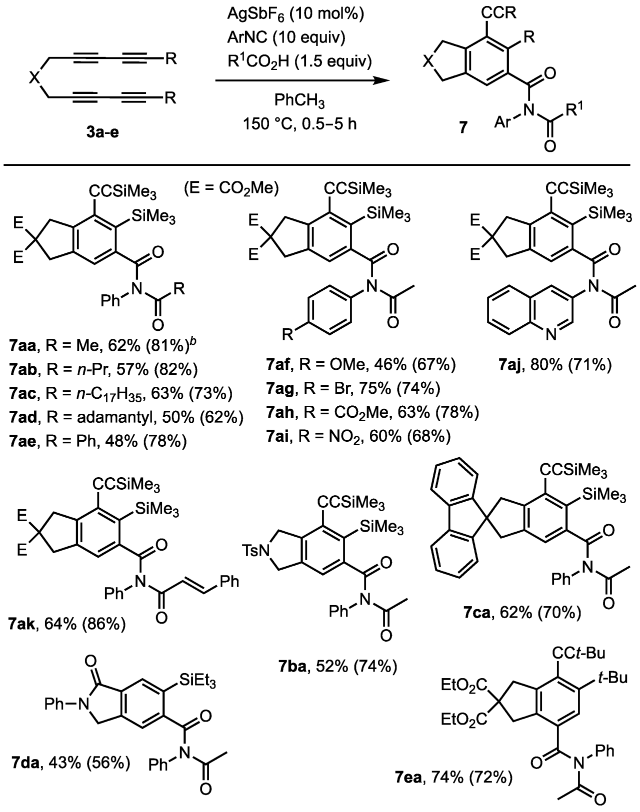
After the failure of these transformations (for example, **3** → **4**) with the thermally generated arynes via HDDA, we turned our attention to promote these aryne-based reactions by using a silver catalyst[10] (Scheme 2). We predicted that isocyanide and carboxylic acid could compete, thus the aryne intermediate generated from **3** can provide either ester **5** or **7**/**7′** depending on the potential role of a silver catalyst. If the silver catalyst can promote a preferential addition of isocyanide onto the aryne followed by carboxylic acid, a putative intermediate **6** would be generated. Depending on the propensity of **6** to undergo either a 1,4-O → C acyl migration (aryne analog of Ugi reaction[11]) or 1,3-O → N acyl migration (Mumm rearrangement[12]), **7** or **7′** would be produced as the major product.

Scheme 2. Modulating the reactivity of arynes by silver ion to promote three-componenet coupling between aryne, isocyanide, and carboxylic acid



Our investigation commenced with three-component coupling of an aryne, phenyl isocyanide (PhNC), and acetic acid (AcOH). With malonate ester tethered tetrayne **3a** (X = $(CO_2Me)_2C$) and catalyst $AgSbF_6$ (10 mol%), employing AcOH (1.5 equiv) and an excess amount of PhNC (10 equiv)[13] and at 150 °C, the corresponding imide **7aa** was isolated in 62% yield (Scheme 3). With the optimized condition in hand, we further investigated the generality of the reaction regarding the components of multiynes, isocyanides, and carboxylic acids. Replacing AcOH with butanoic acid provided the corresponding imide **7ab** in 57% yield. Long – chain fatty acid such as stearic acid and sterically encumbered 1-adamantane carboxylic acid also provided imides **7ac** (63%) and **7ad** (50%), but with benzoic acid **7ae** was obtained in slightly lower yield (48%). Aromatic isocyanide that bears variety of functional groups served as suitable coupling partner. Thus, 4-substituted benzoisonitriles with methoxy (**7af**), bromo (**7ag**), carbomethoxy (**7ah**), and nitro (**7ai**) moieties delivered the corresponding imides in moderate to good yield (46–75%) when AcOH was employed. Bulkier isocyanide such as 3-isocyanoquinoline was also effective and afforded *N*-quinoline imide **7aj** in 80% yield. The reaction with cinnamic acid also delivered the expected product **7ak** in 64% yield. Next, we explored the reaction with different tetraynes. Under the same conditions, *N*-Ts-tethered tetrayne **3b** rendered imide **7ba** in 52% within 30 min. In contrast, tetrayne with fluorenyl tether took much longer time (5 h) to be consumed to generate imide **7ca** (62%). Triyne **3d** containing a phenyl amide tether delivered **7da** in slightly lower yield (43%). In terms of regioselectivity of the isocyanide addition, the *t*-Bu-substituted tetrayne **3e** is the only aryne precursor that generated product **7ea** (74%) with reversed regioselectivity[14]. The structural identity of these regioisomeric products was established unambiguously by nOe-based mutual correlation and the well-established direction effect of the silyl group.[15]

