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Synthesis of Carbazolequinones by Formal [3 + 2] Cycloaddition of Arynes and 2-Aminoquinones

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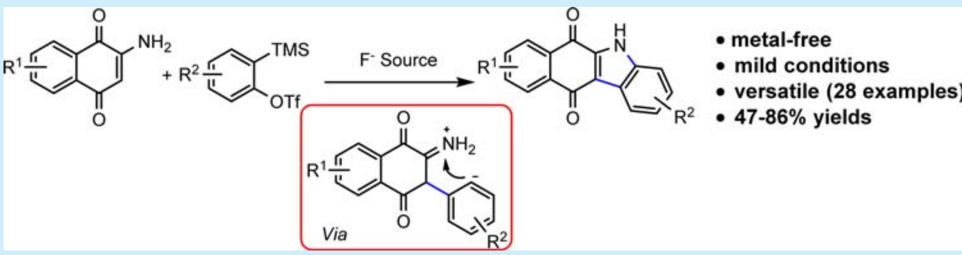
Supporting Information



ABSTRACT: A formal cycloaddition reaction for the synthesis of biologically and pharmaceutically important carbazolequinones via the annulation of aminoquinones with arynes has been developed. This practical and metal-free cascade reaction proceeds through successive C–C/C–N bond formations. Moreover, this novel method has been utilized for the concise synthesis of bioactive murrayaquinone A and koeniginequinone B and their analogues.

Carbazolequinone alkaloids (Figure 1) are a common and important class of compounds, endowed with promising

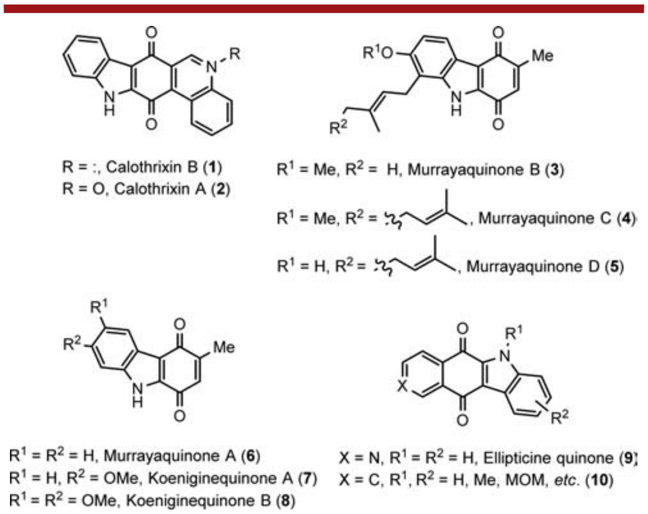


Figure 1. Representative carbazolequinones.

biological properties such as cardiotonic, antituberclosis, and neutronal cell protecting activities,[1] and they are also valuable intermediates for the synthesis of carbazoles, carbazolequinols, and other alkaloids.[2] Examples of such compounds include antimalarial calothrixins (**1** and **2**),[3] antitumor murrayaquinones (**3**–**6**),[4] koeniginequinones (**7** and **8**),[5] cytotoxic ellipticine quinone (**9**), and other benzocarbazolediones (**10**), etc.[6]

As bioactive natural products continue to play a key role in drug discovery,[7] libraries of carbazolequinones would be useful for high-throughput screening and further drug discovery research. Though several approaches[6,8a−j] have been reported for the synthesis of carbazolequinones, they typically rely on appropriately functionalized indoles or arylamines as precursors, establishing one C–C or C–N bond at a time through cross-coupling reaction, radical chemistry, or other tandem cyclization processes to form the carbazolequinone core skeleton. These methods have a number of drawbacks, such as the use of transition metals and highly toxic reagents, strenuous reaction conditions, and inflexibility. A method to construct both C–C and C–N bonds in the carbazolequinone framework in one step was also reported,[8j] but additional transformation was required to furnish the carbazolequinone, and the above-mentioned drawbacks were present. For the rapid synthesis of carbazolequinone libraries, a one-pot, two-component reaction that directly produces the targets is desired.

