Silver-Catalyzed Selective Multicomponent Coupling Reactions of Arynes with Nitriles and Isonitriles

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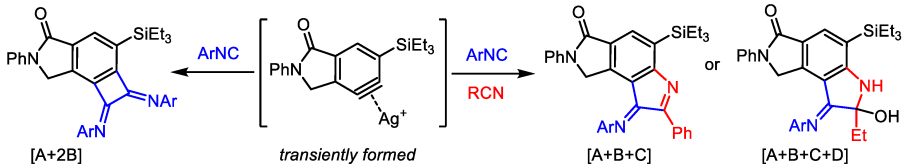
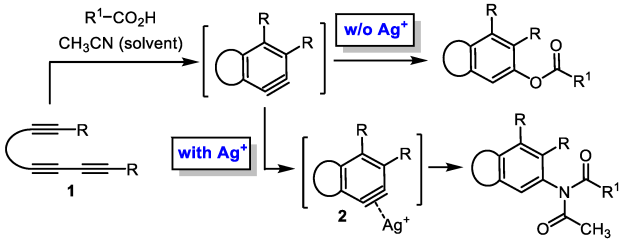
Supporting Information Placeholder



ABSTRACT: Pathway selective aryne-based novel multicomponent coupling reactions with isonitriles and nitriles are described. Crucial to these reactions is the formation of silver-aryne complex, which show differential reactivity toward isonitriles and nitriles to form two different forms of ortho-nitrilium organosilver arene species. Interception of the nitrilium of aryne-isonitrile adduct with another isonitrile leads to the formation of benzocyclobutene-1,2-diimines, whereas the nitrilium of aryne-nitrile adduct render selective formation of 3*H*-indol-3-imines or 3-iminoisoindolin-2-ol depending on the structure of nitrile employed.

Aryne is a versatile intermediate whereby numerous transformations have been developed to generate functionalized aromatic compounds.[1] Base-mediated 1,2-elimination of aryl halide,[2a] fluoride-promoted 1,2-elimination of aryl silyl triflate,[2b] or thermal decomposition of arenediazonium-2-carboxylate[2c] are common methods to generate aryne species among many others. These 1,2-elimination protocols, albeit a powerful synthetic tool in their own right, require the preparation of prefunctionalized aromatic precursors, which often limits the structural and functional diversity of the products. On the other hand, direct cyclization of tri- and tetraynes to form arynes, named as hexadehydro Diels-Alder (HDDA) reaction by Hoye,[3] allows for the construction of structurally more complex and diverse arene products. The temperature range for the aromatization subtly depends on the structure of the linker and the nature of their substituents.[4] The HDDA reaction of tri- and tetraynes pioneered by Johnson and Ueda[5], subsequently rediscovered by Hoye, Lee and others[6] has resulted in a significant expansion of the scope of aryne chemistry. Being formed under neutral reaction condition at varying range of temperature, the HDDA-derived arynes have displayed reactivity profiles different from those generated via base- or fluoride-mediated 1,2-elimination protocols.

Multicomponent coupling reaction (MCR) is a powerful synthetic tool to merge three or more reactants in a single-step operation to generate relatively complex molecular structures with high atom-economy.[7] Aryne-based MCRs involving isonitrile[8] have been explored over the last 20