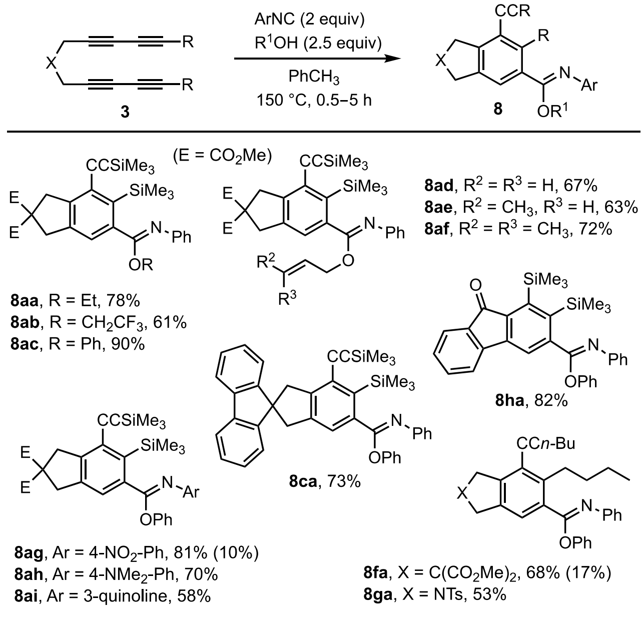
Scheme 3. Three-component coupling reaction of aryne, isocyanide and carboxylic acid[a]



[a] Isolated yields. [b] Yields in parentheses are for the reaction without the silver catalyst.[16]

Next, we explored the trapping of the putative aryne-isocyanide adduct with alcohols to generate the corresponding imidates[17]. Although arynes can directly react with alcohols[18], we expected that the higher nucleophilicity of isocyanide should outcompete alcohols such that the right sequence of events to form imidates will be accomplished with thermally generated arynes especially in the presence of silver ions (Scheme 4). Through several control experiments, it was found that the reactions without silver catalyst provided even higher yields. Thus, under standard conditions employing 2 equivalents of PhNC and 2.5 equivalents of EtOH, tetrayne **3a** afforded *N*-phenyl-imidate **8aa** in 78% yield. With CF_3CH_2OH, imidate **8ab** was isolated in slightly lower yield (61%). Although PhOH was shown to be an efficient ene-reaction counterpart with arynes[17b], under the current reaction conditions, only imidate **8ac** was obtained in 90% yield. Allylic alcohols including allyl, crotyl, and prenyl alcohol provided the corresponding three-component coupled imidates **8ad**, **8ae**, and **8af** in good yields. An electron-donating or an electron-withdrawing group on ArNC did not have an impact on the reactivity, rendering imidates **8ag** (81%) and **8ah** (70%) respectively. However, when 3-isocyanoquinoline was employed the corresponding imidate **8ai** was obtained in a slightly lower yield (58%). Also, multiynes with different tethers and substituents were examined. The reaction of tetrayne **3c** tethered with a fluorenyl moiety afforded imidate **8ca** in 73% yield while reaction with ketoarene-tethered triyne **3h** provided **8ha** in 82% yield. Symmetrical tetraynes **3f** and **3g** with *n*-Bu substituents but with a different tether also afforded imidates **8fa** (68%) and **8ga** (53%) respectively.

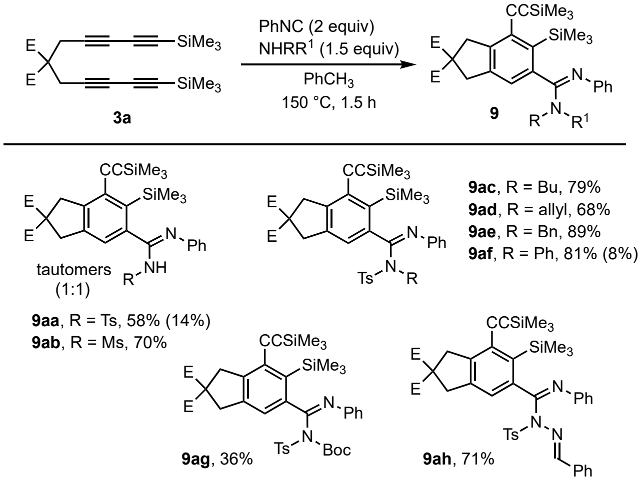
Scheme 4. Three-component coupling of aryne, isocyanide and alcohol[a]



[a] Isolated yields. [b] Yields in parentheses are for the reaction with the silver catalyst.