Arynes are highly reactive intermediates and have been widely used in organic synthesis.[9] In particular, the introduction of 2-(trimethylsilyl)aryl triflates as mild aryne precursors has led to rapid growth of this field.[10] It is well accepted that the low-lying LUMO of arynes makes the triple bond prone to nucleophilic attack or can participate in cycloaddition reactions. Inspired by preparation of carbazoles and indolines from arynes,[11] herein we report a short and a flexible synthetic

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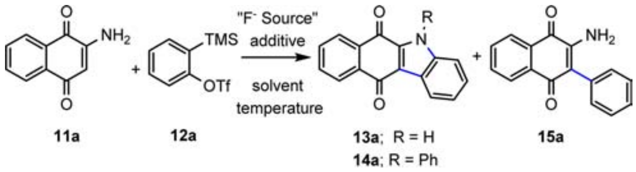
method for the construction of substituted carbazolequinones by treating arynes with 2-aminoquinones.

To explore the feasibility of this cascade reaction, benzyne derived in situ from β-trimethylsilyl triflate **12a** and KF was allowed to react with 2-amino-1,4-naphthoquinone **11a**. The desired carbazolequinone **13a** was indeed obtained in 49% yield (entry 1, Table 1), along with *N*-phenylcarbazolequinone **14a**

Table 1. Optimization of the Cyclization Conditions[a]



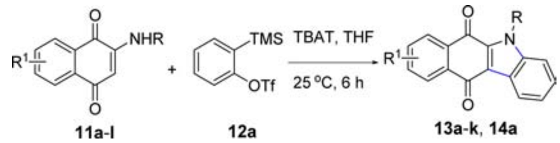
entry	**12a** (equiv)	F^- (equiv)	solvent	yield[b] (%) **13a**	**14a**	**15a**
1	1.25	KF[c]	THF	49	20	8
2	1.25	TBAF[d]	THF	14	6	5
3	1.25	CsF[d]	CH_3CN	25	12	12
4	1.25	TBAT[d]	THF	85	4	4
5	3.0	CsF[e]	THF	31	62	7

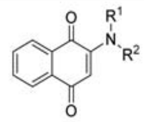
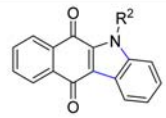
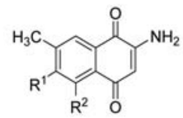
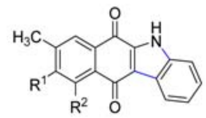
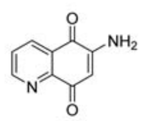
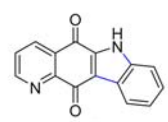
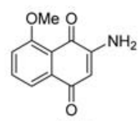
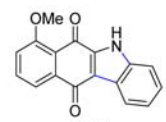
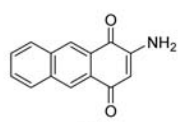
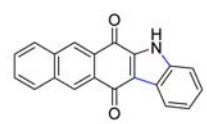
[a]All reactions were carried out on a 0.2 mmol scale in 4.0 mL of solvent (0.05 M) at 25 °C unless otherwise specified. [b]HPLC yields based on standard curve. [c]2.5 equiv of F^-, 1.25 equiv of 18-crown-6 ether as an additive, 0.02 M. [d]2.5 equiv of F^-. [e]6.0 equiv of F^-, 3.0 equiv of 18-crown-6 as an additive.

(20%) and uncyclized *C*-arylated **15a** (8%), while 23% of **11a** remained unreacted. Formation of **14a** could be explained by further reaction of **13a** with the in situ generated benzyne, as more equivalents of aryne led to increased formation of **14a** (entry 5, Table 1). Among the various fluoride sources scanned, it was observed that TBAT resulted in excellent yield and selectivity when the reaction concentration was adjusted to 0.05 M (entries 1, 2, 3 and 4, Table 1). To optimize further the yield and selectivity, the effects of solvent, fluoride source, temperature, additive, and stoichiometry were systematically studied (Supporting Information, Table S1).