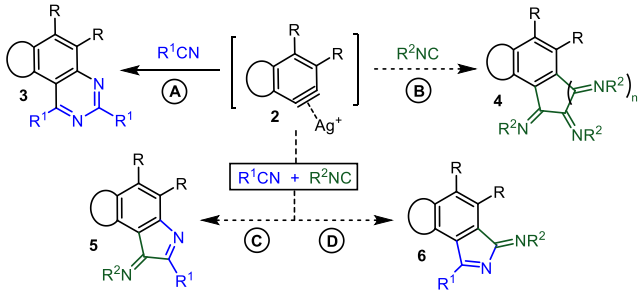


Scheme 1. Different reactivity of aryne with and w/o Ag^+

years mainly with simple benzynes generated from the fluoride- promoted 1,2-elimination of aryl silyl triflates. The research groups of Yoshida, Stoltz and Nishihara independently reported trapping of the isonitrile adduct of benzyne with esters,[8e] aldehydes,[8b-c] cyanoformates,[8k] and imines[8b] to generate benzannulated heterocycles. Biju further extend the reaction with CO_2 to synthesize *N*-substituted phthalimides.[8j,8l] In this regard, we consider the HDDA reaction of multiynes will be a versatile platform that can broaden the scope of aryne-based MCR, which can be further expanded by employing transition metal complexes that can modulate the reactivity of arynes (Scheme 1).[9]

Exploitation of the prowess of silver-catalyzed MCR has shown that the reaction of the putative silver-complexed aryne **2** with nitriles provided amides or imides in the presence of water or carboxylic acid,[10] whereas in the absence of these extra nucleophiles, quinazoline **3** was generated through Path A.[11] Based on this result, we envision a new MCR of **2** with isonitriles, which is expected to generate **4** (n = 0 or 1) via Path B.[12] For the development

Scheme 2. Silver-catalyzed MCRs reactions of arynes with isonitriles and nitriles

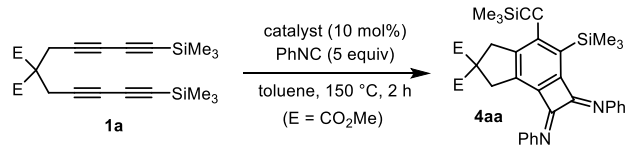


of new isonitrile-based MCRs, we wonder about the possibility of hetero-MCR to generate products **5** and **6**. Depending on the stoichiometry and inherent reactivity of isonitrile and nitrile, aryne intermediate **2** might take Path C or Path D. Herein we report on the discovery of new silver catalyzed MCRs of arynes with isonitriles and nitriles to generate **4** (n = 0) and **5** devoid of its constitutional isomer **6**.

Our investigation commenced with screening of various metal catalysts for maximum yield of an [A+2B] or [A+3B] type MCR products. Several catalysts displaying a good catalytic activity have been identified among which $AgSbF_6$ provided the highest yield of benzocyclobutene-1,2-diimine **4aa** (Table 1). The product **4** (n = 1) incorporating three isonitriles was not detected. AgOTf also displayed a good catalytic activity in promoting this transformation (entry 2), however, AgOAc and $AgCO_3$ were almost inactive (entries 3–5), indicating an important counterion effect. Other catalysts such as $Sm(OTf)_3$, $(CuOTf)_2{\cdot}C_6H_6$ were also generated product **4aa** (55 and 59%, entries 5–6). However, $Sc(OTf)_3$, $Mg(OTf)_2$, $Zn(OTf)_2$, AuCl, and $InCl_3$ were less effective (entries 7–11). In the absence of a catalyst under otherwise identical conditions, product **4aa** was not observed (entry 12).

Employing the optimized conditions, we next explored the generality of [A+2B] type MCR with isonitriles and tetrayne[13] **1a–f** (Scheme 3). Aromatic isonitriles containing either an electron-donating methyl (**4ab**), methoxy (**4ac**), or *para*-*N*,*N*-dimethyl (**4ad**), or an electron-withdrawing carbomethoxy (**4ae**), nitro (**4af**) or bromo (**4ag**) substituent participated in the reaction, delivering desired benzocyclobutene-1,2-diimines in moderate to good (43–