At this juncture, we surmised that the structural diversity of the aryne-based MCR can be further expanded by trapping of the aryne-isocyanide adduct with nitrogen-based nucleophiles. To avoid the complication of the direct addition of amines with arynes, the reactivity of the nitrogen nucleophiles should be reduced. Indeed, the reaction with alkyl and aryl amines such as *n*-$BuNH_2$ and $PhNH_2$ mainly resulted in direct amine addition products[17a] or intractable material. On the other hand, nitrogen nucleophiles containing an electron-withdrawing group such as 4-toluenesulfonamide provided amidine[19] **9aa** (two tautomers in a 1:1 ratio) in 58% yield upon reacting with tetrayne **3a** and PhNC in the absence of a silver catalyst (Scheme 4). With this encouraging initial result in hand, we further examined the generality of this reaction. Similar to 4-toluenesulfonamide, methanesulfonamide also provided the corresponding amidine **9ab** in 70% yield. Alkylated or arylated secondary sulfonamides provided amidines **9ac**, **9ad**, **9ae**, and **9af** in good yield (68–89%). Even highly deactivated amine nucleophile such as Boc–protected 4-toluenesulfonimide could participate in this reaction, affording *N*-Boc-protected amidine **9ag** but in significantly lower yield (36%). Also, (*E*)-*N'*-benzylidene toluenesulfonohydrazide also efficiently participated in this reaction to provide the corresponding **9ah** in good yield.

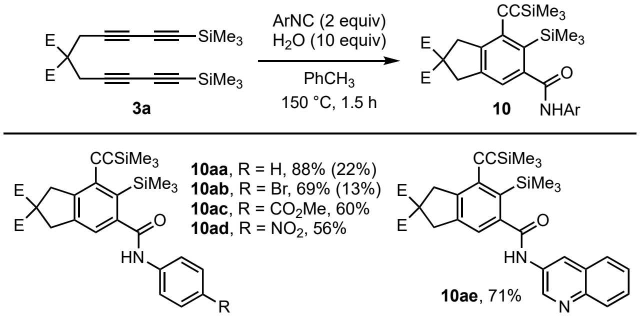
Scheme 5. Three-component coupling of aryne, isocyanide and sulfonamide[a]



[a] Isolated yields. [b] Yields in parentheses are for the reaction with the silver catalyst.

Although hydration of the adduct of aryne-isocyanide to generate amides has been explored[20], this reaction with thermally generated arynes from multiynes has not been reported. Based on our previous study on the hydration of aryne-nitrile adduct to form amides in the presence of a silver catalyst[21], we expected that replacing the nitrile with

Scheme 6. Three-component coupling of aryne, isocyanide and water[a]



[a] Isolated yields. [b] Yields in parentheses are for the reaction with the silver catalyst.

isocyanides should generate amides of reversed connectivity more efficiently. Indeed, heating the mixture of tetrayne **3a**, phenyl isocyanide, and water afforded arylamide **10aa** in 88% yield. (Scheme 6). The reaction with $AgSbF_6$ showed the same reaction profile but lower efficiency. Reactions with ArNC containing bromo (**10ab**), carbomethoxy (**10ac**), and nitro (**10ad**) group afforded the corresponding amides in slightly lower yield (56–69%). The reaction with 3-isocyanoquinoline also provided amide **10ae** in 71% yield.

In conclusion, we have developed new aryne-based multicomponent coupling reactions for the formation of structurally diverse aromatic compounds with functional groups including imide, amidine, imidate or amide. These reactions clearly demonstrate that the reactivity of arynes generated from multiynes via HDDA can be exploited in the classical isocyanide-based MCRs by careful selection of reagents and conditions. Although initially we predicted that a silver catalyst plays a key role in the activation of isocyanides in general the silver catalyst produced more byproducts leading to lower yields of the expected products. For most transformations investigated, excellent regioselectivity was observed. The strong electronic effect of a trimethylsilyl group on arynes effectively directs the addition of isocyanide at its ortho position, which is consistent with the distortion/interaction model proposed by Houk.[15b-c] On the other hand, the reversed directing effect of *t*-Bu substituent is due mainly to its steric effect. Relatively simple one-pot operation and broad substrate scope made these aryne-based MCRs highly useful synthetic tool, distinguishable from existing protocols for aromatic functionalization.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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