In order to gauge the scope and generality of the cascade reaction, a variety of aminoquinones (**11a–l**) were reacted with aryne precursor **12a** under the optimized reaction conditions (TBAT, THF, 0.05 M, 25 °C, 6 h) (Table 2). Secondary amines resulted in the corresponding carbazolequinones in moderate yields (**11b** and **11c**, entries 2 and 3, Table 2), suggesting that primary amine **11a** (entry 1, Table 2) is a better substrate than secondary amines (**11b** and **11c**). Tertiary amine **11d** (entry 4) did not react under the reaction conditions. The cascade process was efficient with a number of other aminoquinones and tolerated alkyl (**11e**, **11f**, and **11g**, entries 5, 6 and 7), alkoxy (**11h** and **11k**, entries 8 and 11), benzoyl (**11i**, entry 9), or halo groups (**11h** and **11i**, entries 8 and 9) on the aromatic ring of aminoquinones **11**. Intriguingly *N*-heterocyclic aminoquinone **11j**, which has been reported to react with aryne through aromatic nitrogen,[12] also afforded carbazolequinone **13i** (entry 10) in moderate yield. This may be attributed to reduced nucleophilicity of the pyridine nitrogen over quinoneamine. It is noteworthy that bromocarbazolequinones (**13g** and **13h**) could potentially be employed in metal-catalyzed coupling reactions to afford substituted carbazolequinones.

Table 2. Substrates Scope: Variation of the 2-Aminoquinones[a]



entry	aminoquinones **11a-l**	products **13a-k**	yield [%][b]
			
1	**11a**; $R^1 = R^2 = H$	**13a**; $R^2 = H$	80
2	**11b**; $R^1 = H$, $R^2 = CH_3$	**13b**; $R^2 = CH_3$	68 (90)[c]
3	**11c**; $R^1 = H$, $R^2 = PMB$	**13c**; $R^2 = PMB$	61 (88)[c]
4	**11d**; $R^1 = R^2 = CH_3$		0
			
5	**11e**; $R^1 = CH_3$, $R^2 = H$	**13d**; $R^1 = CH_3$, $R^2 = H$	62
6	**11f**; $R^1 = R^2 = H$	**13e**; $R^1 = R^2 = H$	68
7	**11g**; $R^1 = Ph$, $R^2 = H$	**13f**; $R^1 = Ph$, $R^2 = H$	58
8	**11h**; $R^1 = OCH_3$ $R^2 = Br$	**13g**; $R^1 = OCH_3$ $R^2 = Br$	60
9	**11i**; $R^1 = OBz$ $R^2 = Br$	**13h**; $R^1 = OBz$ $R^2 = Br$	67
10	 **11j**	 **13i**	23 (40)[c]
11	 **11k**	 **13j**	61
12	 **11l**	 **13k**	65

[a]**11** (0.25 mmol), **12a** (0.25 mmol), TBAT (0.5 mmol), THF (4.0 mL), 25 °C, 6 h. [b]Isolated yields. [c]Yields calculated brsm.

To further understand the scope of this novel transformation, a wide range of β-trimethylsilyl triflates **12** were then examined with **11a** as the amine source, and the results are summarized in Table 3. 4,5-Dimethylbenzyne aryne precursor **12b** with 2-amine-1,4-naphthoquinone **11a** delivered the corresponding carbazolequinone **13l** in 85% yield. Different 4,5-disubstituted symmetrical aryne precursors (**12c–e**), including indane derivative **12f**, benzodioxole derivative **12g**, and naphthalene derivative **12h**, reacted smoothly to provide the corresponding products in moderate to good yields. The structure of **13n** was confirmed by single-crystal X-ray analysis (Supporting Information).[13a] In general, electron-rich arynes (**12b,d–g**) gave higher yields than the electron-deficient aryne (**12c**). The