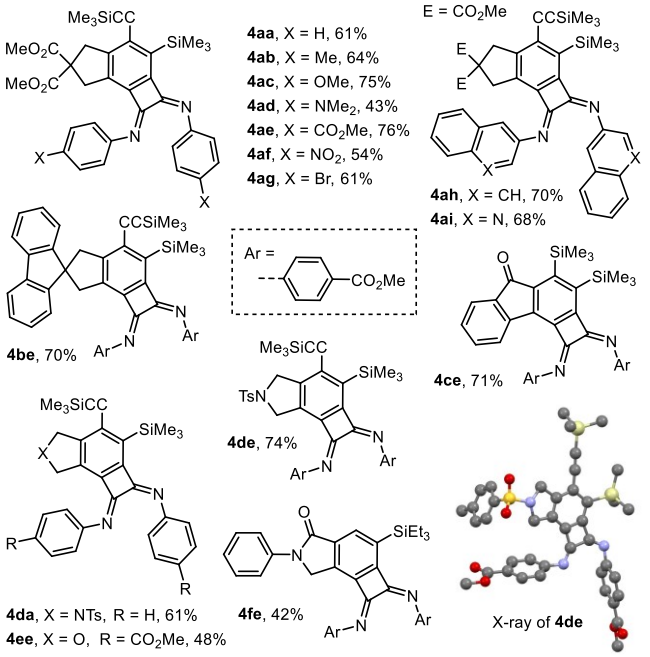
Table 1. Optimization for metal catalyst



entry	catalyst	yield (%)[a]	entry	catalyst	yield (%)[a]
1	$AgSbF_6$	62	7	$Sc(OTf)_3$	13
2	AgOTf	61	8	$Mg(OTf)_2$	32
3	AgOAc	5	9	$Zn(OTf)_2$	15
4	Ag_2CO_3	7	10	AuCl	10
5	$Sm(OTf)_3$	55	11	$InCl_3$	trace
6	$(CuOTf)_2 \cdot C_6H_6$	59	12	none	trace

[a] Measured by NMR with an internal standard (CH_2Br_2).

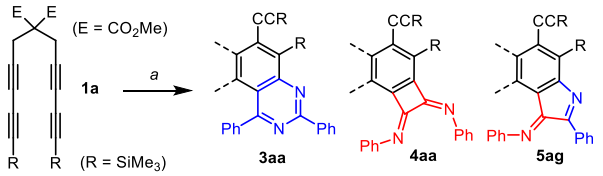
Scheme 3. [A+2B] MCR reaction for benzocyclobutene-1,2 diimines[a]



[a] $AgSbF_6$ (10 mol%), PhNC (5 equiv), toluene, 150 °C, 0.5–5 h.

76%) yield. Bulkier isonitriles such as 2- isocyanonaphthalene and 3-isocyanoquinoline provided products **4ah** (70%) and **4ai** (68%) in increased yield. Compared to the broad scope of aromatic isonitriles, aliphatic isonitriles[14] did not afford benzo cyclobutene-1,2-diimine products. The MCR reactions of different aryne precursors were also examined. The reaction of tetrayne tethered with a fluorenyl moiety afforded product **4be** in 70% yield while that with ketoarene-tethered triyne provided **4ce** in 71% yield. Tetraynes with an *N*-Ts and an ether linker participated in the reaction smoothly to generate **4da** and **4ee** in 61 and 48% yield. An *N*-Ts-tethered tetrayne provided product **4de**, the X-ray

Table 2. The influence of nitrile and isonitrile stoichiometry on the yield and product distribution



entry	PhCN : PhNC (equiv)	3aa + 4aa + 5ag (%)[b]	3aa : 4aa : 5ag[b]
1	1 : 1	30	0 : 0.45 : 1
2	2 : 2	43	0 : 1.2 : 1
3	2 : 1	48	0 : 0.8 : 1
4	3 : 1	52	0 : 0.7 : 1
5	5 : 5	63	0 : 10 : 1
6[c]	300 : 3	85	0.1 : 0 : 1
7[c]	300 : 5	83	0.1 : 0.1 : 1

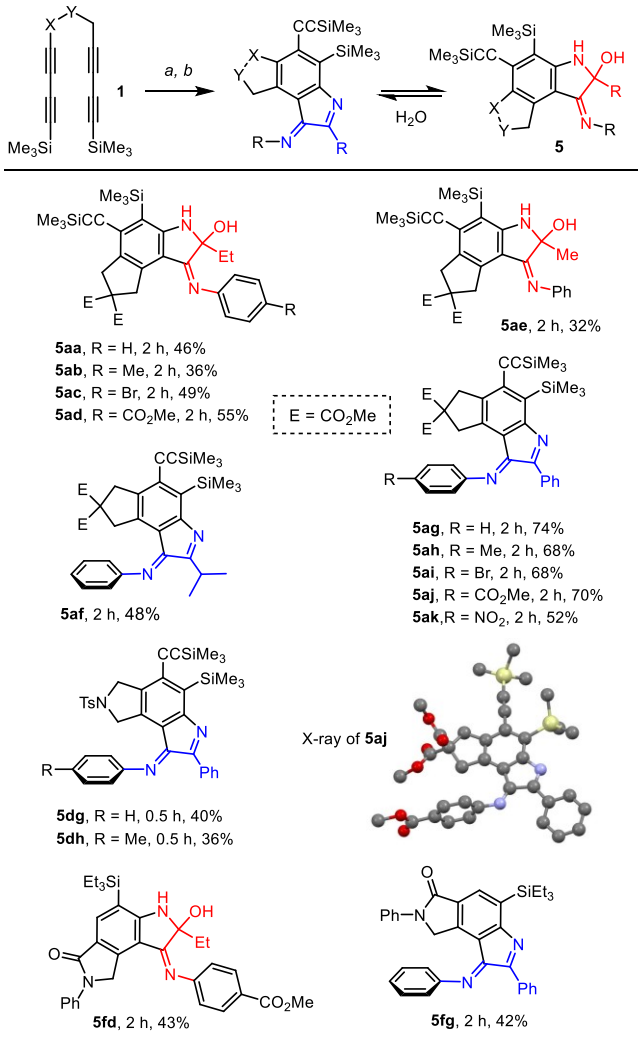
[a] $AgSbF_6$ (10 mol%), PhCN, PhNC, toluene, 150 °C, 2 h. [b] Measured by NMR with an internal standard (CH_2Br_2). [c] toluene is replaced with PhCN.

diffraction analysis of which provided additional confirmation for these benzocyclobutene-1,2- diimine structures.[15] Also, an amide-tethered triyne afforded product **4fe** in slightly lower yield (42%).

Once formation of homo-coupled benzocyclobutene-1,2-diimine **4** was realized efficiently (Path B in Scheme 2), we pursued the possibility of generating a hetero-coupled aryne-ntrile-isonitrile adduct **5** (Path C in Scheme 2). We hypothesized that by controlling the stoichiometry of nitrile and isonitrile under the optimized conditions, appropriate kinetic and thermodynamic parameters could be found to favor the reaction Path C, leading to selective formation of adduct **5**. Because of the higher reactivity of isonitrile as a nucleophile,[24] the incorporation of less reactive nitrile could be feasible either with its significantly higher concentration compared to that of isonitrile or activating aryne towards nitrile.

To verify these hypotheses, we first examined the impact of the stoichiometry of nitrile and isonitrile on the product distribution and yield (Table 2). With less than 5 equivalents of nitrile, hetero-coupled product **5ag** and a

Scheme 4. Aryne-nitrile-isonitrile hetero-coupling to generate 3*H*-indol-3-imine and 3-iminoisoindolin-2-ol