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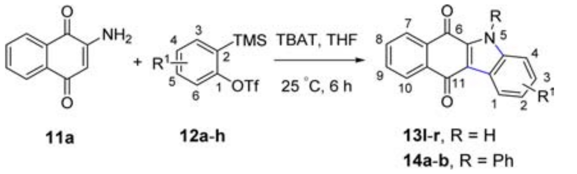
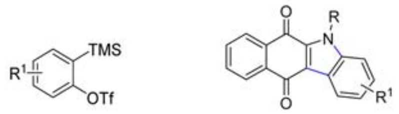
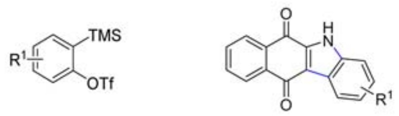
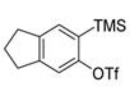
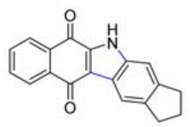
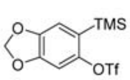
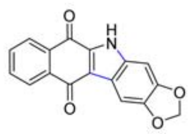
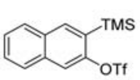
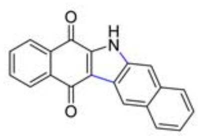
Table 3. Substrates Scope: Variation of the Arynes[a]



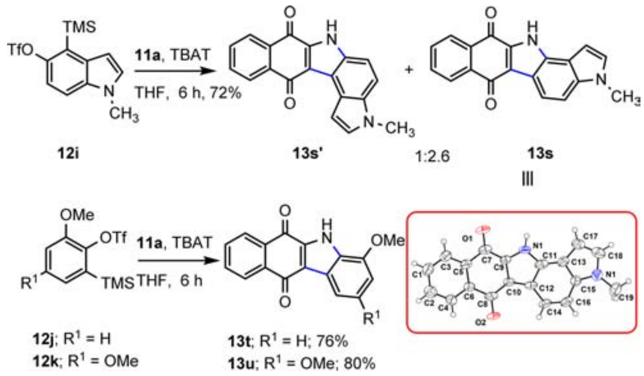
entry	aryne precursor 12a-h	product 13l-r, 14a-b	yield [%][b]
			
1	12a; R[1] = H	14a; R = Ph, R[1] = H	64[c]
2	12b; R[1] = 4,5-$(CH_3)_2$	13l; R = H, R[1] = 2,3-$(CH_3)_2$	85
3		14b; R = Ar, R[1] = 2,3-$(CH_3)_2$	70[c]
			
4	12c; R[1] = 4,5-$(F)_2$	13m; R[1] = 2,3-$(F)_2$	51
5	12d; R[1] = 4,5-$(OMe)_2$	13n; R[1] = 2,3-$(OMe)_2$	86
6	12e; R[1] = 3,6-$(CH_3)_2$	13o; R[1] = 1,4-$(CH_3)_2$	68
7	 12f	 13p	74[d]
8	 12g	 13q	84
9	 12h	 13r	48

[a]11a (0.2 mmol), 12 (0.25 mmol), TBAT (0.5 mmol), THF (4.0 mL), 25 °C, 6 h. [b]Isolated yields. [c]11a (0.2 mmol), 12 (0.6 mmol), CsF (1.2 mmol), 18-crown-6 (0.6 mmol), THF (4.0 mL), 25 °C, 6 h. [d]12f (0.3 mmol).

extended π conjugate naphthalyne derived from **12h** afforded relatively lower yield. The sterically crowded 3,6-dimethylaryne derived from **12e** also furnished the expected product **13o** in moderate yield.