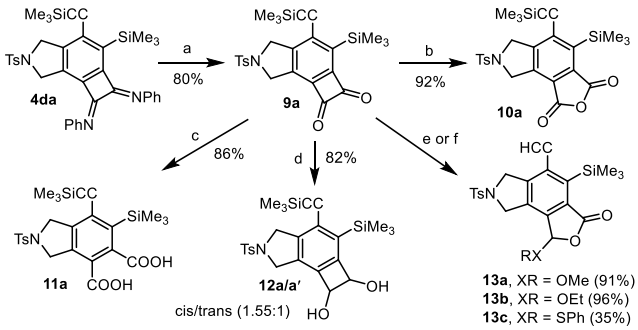


[a] $AgSbF_6$ (10 mol%), ArNC (3 equiv), RCN (solvent), 150 °C, 0.5–2 h.

homo-coupled product **4aa** was obtained in low yield and selectivity (entries 1-4). When 5 equivalents of nitrile and isonitrile were employed, a good total yield of products **4aa** and **5ag** was observed with a 10:1 ratio (entry 5). Ultimately, by running the reaction in nitrile as the solvent with 3–5 equivalents of isonitrile, excellent yield and selectivity for the aryne-nitrile-isonitrile coupled product **5ag** was realized (entries 6 and 7). With large excess of nitrile, the small difference in isonitrile stoichiometry (3 equiv vs 5 equiv) did not cause a significant difference for yield and selectivity. Surprisingly, even in nitrile solvent, the formation of nitrile homo-coupled quinazoloine **3aa** was observed only to a very minor extent.

With the optimized conditions in hand, we next explored the aryne-nitrile-isonitrile cross condensation different combinations of substrates, nitriles and isonitriles to generate 3-iminoisoindolin-2-ol and 3*H*-indol-3-imine[25] depending on the structure of nitrile (Scheme 4). When sterically unhindered nitriles such as acetonitrile or propionitrile were used, the expected product 3*H*-indol-3-imines were not obtained. instead 3-iminoisoindolin-2-ol **5aa–5ae** and **5fd** were obtained in moderate yields (36–55%). Based on extensive experimentations, we conclude that these products are derived from 3*H*-indol-3-imines via hydration by adventitious water in the reaction medium. On the contrary, sterically more hindered isobutyronitrile provided 3*H*-indol-3-imine **5af** (48%). This difference between methyl/ethyl versus isopropyl is due to the increased steric bulkiness of the isopropyl group, which disfavors the conversion the sp^2-hybridized imine to the sp^3-hybridized hemiaminal moiety. We suspect that other substituents that can electronically stabilize an imine[26] should also provide 3*H*-indol-3-imine products without hydration. Indeed, the reactions with benzonitrile provided 3*H*-indol-3-imines **5ag–5ak** with improved yield. The reaction of *N*-Ts-tethered tetrayne with benzoisonitrile and *para*-toluene isonitrile provided 3*H*-indol-3-imines **5dg** and **5dh** in 40% and 36% yield, respectively. Triyne containing a phenyl amide tether provided 3-iminoisoindolin-2-ol **5fd** in 43% yield in propionitrile,

Scheme 5. Transformations of a benzocyclobutene-1,2-diimine



Conditions: a) 12 N HCl (10 equiv), THF:H_2O (4:1), 0 °C, 30 min. b) *m*-CPBA (5 equiv), CH_2Cl_2, 0 °C, 6 h. c) H_2O_2 (4 equiv), Na_2CO_3 (4 equiv), THF:H_2O (4:1), 10 min. d) $NaBH_4$ (5 equiv), THF/MeOH, rt, 5 h. e) RONa (3 equiv), ROH, THF:H_2O (4:1), rt, 1 h. f) PhSH (2 equiv), $NaHCO_3$ (2 equiv), THF:H_2O (4:1), rt, 5 h.