In the case of unsymmetrical aryne precursor **12i**, two regioisomers **13s** and **13s′** were obtained in good yield (Scheme 1). The regioselectivity[14] of the major isomer is attributed to nucleophilic addition of the enamine carbon onto aryne, followed by cyclization. To shed further light on the reaction pathway, unsymmetrical aryne precursors **12j** and **12k** were treated with **11a** under optimized conditions. Gratifyingly, **13t** and **13u** were formed regioselectively in good yields confirming *C*-arylation as the initial step of the cascade reaction

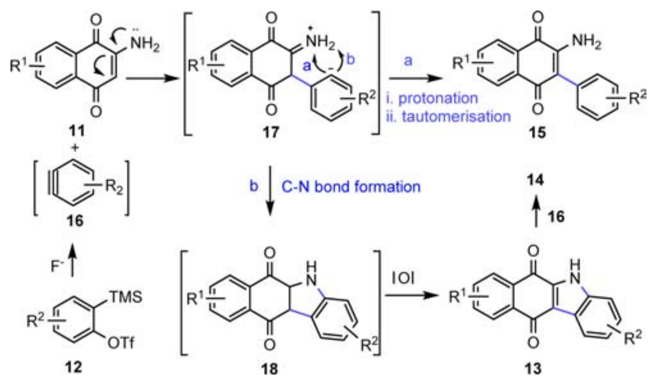
Scheme 1. Reaction with Unsymmetrical Aryne Precursors



over *N*-arylation.[13b] Structure of **13s** was unequivocally confirmed by single-crystal X-ray analysis (Scheme 1).[13a]

On the basis of the regioselectivity shown in the formation of **13s−u** and previous reports,[14−16] a tentative mechanism is proposed in Scheme 2. Initially, carbon of enamine moiety in

Scheme 2. Plausible Mechanisms for Construction of Carbazolequinones



11 undergoes a nucleophilic addition to an aryne formed in situ from the precursor **12**, leading to the generation of the *C*-arylated[17] zwitterionic intermediate **17**, which can abstract a proton in an intramolecular fashion, followed by imine−enamine tautomerization to form **15** (path a). Alternatively, the nucleophilic aryl anion **17** can add to the iminium nitrogen followed by oxidation to provide cyclized product **13** (path b). The electron-withdrawing character of naphthalenedione makes the iminium nitrogen act as an electrophile, resulting in C−N bond formation,[18] and rearomatization is the driving force for the oxidation to form **13** as the main products. For unsymmetrical arynes, the first step, namely nucleophilic addition, determines the regioselectivity.

A wide range of synthetic applications of this method is readily envisaged and is amply illustrated in the synthesis of murrayaquinone A (**6**), its analogues (**6a**, **6b**), and koeniginequinone B (**8**) (Table 4). Murrayaquinone A (**6**) is a cardiotonic active compound isolated from the genus *Murraya*, which has been used as a folk medicine for analgesia, as a local anesthesia, and also for the treatment of eczema, rheumatism, and dropsy.[4,5] Treatment of aryne precursors (**12a**, **12b**, **12j**, and **12d**) and aminoquinone (**11m**) under optimized reaction conditions provided the target compounds, respectively, in one simple operation.

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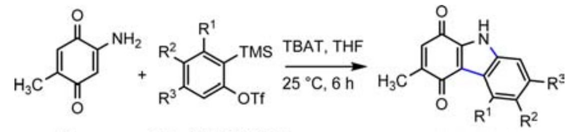
Table 4. Concise Synthesis of Murrayaquinone A (6), Koeniginequinone B (8), and Their Analogues (6a and 6b)



11m 12a, 12b, 12j, 12d 6, 6a, 6b, 8

entry	aryne precursor	R[1]	R[2]	R[3]	product (yield, %)
1	**12a**	H	H	H	**6** (58)
2	**12b**	H	CH_3	CH_3	**6a** (48)
3	**12j**	OCH_3	H	H	**6b** (47)
4	**12d**	H	OCH_3	OCH_3	**8** (50)

In summary, a highly practical, transition-metal-free method has been developed for the flexible synthesis of carbazolequinones. In these cascade reactions, one C−Si and one C−O bond are broken, while a C−C bond along with one C−N bond are formed in one pot. In addition, with an excess of arynes, the products could react further with arynes to provide arylated carbazolequinones (**14a** and **14b**), demonstrating potential expandability and flexibility of this method in forming molecular diversity. Application of this methodology in synthesizing more complex carbazolequinones and biological evaluations of the synthesized carbazolequinones are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01090.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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