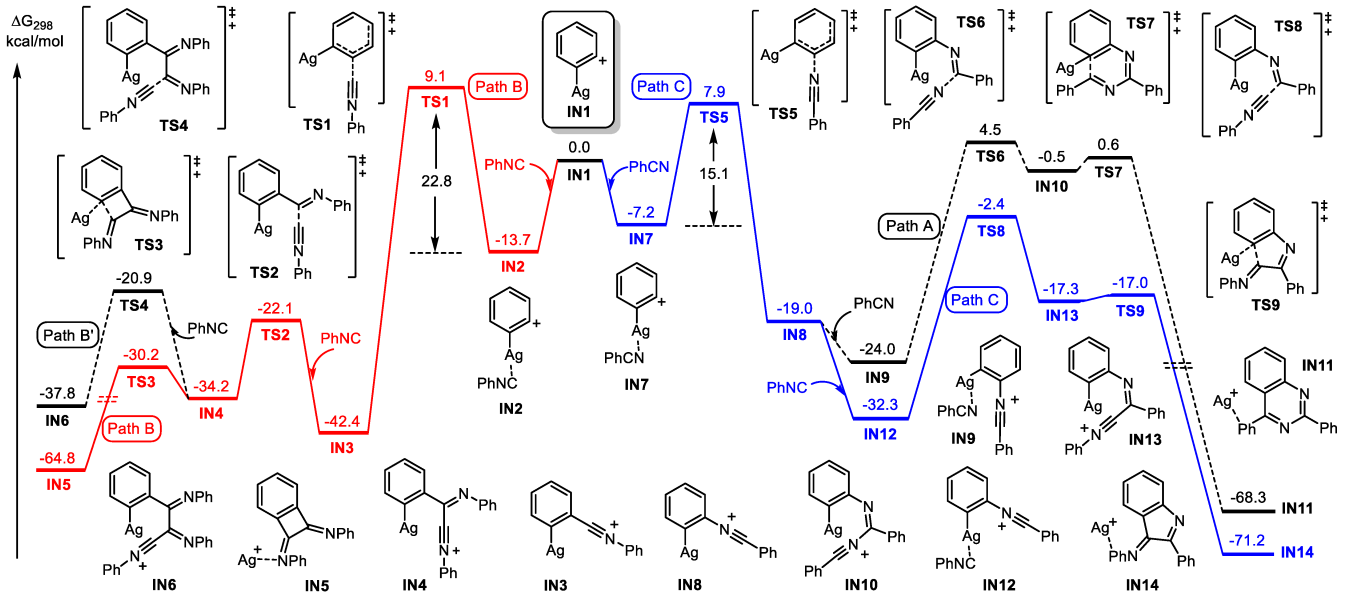


Figure 1. Calculated potential energy profiles for the formations of benzocyclobutene-1,2-diimine (in red) and 3*H*-indol-3-imine (in blue); all substituents on the phenyl moiety from the HDDA reaction are omitted for clarity, and full computational models are given in the supporting information.

whereas 3*H*-indol-3-imine **5fg** was obtained in benzonitrile in 42% yield.

The structural identity of 3*H*-indol-3-imine was ensured by X-ray crystallographic analysis of **5aj** and that of iminoisoindolin-2-ol was confirmed by extensive nOe experiments. It is worth to mention that the stereochemistry of the 3-imino moiety in 3*H*-indol-3-imines (**5ag–5ak**, **5fg)** is *E*-configuration, which is opposite to the *Z*-configuration of 3-iminoisoindolin-2-ols (**5aa–5ae**, **5fd)**. Because of the *E*- configuration, the *N*-phenyl group on these 3*H*-indol-3-imines is perpendicular to the main frame of the molecule to avoid the steric clash.

Next, we explored conversion of benzocyclobutene-1,2-diimine to other functional groups (Scheme 5). Under acidic conditions, 1,2-diimine moiety in **4da** was readily hydrolyzed to generate 1,2-diketone **9a**.[19] Treating **9a** with *m*-CPBA induced Baeyer-Villiger oxidation to generate phthalic anhydride **10a** in excellent yield,[20] whereas with H_2O_2 in a basic medium formed phthalic acid **11a**.[21] Reaction with $NaBH_4$ afforded a mixture of cis/trans-diols **12a/a'** in 82% yield.[22] Interestingly, treating 1,2-diketone **9a** with sodium alkoxide in alcoholic solvent provided 3-alkoxyphthalides **13a**,**b**[23] in excellent yield, whereas sodium thiolate afforded **13c** in low yield.[24]

To gain further insight into the mechanism and selectivity for the formation of benzocyclobutene-1,2-diimine, we carried out DFT calculations.[25] Starting from **IN1**, the cyclization of bis-isonitrile adduct **IN4** prefers to form benzocyclobutene-1,2-diimine **IN5** (Path B) via **TS3** (Figure 1). The barrier for isonitrile addition to **IN4** (Path B') to form adduct I**N6** is 9.3 kcal/mol higher and the formation of product of triple isonitrile adduct via **TS4** is unfavorable, thus was not observed.

For selective formation of 3*H*-indol-3-imines, the calculated reaction profiles show that the partitioning of **Path B** and **Path C** is dictated by the lower activation barrier of **IN7** to form nitrile adduct **IN8** via **TS5** (15.1 Kcal/mol) compared to that of **IN2** to form **IN3** via **TS1** (22.8 kcal/mol). Once intermediate **IN8** is generated, it reacts with isonitrile or nitrile in the subsequent step. In Path A, **IN8** reacts with nitrile to generate **IN9**, which proceeds to generate intermediate **IN10** via **TS6**, and the final ring closure of **IN10** through low barrier **TS7** yields **IN11**. On the other hand, in Path C, **IN8** forms isonitrile complex **IN12**, which leads to the next intermediate **IN13** via transition state **TS8**. Subsequently, **IN13** proceeds through a low barrier **TS9** to provide a silver complexed 3*H*-indol-3-imine **IN14**. The reaction profile in Path C, calculated to be the most favorable one, is consistent with the actual reaction occurred to generate 3*H*-indol-3-imines or 3-iminoisoindolin-2-ols.

In conclusion, we developed pathway-selective silver-catalyzed [A+2B], [A+B+C], and [A+B+C+D] type MCRs of arynes with isonitriles and nitriles. In the presence of isonitrile, a silver-complexed aryne undergo double addition to provide benzocyclobutene-1,2-diimines as the sole product. DFT calculations revealed that the intramolecular ring closure of the bis-isonitrile adduct (**IN4**) to form benzocyclobutene-1,2-diimines is the consequence of both kinetic and thermodynamic preference over triple isonitrile adduct formation. MCR with both isonitrile and isonitrile produced 3H-indol-3-imines and 3-iminoisoindolin-2-ols via the incorporation of each molecule of nitrile and isonitrile rather than generating quinazolines via double nitrile addition. This intriguing pathway selectivity can be justified by DFT calculations, which show that in the first committed step the kinetically favored aryne-nitrile adduct **IN8** over aryne-isonitrile adduct **IN3**. The reversal of common reactivity trend of nitrile and isonitrile in this step is due to the presence of a silver catalyst, which forms more stable

isonitrile complex **IN2** than nitrile complex **IN7**. In the second selectivity-determining step, the predominant formation of isonitrile complex **IN12** from **IN8** steers the overall reaction to proceed toward the formation of 3*H*-indol-3-imines and 3-iminoisoindolin-2-ols. The different types of aryne-based MCRs render a broad substrate scope for all three components and show excellent regio- and pathway selectivity to generate novel molecular structures.[26]

ASSOCIATED CONTENT

Supporting Information

The 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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ACKNOWLEDGMENT

Authors thank NSF (CHE-1764141, D.L.) and NSFC (21572163 and 21873074, Y.X.) for financial supports. The Mass Spectrometry Laboratory at UIUC is acknowledged.

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(24) The mechanism of these transformations is under investigations by DFT calculations.

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(26) Based on a reviewer's suggestion, we carried out the following experiments to compare the reaction profiles of arynes generatd via a hexadehydro Diels-Alder reaction and fluoride-induced 1,2-elimination of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate.