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PAPER

Aryne cycloaddition with 3-oxidopyridinium species†

Hailong Ren, Chunrui Wu, Xiuxiu Ding, Xiaoge Chen and Feng Shi*

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The [3 + 2] cycloaddition of arynes with 3-oxidopyridinium species is examined using the Kobayashi benzyne precursor. The reaction affords a bicyclo[3.2.1] skeleton under mild conditions. A [7 + 2] cycloaddition mode with a subsequent pyridine ring-opening event has also been observed.

Introduction

The 3-oxidopyridinium species (Fig. 1, **1**) is well known as a latent dipole[1] with several possible modes of cycloaddition arising from different resonance structures thereof. For instance, olefin and alkyne cycloaddition typically takes place in a [3 + 2] (sometimes called [5 + 2] in literature) mode with a 2,6-peri-selectivity engaging resonance structure **A** or **B**.[2] In contrast, ketene cycloaddition typically engages resonance structure **C** or **D** in a [7 + 2] mode with a 2,*O*- or *O*,4-periselectivity.[3] Diene cycloaddition, on the other hand, typically engages resonance structure **E** or **F** with a 2,4-periselectivity in a [5 + 4] mode.[4] The FMO analysis of these cycloadditions has been carried out to account for these observations.[5]

Among these reactions, the olefin and alkyne cycloaddition has found the greatest application in synthetic chemistry, as witnessed by a number of elegant total syntheses employing this cycloaddition as a strategic step.[6] The closely related cycloaddition employing arynes as a 2e dipolarophile, however, has not been much studied. In the 1970's, Katritzky and co-workers briefly visited this reaction[7] using diazotized anthranilic acid as the benzyne precursor, and found that *N*-phenyl-3-oxidopyridinium afforded a bicyclo[3.2.1] scaffold **2** (eqn (1)) in low yield. In sharp contrast, the *N*-methyl variant over-reacted with a second equivalent of benzyne affording a bicyclo[4.3.1] scaffold (eqn (2)). The incorporation of a second benzyne was presumably triggered by the more electron-releasing nature of the methyl group as well as the forcing conditions employed in the diazotized anthranilic acid decomposition. About two decades later, Carroll and co-workers used this aryne cycloaddition strategy to synthesize MK801,[8] a channel-blocking antagonist of the NMDA receptor complex, using the Kobayashi benzyne precursor[9] and a 4-oxidoisoquinolinium species (eqn (3)). Clearly, the Kobayashi precursor allowed for milder reaction conditions and a better yield. Yet unfortunately, both studies above targeted a very limited number of substrates and to date, no follow-up studies have been performed to systematically examine the reaction or to expand the scope.[10]

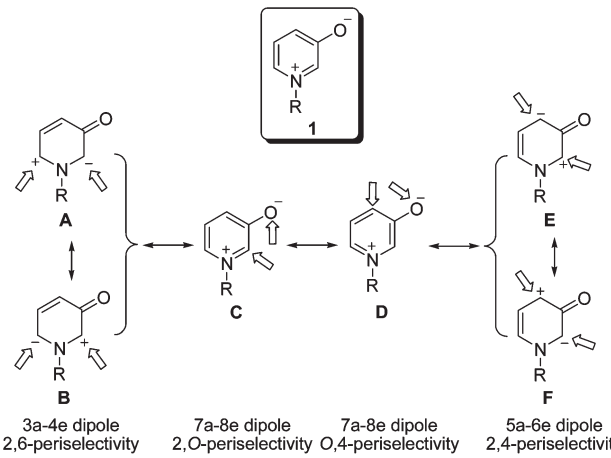
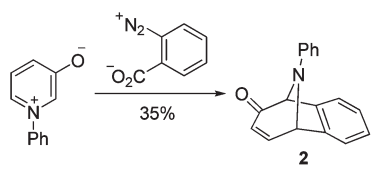
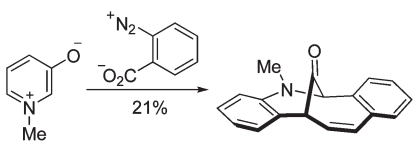


Fig. 1 3-Oxidopyridinium species: resonance structures and cycloaddition modes.



(1)



(2)

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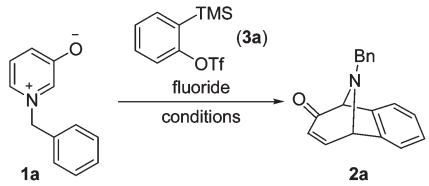
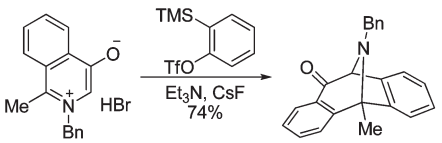
†Electronic supplementary information (ESI) available: Procedures and characterization data for the substrates, and full NMR spectra for the products. See DOI: 10.1039/c2ob26519b

Table 1 Reaction optimization[a]



Entry	**3a**/equiv	F^-/equiv	Conditions	Yield[b]/%
1	1.1	CsF/1.5	MeCN, 80 °C, 12 h	33
2	1.1	CsF/1.5	THF, 70 °C, 12 h	Trace
3	1.1	CsF/1.5	Dioxane, 100 °C, 12 h	0
4	1.3	TBAF/1.5	THF, 25 °C, 12 h	38
5	1.3	CsF/1.5	MeCN, 25 °C, 48 h	59
6	1.3	CsF/2.6	MeCN, 25 °C, 12 h	62
7	**1.3**	**CsF/2.6**	**MeCN, ~17 °C, 18 h**	**78**
8	1.3	CsF/1.5	MeCN, ~17 °C, 18 h	65

[a] Reactions were carried out on an approximately 0.2 mmol scale in 5 mL of solvent. Compound **1a** was obtained as a monohydrate. [b] Isolated yields.



(3)

With our continuing interest in aryne cycloaddition chemistry,[11] we wished to revisit this cycloaddition reaction using the Kobayashi aryne precursor in the hope to cover more substrates, expand the reaction scope, examine detailed substitution compatibility, and seek other possible periselectivities in the cycloaddition. At a minimum, we wished to develop reaction conditions to afford **2** universally regardless of the N-substitution. Herein we report our results.

Results and discussion

Reaction optimization

Our journey began with *N*-benzyl-3-oxidopyridinium **1a** and the parent benzyne precursor **3a** (Table 1). Running the reaction in refluxing MeCN using CsF as the fluoride source with 1.1 equiv of **3a** gave the desired product **2a** in 33% yield (entry 1). Replacing MeCN with THF or dioxane resulted in complete failure (entries 2 and 3). Since **1a** was poorly converted in all cases, we increased **3a** to 1.3 equiv. for the following studies. With this change, running the reaction in THF with TBAF as the fluoride source afforded 38% yield (entry 4). A higher yield of 59% could be obtained using CsF in MeCN at room temperature, but the reaction proceeded much more slowly. Increasing CsF to 2.6 equiv could shorten the reaction time but the yield remained moderate (entry 6). Somewhat unexpectedly, by simply lowering the temperature by another 7–8 °C (from ~25 °C to about 16–18 °C), the yield increased to 78% (entry 7). This is the first time in aryne chemistry that we have observed such a significant temperature dependency. Nonetheless, it is NOT suggested to further lower the temperature, as the solubility of CsF is decreased and the reaction affords low conversion after prolonged stirring. Even at 16–18 °C, clogging of CsF was commonly observed if the CsF used was not a fine powder. Under these conditions, **1a** was still incompletely converted, but charging additional **3a** or CsF did not improve the yield.

Scope of 3-oxidopyridinium species

With the optimal reaction conditions in hand, we moved forward to screen additional substrates (Table 2). Substitution at the pyridine ring was tolerated at 2, 5, or 6-positions (entries 1–3). Substitution at the nitrogen was also broadly tolerated. Other than the benzyl group, primary (entries 4 and 5), secondary (entry 6), and tertiary (entry 7) alkyl groups were all tolerated. It is noteworthy that over-phenylation of **1e** with benzyne, as described in eqn (2), was diminished under our conditions. Aryl groups (entries 8–10) and heteroaryl groups (entries 11 and 12) were also compatible, and electronic or steric factors posed no big influence on yield. Additionally, functionalized substitutions were also tested. While the *N*-MOM pyridinium species **1n** (entry 13) and the *N*-ethoxycarbonylmethyl variant (not shown) both afforded complex mixtures, the alcohol-containing **1o**, despite its poor solubility in MeCN, was successfully employed (entry 14) where the benzylic hydroxyl group remained intact.[12]

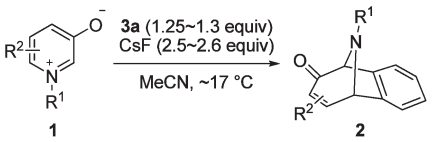
Scope of arynes and the observation of the [7 + 2] cycloaddition mode

Our next effort was directed to examine different aryne precursors (Table 3). First, the symmetrical 4,5-dimethoxybenzyne derived from **3b** afforded **2p** smoothly in good yield (entry 1), despite being slow. The unsymmetrical 4-methoxybenzyne derived from **3c** afforded two regioisomeric products **2q** and **2q′** in approximately equal amounts (entry 2). However, when the benzyne is equipped with a 3-methoxy group, the reaction started to deviate from the expected [3 + 2] pathway. Thus, when the 3-methoxybenzyne derived from **3d** was employed, in addition to the desired two regioisomeric products **2r** and **2r′**,[13] a third product with a benzofuran core (**4a**) was observed in significant quantity (entry 3). A similar outcome was observed for the 3,5-dimethoxybenzyne derived from **3e** (entry 4). This trend was followed for other 3-oxidopyridinium species, as **4a** was always observed regardless of the N-substitution (entries 5 and 6), and it seemed difficult to correlate the yield of **4a** with the nature of the N-substitution as well.

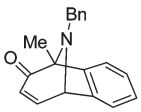
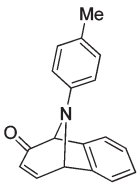
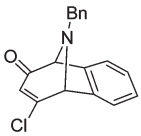
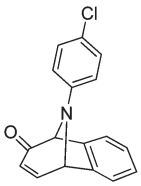
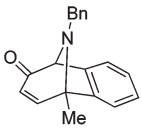
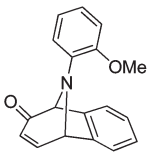
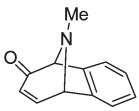
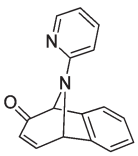
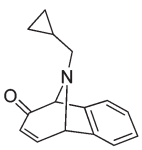
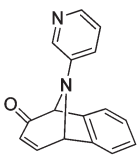
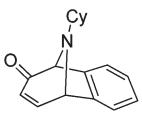
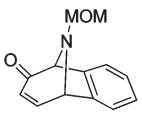
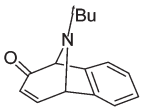
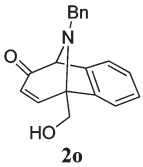
These apparently unexpected results raised several questions. First, for benzynes derived from **3d** and **3e**, almost all nucleophilic addition and dipolar cycloaddition reactions have been demonstrated to be regioselective where the nucleophile or the nucleophilic end of the dipole attacks distal to the methoxyl group.[14] So why then was such a regioselectivity not realized in our reaction (assuming that resonance structure **A** is more dominant than **B**, *cf.* Fig. 1)? Secondly, how was **4** formed, and what role did the 3-methoxy group play in this transformation?

Although we are not prepared to answer the first question in this report, we need to mention that similar observations are known. Thus ethyl vinyl ether reacted with **1** to afford the same regioisomer as methacrylaldehyde.[4a] FMO analysis supported[15] that shifting from electron-poor olefins to electron-rich olefins,

Table 2 Scope of 3-oxidopyridinium species[a]



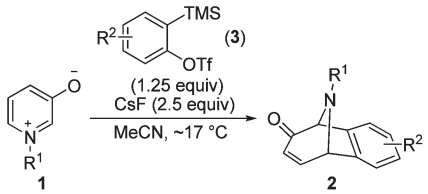
1 **2**

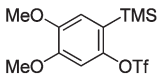
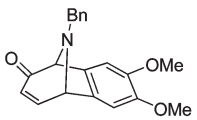
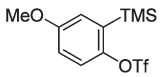
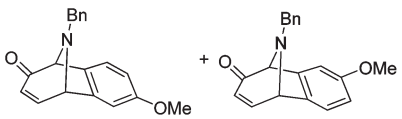
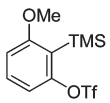
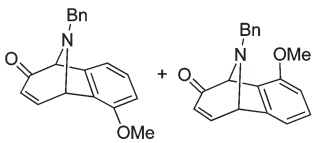
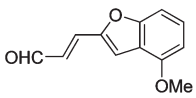
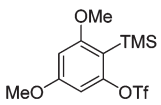
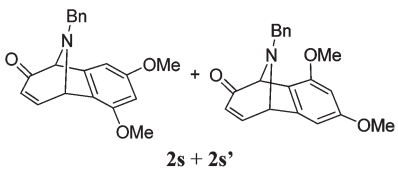
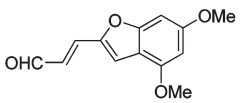
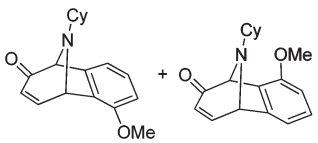
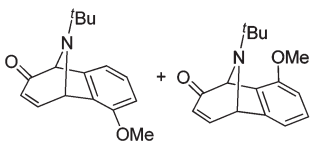
Entry	**1** (R^1, R^2)	Time/h	Product	Yield[b]/%	Entry	R^1, R^2	Time/h	Product	Yield[b]/%
1	**1b** R^1 = Bn R^2 = 2-Me	20	 **2b**	55	8	**1i**[c] R^1 = 4-MeC_6H_4 R^2 = H	18	 **2i**	48
2	**1c** R^1 = Bn R^2 = 5-Cl	18	 **2c**	76	9	**1j**[c] R^1 = 4-ClC_6H_4 R^2 = H	16	 **2j**	<63[e]
3	**1d**[c] R^1 = Bn R^2 = 6-Me	18	 **2d**	67	10	**1k**[c] R^1 = 2-(MeO)C_6H_4 R^2 = H	5	 **2k**	49
4	**1e**[c] R^1 = Me R^2 = H	14	 **2e**	39	11	**1l**[d] R^1 = 2-pyridyl R^2 = H	20	 **2l**	62
5	**1f** R^1 = *c*-$PrCH_2$ R^2 = H	37	 **2f**	46	12	**1m**[c] R^1 = 3-pyridyl R^2 = H	18	 **2m**	58
6	**1g**[c] R^1 = Cy R^2 = H	12	 **2g**	66	13	**1n**[c]	20 R^1 = MOM R^2 = H	 **2n**	Complex mixture
7	**1h**[c] R^1 = *t*-Bu R^2 = H	20	 **2h**	57	14	**1o**[c] R^1 = Bn R^2 = 6-CH_2OH	20	 **2o**	54

[a] All reactions were carried out in an approximately 0.2 mmol scale. Reaction time was individually optimized and prolonged reaction led to lowered yields. [b] Isolated yield. [c] Prepared as a monohydrate. [d] Prepared as an HBr salt. One additional equiv of CsF was used to neutralize the HBr. [e] We are unable to completely purify this compound. The ^{13}C NMR is clean, but ^1H NMR shows ~95 mol% purity, with an extra signal at 9.72 ppm (0.05 H). The impurity may correspond to product type **4** (*vide infra*) but was not isolable.

the major contribution to the reaction accordingly shifted from the HOMO(**1**)–LUMO(olefin) interaction to the HOMO(olefin)–LUMO(**1**) interaction. Although we do not know whether a similar explanation is valid in our case for 3-methoxybenzyne,

Table 3 Scope of arynes[a]

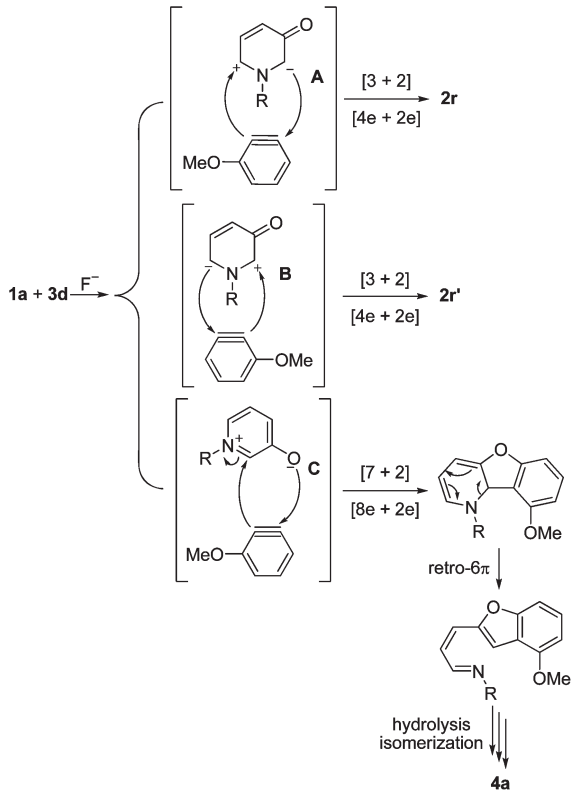


Entry	1	3	Time/h	Desired product	Yield[b]/%	Unexpected product	Yield[b]/%
1	**1a**	 **3b**	68	 **2p**	66	—	—
2	**1a**	 **3c**	18	 **2q + 2q'**	51 (1.3 : 1)[c]	—	—
3	**1a**	 **3d**	20	 **2r + 2r'**	19 + 19	 **4a**	23
4	**1a**	 **3e**	20	 **2s + 2s'**	18 + 20	 **4b**	11
5	**1g**	**3d**	20	 **2t + 2t'**	20 + 15	**4a**	27
6	**1h**	**3d**	20	 **2u + 2u'**	20 + 22	**4a**	12

[a] All reactions were carried out in an approximately 0.2 mmol scale. Reaction time was individually optimized and prolonged reaction led to lowered yields. All substrates were prepared as monohydrates. [b] Isolated yield. [c] Since the two products were inseparable and NMR signals are seriously overlapping, no attempts were made to identify the major isomer.

we consider that a detailed and professional FMO analysis might bring the eventual clue to the question.

The second question can be explained in Scheme 1. Taking the reaction between **1a** and **3d** as an example, the two desired products can be obtained from the expected [3 + 2] cycloaddition pathways involving resonance structures **A** and **B**, respectively (the arrow-pushing for **2r′** might appear arbitrary before a detailed FMO analysis is done). Formation of **4a**, however, must come from a [7 + 2] cycloaddition mode in a 2, *O*-periselectivity involving resonance structure **C**. This shift in periselectivity can be explained by a large coefficient of *O* in the HOMO of **1**.[5] It is noteworthy that Katritzky and co-workers have observed similar events. For example, cycloaddition of **1** with phenylacetylene gave rise to exclusive [3 + 2] adducts, while when moving to the more electron-negative dimethyl acetylenedicarboxylate (DMAD), the formation of the [7 + 2] adducts increased significantly in certain 3-oxidopyridinium species.[16] Additionally, the more electrophilic ketene undergoes the [7 + 2] cycloaddition in contrast to the [3 + 2] cycloaddition for typical alkenes.[3] Thus shifting from the traditional [3 + 2]



Scheme 1 Mechanistic paths for reactions involving 3-methoxybenzyne.

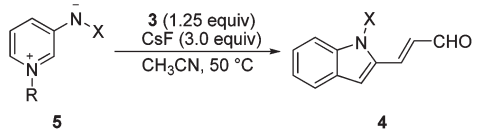
mode to the [7 + 2] mode seems to be caused by electronic perturbation of the FMO's, particularly those of the dipolarophile. Thus, the role that the 3-methoxy group plays should possibly lie in its electron-withdrawing nature (on the σ-skeleton), which may polarize the "third" bond of the aryne, leading to a redistribution of the coefficients of the HOMO and LUMO. Accordingly, benzynes generated from **3b** and **3c** do not have enough electronic perturbation, as the methoxy groups are not proximal enough to cause the polarization. However, we do not have a reasonable explanation as to why the parent benzyne does not undergo the [7 + 2] cycloaddition, given the large coefficient of *O* in the HOMO.

Nonetheless, as shown in Scheme 1, this [7 + 2] cycloaddition breaks the aromaticity of the pyridine ring, and triggers a ring-opening event through the retro 6π-electrocyclization process,[17] affording a benzofuran core with an α,β-unsaturated imine side chain. Under the reaction conditions, hydrolysis and *E*–*Z* isomerization took place to afford **4a** as the final product.

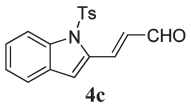
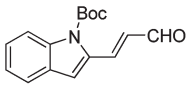
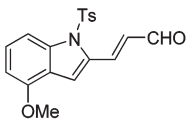
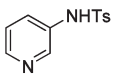
Reaction of 3-amidopyridinium species

These results above triggered our attention to examining the closely related 3-amidopyridinium species (**5**, Table 4). For reasons we do not understand well, nitrogen nucleophiles are more "arynophilic" than the corresponding oxygen nucleophiles.[12] Thus, by replacing the oxyanion with the isoelectronic nitrogen anion, we hoped to increase the [7 + 2] cycloaddition product **4**.

Table 4 Reaction of 3-amidopyridinium species[a]



5 **4**

Entry	**5** (R, X)	**3**	Time/h	Product	Yield[b]/%
1	**5a** R = Bn, X = Ts	**3a**	18	 **4c**	22
2	**5b** R = *c*-PrCH$_2$, X = Ts	**3a**	20	**4c**	19
3	**5c** R = Bn, X = Boc	**3a**	16	 **4d**	18
4	**5a**	**3d**	22	 **4e**	19
5[c]	 **pre-5d**	**3a**	5	**4c**	30

[a] Reactions were carried out on an approximately 0.2 mmol scale in 5 mL of solvent. Except for the last entry, **5** were obtained as HBr salts. [b] Isolated yields. [c] Reaction performed with 2.5 equiv of **3a** and 3.5 equiv of CsF.

This hypothesis proved only partially correct. While we have found that reaction of **5** with **3a** indeed led to the formation of indole **4** as the only isolable product, we were unable to optimize the yields to a synthetically useful level (Table 4). Thus, the 3-tosylimidopyridinium species **5a** and **5b** afforded only 20% yields of the indole **4c** (entries 1 and 2). The Boc variant **5c** also afforded a same yield (entry 3). Now the reaction became no longer sensitive to the nature of benzyne, as use of either **3a** or **3d** afforded the same outcome and similar yields (entry 4).

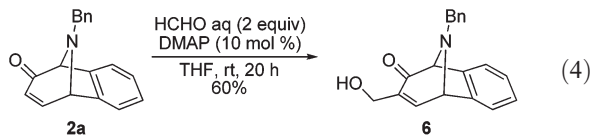
Considering that the substitution on the pyridine nitrogen was completely irrelevant to the final products, we next attempted to use 3-tosylamidopyridine directly in the reaction. Here an excess of benzyne was charged and an *N*-phenyl-3-tosylimidopyridinium species was expected to be generated *in situ*. However, even under these conditions, the yield remained modest (entry 5). Given these results, examining the substitution on the pyridine did not seem to make much sense and thus was not attempted.

Manipulations of the product

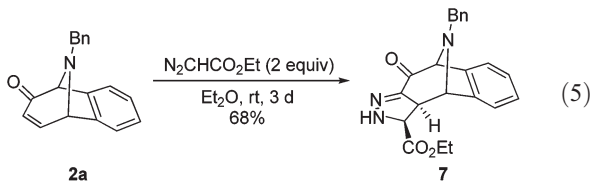
As stated before, the bicyclo[3.2.1] scaffold has been actively manipulated, mainly through reductions, in the early literature, particularly during the total syntheses of natural and unnatural

products.[6,8,18] Thus, we sought other possibilities in the manipulation of the [3 + 2] adducts.

The Michael acceptor moiety of **2** could be utilized in a Baylis–Hillman reaction. Reaction of **2a** with formaldehyde afforded 60% yield of the adduct **6** (eqn (4)).[19] This transformation not only increases the functionality of **2**, but also complements its scope, since 4-substituted 3-oxidopyridinium species are difficult to access. The electron-deficient olefin moiety could be exploited in a further dipolar cycloaddition event. Thus reaction of **2a** with ethyl diazoacetate fused another 5-membered ring to the bicyclo[3.2.1] scaffold (eqn (5)). Disappointingly, all attempts to oxidatively cleave the olefin were unsuccessful in our hands.



(4)



(5)

Conclusions

In summary, the Kobayashi aryne precursor proves suitable in the [3 + 2] cycloaddition with 3-oxidopyridinium species. Under mild conditions, the reaction can afford the bicyclo[3.2.1] scaffold in moderate to good yields irrespective of the N-substitution. Interestingly, benzynes with a 3-methoxy group can trigger a [7 + 2] cycloaddition mode unprecedented for benzyne reaction, leading to a benzofuran derivative. The analogous 3-amidopyridinium species underwent the [7 + 2] cycloaddition as the only productive path leading to the formation of indoles in low yields. The analogous aryne cycloaddition with 3-oxidopyrylium species is under active investigation in our group.

Experimental section

General information

All materials supplied from commercial sources were used as received unless otherwise noted. MeCN and THF were distilled over CaH_2 and Na–benzophenone, respectively. Silica gel for column chromatography was supplied as 300–400 mesh from Haiyang Chemicals (Qingdao, China, which gives a different retardation compared with silica gel typically used in the western countries). CsF was stored in a desiccator and only the powders were used. All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were referenced to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$, 4.79 ppm for ^1H and uncorrected for ^{13}C in D_2O, 2.50 ppm for ^1H and 39.52 ppm for ^{13}C in DMSO-d_6).

Preparation of the substrates is listed in the ESI.†

Representative procedures for reactions of 3-oxidopyridinium species with arynes (Tables 2 and 3, outlined for compound 2a)

To a 10 mL round-bottom flask equipped with a stir bar was added **1a** (as monohydrate, 37 mg, 0.182 mmol) followed by **3a** (71 mg, ~0.24 mmol, 1.3 equiv). MeCN (5 mL) was added and the mixture was briefly stirred before addition of CsF (72 mg, 0.47 mmol, 2.6 equiv). The mixture was stirred in a 17 °C bath for 18 h before being diluted with EtOAc and water. Layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc) to afford 37 mg of **2a** as a light-yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.44 (m, 1 H), 7.35–7.26 (m, 7 H), 7.22–7.19 (m, 2 H), 5.55 (dd, J = 9.7, 1.4 Hz, 1 H), 4.44–4.39 (m, 2 H), 3.75 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 151.0, 145.8, 138.5, 137.3, 129.0, 128.5, 127.6, 127.5, 127.2, 125.9, 123.1, 123.0, 76.7, 64.6, 56.0; IR (KBr) 1685, 1454 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}NO$ (M + H) 262.1226, found 262.1225.

Characterization data for other products 2 and 4 (Tables 2 and 3)

Product 2b. The general procedure was applied to 39.8 mg of **1b**, 75 mg of **3a**, and 77 mg of CsF to afford 30.3 mg of **2b** as a yellow solid, mp 97–98 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 6 H), 7.24–7.14 (m, 3 H), 7.03 (dd, J = 9.7, 4.9 Hz, 1 H), 5.64 (d, J = 9.6 Hz, 1 H), 4.34 (d, J = 4.9 Hz, 1 H), 3.91 (s, 2 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 147.9, 146.0, 143.2, 138.1, 128.9, 128.5, 127.4, 127.3, 126.9, 123.9, 123.6, 121.6, 76.5, 61.5, 49.9, 14.8; IR (KBr) 1680, 1454 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO$ (M + H) 276.1383, found 276.1384.

Product 2c. The general procedure was applied to 44 mg of **1c**, 75 mg of **3a**, and 77 mg of CsF to afford 45 mg of **2c** as a yellow solid, mp 114–116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.31 (m, 7 H), 7.26–7.21 (m, 2 H), 5.72 (t, J = 1.2 Hz, 1 H), 4.47 (d, J = 0.6 Hz, 1 H), 4.43 (d, J = 0.7 Hz, 1 H), 3.93 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 157.0, 144.2, 138.8, 136.6, 129.1, 128.6, 127.84, 127.75 (overlap), 125.0, 122.3, 120.8, 74.2, 70.6, 54.3; IR (KBr) 1686, 1589 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}NO^{35}Cl$ (M + H) 296.0837, found 296.0834.

Product 2d. The general procedure was applied to 43.4 mg of **1d** (as monohydrate), 75 mg of **3a**, and 77 mg of CsF to afford 37 mg of **2d** as a light yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 6 H), 7.25–7.20 (m, 2 H), 7.15 (ddd, J = 7.1, 6.5, 2.3 Hz, 1 H), 6.90 (d, J = 9.8 Hz, 1 H), 5.54 (dd, J = 9.8, 1.6 Hz, 1 H), 4.25 (d, J = 1.5 Hz, 1 H), 3.89 and 3.93 (ABq, J = 13.1 Hz, 2 H), 1.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 152.0, 149.8, 138.9, 137.7, 129.1, 128.4, 127.5, 127.3, 126.9, 124.7, 122.3, 120.6, 73.4, 67.1, 50.5, 18.6; IR (KBr) 1691, 1454 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO$ (M + H) 276.1383, found 276.1377.

Product 2e. The general procedure was applied to 32.7 mg of **1e** (0.257 mmol) (as monohydrate), 102 mg of **3a** (1.33 equiv), and 104 mg of CsF (2.65 equiv) to afford 18.5 mg of **2e** as a light green solid, mp 50–51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.44 (m, 1 H), 7.36–7.30 (m, 2 H), 7.20–7.16 (m, 2 H), 5.51 (dd, J = 9.7, 1.1 Hz, 1 H), 4.37 (d, J = 5.6 Hz, 1 H), 4.31 (s, 1 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 151.4, 145.4, 138.0, 127.7, 127.2, 126.1, 123.1, 122.6, 78.8, 67.3, 39.9; IR (KBr) 1690, 1456 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}NO$ (M + H) 186.0913, found 186.0911.

Product 2f. The general procedure was applied to 33.4 mg of **1f**, 83 mg of **3a**, and 85 mg of CsF to afford 23.1 mg of **2f** as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.42 (m, 1 H), 7.31–7.27 (m, 2 H), 7.20–7.14 (m, 2 H), 5.52 (dd, J = 9.7, 1.4 Hz, 1 H), 4.68 (d, J = 5.5 Hz, 1 H), 4.58 (s, 1 H), 2.57 and 2.45 (d of ABq, J_{AB} = 12.3 Hz, ^3J = 6.5 Hz, 2 H), 1.01–0.89 (m, 1 H), 0.56–0.50 (m, 2 H), 0.09–0.00 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 150.5, 145.8, 138.5, 127.5, 127.1, 125.7, 123.0, 122.7, 76.5, 64.6, 56.2, 9.3, 3.6, 3.4; IR (KBr) 1685, 1456 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NO$ (M + H) 226.1226, found 226.1221.

Product 2g. The general procedure was applied to 39 mg of **1g** (as monohydrate), 75 mg of **3a**, and 77 mg of CsF to afford 33.5 mg of **2g** as a yellow solid, mp 106–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.40 (m, 1 H), 7.30–7.27 (m, 1 H), 7.22–7.14 (m, 2 H), 7.11 (dd, J = 9.8, 5.0 Hz, 1 H), 5.56 (dd, J = 9.7, 1.5 Hz, 1 H), 4.76 (d, J = 5.0 Hz, 1 H), 4.66 (d, J = 1.3 Hz, 1 H), 2.76–2.65 (m, 1 H), 2.07–1.93 (m, 1 H), 1.91–1.70 (m, 3 H), 1.67–1.51 (m, 1 H), 1.35–1.08 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 147.5, 146.5, 139.3, 127.4, 126.8, 124.8, 123.7, 121.7, 72.9, 60.6, 55.0, 31.3, 30.8, 25.7, 24.6, 24.5; IR (KBr) 1684, 1122, 756 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO$ (M + H) 254.1539, found 254.1534.

Product 2h. The general procedure was applied to 30.9 mg of **1h** (as monohydrate), 71 mg of **3a**, and 72 mg of CsF to afford 23.8 mg of **2h** as an orange solid, mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 9.5, 5.9 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.23–7.20 (m, 1 H), 7.14–7.11 (m, 2 H), 5.40 (dd, J = 9.5, 1.2 Hz, 1 H), 4.82 (d, J = 6.0 Hz, 1 H), 4.77 (s, 1 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 154.3, 147.7, 140.3, 127.4, 126.9, 124.3, 122.1, 121.1, 73.3, 61.7, 54.5, 28.1; IR (KBr) 1687, 1456, 1365, 1222, 754 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}NO$ (M + H) 228.1383, found 228.1383.

Product 2i. The general procedure was applied to 37 mg of **1i** (as monohydrate), 71 mg of **3a**, and 72 mg of CsF to afford 23 mg of **2i** as a yellow solid, mp 164–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.52 (m, 1 H), 7.38–7.34 (m, 1 H), 7.26–7.21 (m, 3 H), 7.09 (d, J = 8.1 Hz, 2 H), 6.83–6.77 (m, 2 H), 5.46–5.41 (m, 2 H), 5.25 (d, J = 1.4 Hz, 1 H), 2.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 149.7, 145.5, 143.8, 138.5, 130.1, 129.7, 127.8, 127.2, 124.7, 124.1, 121.5, 116.6, 73.4, 62.2, 20.4; IR (KBr) 1688, 1676, 1512, 1460 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}NO$ (M + H) 262.1226, found 262.1227.

Product 2j. The general procedure was applied to 41 mg of **1j** (as monohydrate), 71 mg of **3a**, and 72 mg of CsF to afford 32.5 mg of **2j** as a yellow solid, mp 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (m, 1 H), 7.38–7.35 (m, 1 H), 7.28–7.25 (m, 2 H), 7.25–7.23 (m, 2 H), 7.22–7.21 (m, 1 H), 6.83–6.78 (m, 2 H), 5.45–5.40 (m, 2 H), 5.24 (d, J = 1.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 149.6, 145.1, 144.7, 138.0, 129.5, 127.9, 127.4, 125.3, 124.7, 124.1, 121.5, 117.6, 73.3, 62.1; IR (KBr) 1687, 1495, 1336 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}{}^{35}ClNO$ (M + H) 282.0680, found 282.0685.

Product 2k. The general procedure was applied to 40.2 mg of **1k** (as monohydrate), 71 mg of **3a**, and 72 mg of CsF to afford 25 mg of **2k** as a green solid, mp 181–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 1 H), 7.37–7.33 (m, 1 H), 7.25 (dd, J = 9.8, 5.1 Hz, 1 H), 7.22–7.16 (m, 2 H), 6.99 (ddd, J = 8.1, 7.4, 1.5 Hz, 1 H), 6.92–6.83 (m, 2 H), 6.75 (dd, J = 7.8, 1.5 Hz, 1 H), 5.62 (d, J = 5.1 Hz, 1 H), 5.51 (dd, J = 9.7, 1.5 Hz, 1 H), 5.24 (s, 1 H), 3.91 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 151.5, 149.9, 146.1, 138.5, 135.2, 127.6, 127.0, 124.7, 123.2, 122.9, 121.7, 121.0, 119.1, 111.5, 74.2, 62.6, 55.5; IR (KBr) 1693, 1502, 1244 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}NO_2$ (M + H) 278.1176, found 278.1180.

Product 2l. The general procedure was applied to 50.4 mg of **1l** (as HBr salt), 75 mg of **3a**, and 106 mg of CsF to afford 30.6 mg of **2l** as a yellow solid, mp 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.24 (m, 1 H), 7.56–7.51 (m, 2 H), 7.39–7.35 (m, 2 H), 7.26–7.19 (m, 2 H), 6.78–6.73 (m, 2 H), 5.82 (d, J = 4.6 Hz, 1 H), 5.48 (d, J = 1.4 Hz, 1 H), 5.36 (dd, J = 9.7, 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 157.2, 151.6, 148.5, 145.0, 138.2, 137.7, 127.8, 127.2, 124.5, 123.4, 121.5, 115.5, 109.9, 72.2, 60.8; IR (KBr) 1699, 1473, 1434 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ (M + H) 249.1022, found 249.1018.

Product 2m. The general procedure was applied to 38 mg of **1m** (as monohydrate), 75 mg of **3a**, and 77 mg of CsF to afford 28.8 mg of **2m** as a yellow solid, mp 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dd, J = 2.7, 0.8 Hz, 1 H), 8.15 (dd, J = 4.2, 1.7 Hz, 1 H), 7.57–7.53 (m, 1 H), 7.40–7.36 (m, 1 H), 7.31 (dd, J = 9.8, 4.5 Hz, 1 H), 7.28–7.22 (m, 2 H), 7.21–7.14 (m, 2 H), 5.49 (d, J = 4.5 Hz, 1 H), 5.43 (dd, J = 9.8, 1.6 Hz, 1 H), 5.30 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 149.5, 144.8, 142.2, 141.5, 138.6, 137.6, 128.0, 127.4, 124.7, 124.1, 123.8, 123.2, 121.5, 73.0, 61.4; IR (KBr) 1689, 1483, 1334 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ (M + H) 249.1022, found 249.1020.

Product 2o. The general procedure was applied to 43 mg of **1o** (as monohydrate), 71 mg of **3a**, and 72 mg of CsF to afford 29.2 mg of **2o** as an orange solid, mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 8 H), 7.17 (td, J = 7.4, 1.2 Hz, 1 H), 6.80 (d, J = 9.9 Hz, 1 H), 5.65 (dd, J = 9.9, 1.6 Hz, 1 H), 4.36 (d, J = 1.1 Hz, 1 H), 4.28 (left side of a d of ABq, J_{AB} = 11.8 Hz, J_{AX} = 6.0 Hz, 1 H), 4.09 (right of a d of ABq, J_{AB} = 11.8 Hz, J_{BX} = 0 Hz, 1 H), 4.09 and 3.83 (ABq, J = 13.3 Hz, 2 H), 2.26 (d, J = 4.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 146.6, 145.7, 138.8, 137.0, 129.0, 128.7, 127.7, 127.6, 127.3, 124.6, 123.6, 120.9, 73.4, 70.6, 58.9, 50.0; IR (KBr) 3632–3024 (br), 1684 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ (M + H) 292.1332, found 292.1335.

Product 2p. The general procedure was applied to 40.6 mg of **1a** (as monohydrate), 90 mg of **3b**, and 77 mg of CsF to afford 42.5 mg of **2p** as a brown solid, mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 6 H), 7.03 (s, 1 H), 6.90 (s, 1 H), 5.52 (dd, J = 9.7, 1.3 Hz, 1 H), 4.35–4.31 (m, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.74 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 151.5, 148.2, 148.0, 138.5, 137.3, 130.0, 128.9, 128.4, 127.4, 122.8, 109.7, 107.2, 76.7, 64.8, 56.2, 56.1 (overlap); IR (KBr) 1685, 1493, 1298 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ (M + H) 322.1438, found 322.1431.

Product 2q and 2q′. The general procedure was applied to 40.6 mg of **1a** (as monohydrate), 82 mg of **3c**, and 77 mg of CsF to afford 29.4 mg of **2q** and **2q′** as an inseparable mixture as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 6 H from isomer A + 7 H from isomer B), 7.19 (d, J = 8.0 Hz, 1 H from isomer A), 7.04 (d, J = 2.2 Hz, 1 H from isomer A), 6.89 (d, J = 2.2 Hz, 1 H from isomer B), 6.72–6.67 (m, 1 H from isomer A + 1 H from isomer B), 5.58–5.52 (m, 1 H from isomer A + 1 H from isomer B), 4.37–4.33 (m, 2 H from isomer A + 2 H from isomer B), 3.80 (s, 3 H from isomer B), 3.79 (s, 3 H from isomer A), 3.73 (s, 2 H from isomer A + 2 H from isomer B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 194.6, 159.5, 159.2, 151.7, 150.6, 147.9, 140.5, 137.6, 137.4, 129.8, 129.0, 128.5, 127.5, 126.6, 123.5, 123.4, 122.7, 112.7, 112.2, 111.0, 110.6, 76.9, 76.0, 64.6, 64.1, 56.2, 56.1, 55.5; IR (KBr) 1690, 1477, 1284, 1255, 1234 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ (M + H) 292.1332, found 292.1336.

Product 2r, 2r′ and 4a. The general procedure was applied to 40.6 mg of **1a** (as monohydrate), 82 mg of **3d**, and 77 mg of CsF to afford 11.3 mg of **2r** as a yellow oil and 11.0 mg of **2r′** as a yellow oil.

Data for 2r. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 9.7, 5.6 Hz, 1 H), 7.36–7.29 (m, 5 H), 7.20 (dd, J = 8.1, 7.4 Hz, 1 H), 7.08 (d, J = 7.2 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 5.56 (dd, J = 9.6, 1.4 Hz, 1 H), 4.64 (d, J = 5.5 Hz, 1 H), 4.42 (s, 1 H), 3.85 (s, 3 H), 3.74 and 3.70 (ABq, J = 12.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 155.3, 151.2, 140.4, 137.3, 133.0, 129.1, 129.0, 128.5, 127.4, 123.2, 118.2, 110.6, 77.1, 62.2, 56.2, 55.3; IR (KBr) 1686, 1604, 1479, 1267 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ (M + H) 292.1332, found 292.1327.

Data for 2r′. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.17 (m, 7 H), 6.93 (d, J = 7.2 Hz, 1 H), 6.76 (d, J = 8.3 Hz, 1 H), 5.57 (d, J = 9.6 Hz, 1 H), 4.65 (s, 1 H), 4.38 (d, J = 5.6 Hz, 1 H), 3.84 (s, 3 H), 3.92 and 3.57 (ABq, J = 12.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 158.0, 150.5, 148.1, 137.4, 129.8, 129.0, 128.5, 127.4, 124.3, 123.3, 115.6, 110.6, 74.0, 64.9, 56.2, 55.6; IR (KBr) 1686, 1479, 1068 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ (M + H) 292.1332, found 292.1328.

Product 4a. (9.1 mg) was obtained as a side-product from the above reaction as light-yellow needles: mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 7.9 Hz, 1 H), 7.33 (t, J = 8.2 Hz, 1 H), 7.32 (d, J = 15.6 Hz, 1 H), 7.17 (s, 1 H), 7.12 (d, J = 8.4 Hz, 1 H), 6.77 (dd, J = 15.6, 7.9 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 157.1, 154.1, 150.6, 137.9, 128.2, 127.7, 119.1, 110.8, 104.5, 103.5, 55.6; IR (KBr) 1688 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}O_3$ (M + H) 203.0703, found 203.0701.

Product 2s and 2s′. The general procedure was applied to 40.6 mg of **1a** (as monohydrate), 89.5 mg of **3e**, and 77 mg of CsF to afford 11.3 mg of **2s** as a brown oil and 12.8 mg of **2s′** as a yellow oil.

Data for 2s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 9.7, 5.5 Hz, 1 H), 7.34–7.27 (m, 5 H), 6.65 (d, J = 1.8 Hz, 1 H), 6.32 (d, J = 1.9 Hz, 1 H), 5.53 (dd, J = 9.6, 1.4 Hz, 1 H), 4.54 (d, J = 5.5 Hz, 1 H), 4.34 (s, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.75 and 3.69 (ABq, J = 13.0 Hz, 2 H), an impurity shows up at 3.74; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 161.1, 155.9, 152.0, 141.6, 137.4, 129.0, 128.5, 127.4, 125.3, 122.8, 103.3, 97.9, 77.4, 62.0, 56.4, 55.7, 55.4; IR (KBr) 1689, 1603, 1435, 1206 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ (M + H) 322.1438, found 322.1442.

Data for 2s′. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5 H), 7.23 (dd, J = 9.7, 5.6 Hz, 1 H), 6.53 (d, J = 1.8 Hz, 1 H), 6.30 (d, J = 1.9 Hz, 1 H), 5.57 (dd, J = 9.7, 1.5 Hz, 1 H), 4.55 (s, 1 H), 4.28 (d, J = 5.6 Hz, 1 H), 3.81 (s, 6 H), 3.76 and 3.66 (ABq, J = 13.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 161.6, 158.6, 150.2, 149.4, 137.5, 129.0, 128.5, 127.4, 123.7, 115.9, 101.9, 97.0, 73.6, 65.0, 56.3, 55.7, 55.6; IR (KBr) 1686, 1602, 1261, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ (M + H) 322.1438, found 322.1440.

Product 4b. (5.1 mg) was obtained as a side-product from the above reaction as a green solid, mp 143–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, J = 7.9 Hz, 1 H), 7.26 (d, J = 15.5 Hz, 1 H), 7.09 (s, 1 H), 6.68 (dd, J = 15.5, 7.9 Hz, 1 H), 6.62 (dd, J = 1.7, 0.8 Hz, 1 H), 6.30 (d, J = 1.8 Hz, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 161.8, 158.1, 154.3, 149.9, 137.9, 126.3, 113.3, 111.4, 94.9, 87.9, 55.8, 55.6; IR (KBr) 1663, 1501, 1262, 1111 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{15}O_4$ (M + H) 247.0925, found 247.0924.

Product 2t and 2t′. The general procedure was applied to 39 mg of **1g** (as monohydrate), 82 mg of **3d**, and 77 mg of CsF to afford 11.5 mg of **2t** as a brown solid and 8.4 mg of **2t′** as a yellow solid.

Data for 2t. mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 9.7, 4.9 Hz, 1 H), 7.13 (dd, J = 8.2, 7.3 Hz, 1 H), 7.04 (d, J = 7.2 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 5.56 (dd, J = 9.7, 1.5 Hz, 1 H), 4.93 (d, J = 4.9 Hz, 1 H), 4.65 (d, J = 1.4 Hz, 1 H), 3.83 (s, 3 H), 2.74–2.59 (m, 1 H), 2.06–1.91 (m, 1 H), 1.91–1.68 (m, 3 H), 1.66–1.55 (m, 1 H), 1.33–1.07 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 153.8, 147.7, 141.3, 134.0, 128.6, 123.8, 117.3, 110.4, 73.4, 57.7, 55.4, 55.1, 31.3, 30.8, 25.8, 24.7, 24.6; IR (KBr) 1695, 1483, 1277 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_2$ (M + H) 284.1645, found 284.1640.

Data for 2t′. mp 71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.3, 7.3 Hz, 1 H), 7.09 (dd, J = 9.8, 5.0 Hz, 1 H), 6.92 (d, J = 7.2 Hz, 1 H), 6.71 (d, J = 8.2 Hz, 1 H), 5.57 (dd, J = 9.7, 1.5 Hz, 1 H), 4.85 (d, J = 1.5 Hz, 1 H), 4.72 (d, J = 5.0 Hz, 1 H), 3.83 (s, 3 H), 2.73–2.61 (m, 1 H), 2.07–1.96 (m, 1 H) 1.90–1.71 (m, 3 H), 1.66–1.55 (m, 1 H), 1.33–1.09 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 156.7, 148.8,

147.0, 129.5, 125.5, 123.9, 114.5, 110.3, 69.8, 60.9, 55.6, 55.0, 31.3, 30.8, 25.8, 24.7, 24.6; IR (KBr): 1686, 1483, 1273 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_2$ (M + H) 284.1645, found 284.1640.

Product 2u and 2u′. The general procedure was applied to 33.8 mg of **1h** (as monohydrate), 82 mg of **3d**, and 77 mg of CsF to afford 10.1 mg of **2u** as a green solid and 11.4 mg of **2u′** as a green solid.

Data for 2u. mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 9.5, 5.9 Hz, 1 H), 7.11 (dd, J = 8.1, 7.3 Hz, 1 H), 7.01 (d, J = 7.2 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 5.40 (dd, J = 9.5, 1.2 Hz, 1 H), 4.97 (dd, J = 5.8, 0.8 Hz, 1 H), 4.77 (s, 1 H), 3.83 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 154.2, 153.7, 142.6, 135.1, 128.9, 122.3, 116.8, 110.2, 73.8, 58.9, 55.3, 54.5, 28.1; IR (KBr) 1685, 1479, 1265 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ (M + H) 258.1489, found 258.1485.

Data for 2u′. mp 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 9.5, 5.9 Hz, 1 H), 7.12 (dd, J = 8.1, 7.4 Hz, 1 H), 6.86 (d, J = 7.2 Hz, 1 H), 6.68 (d, J = 8.2 Hz, 1 H), 5.41 (d, J = 9.5 Hz, 1 H), 4.95 (s, 1 H), 4.77 (d, J = 6.0 Hz, 1 H), 3.83 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 156.6, 153.6, 150.3, 129.6, 126.4, 122.4, 113.8, 110.2, 70.2, 62.1, 55.6, 54.5, 28.1; IR (KBr) 1686, 1477, 1265 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ (M + H) 258.1489, found 258.1485.

Representative procedures for reactions of 3-amidopyridinium species with arynes (Table 4, outlined for compound 4c)

To a 10 mL round-bottom flask equipped with a stir bar was added **5a** (as an HBr salt, 83.6 mg, 0.2 mmol) followed by **3a** (75 mg, 0.25 mmol, 1.25 equiv). MeCN (5 mL) was added and the mixture was briefly stirred before addition of CsF (91 mg, 0.6 mmol). The mixture was stirred in a 50 °C bath for 18 h before being diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc) to afford 14.6 mg of **4c** as a brown glass; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, J = 7.9 Hz, 1 H), 8.33 (d, J = 15.9 Hz, 1 H), 8.23 (dd, J = 8.5, 0.7 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.41 (ddd, J = 8.5, 7.3, 1.3 Hz, 1 H), 7.31–7.27 (m, 1 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.10 (s, 1 H), 6.66 (dd, J = 15.9, 7.9 Hz, 1 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 145.4, 141.4, 138.5, 135.8, 134.8, 130.4, 129.9, 129.2, 126.9, 126.5, 124.6, 121.9, 115.4, 113.8, 21.6; IR (KBr) 1675, 1372, 1120 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}NO_3S$ (M + H) 326.0845, found 326.0849.

Characterization data for other products 4 (Table 4)

Product 4d. The general procedure was applied to 72.8 mg of **5c** (as an HBr salt) and 75 mg of **3a** to afford 11.2 mg of **4d** as a brown oil (contaminated by petroleum ether residue, ^{1}H NMR ratio 1 : 0.15 (product to PE, as dodecane), corresponding to 10.2 mg of pure **4d**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, J = 7.9 Hz, 1 H), 8.29 (d, J = 15.9 Hz, 1 H), 8.10 (dd, J = 8.5, 0.7 Hz, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 7.38 (ddd, J = 8.5, 6.6, 1.0 Hz, 1 H), 7.30–7.23 (m, 1 H), 7.10 (s, 1 H), 6.68 (dd, J = 15.9, 7.9 Hz, 1 H), 1.73 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 150.3, 143.8, 137.8, 135.8, 129.3, 128.6, 126.3, 123.6, 121.6, 116.0, 111.8, 85.3, 28.2; IR (KBr) 1732, 1681, 1370, 1328 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO_3$ (M + H) 286.1438, found 286.1443.

Product 4e. The general procedure was applied to 83.6 mg of **5a** (as an HBr salt) and 82 mg of **3d** to afford 13.8 mg of **4e** as an orange solid: mp 199–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, J = 7.9 Hz, 1 H), 8.31 (dd, J = 15.8, 0.6 Hz, 1 H), 7.81 (d, J = 8.5 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 2 H), 7.32 (dd, J = 14.8, 6.4 Hz, 1 H), 7.24 (s, 1 H), 7.17 (d, J = 8.0 Hz, 2 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.65 (dd, J = 16.0, 7.9 Hz, 1 H), 3.90 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 153.5, 145.4, 141.5, 139.7, 134.8, 134.4, 129.9, 129.8, 128.1, 126.5, 120.2, 111.2, 108.0, 104.3, 55.5, 21.6; IR (KBr) 1680, 1372, 1106 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_4S$ (M + H) 356.0951, found 356.0955.

Manipulations of 2a

Compound 6. A mixture of **2a** (51.6 mg, 0.2 mmol), formaldehyde (36 wt% in water, 30 μL, 0.4 mmol), and DMAP (~2.5 mg, 0.02 mmol), in 1 mL of THF was stirred for 20 h at room temperature. After being acidified by dropwise addition of 1.5 M HCl, the reaction mixture was extracted with DCM, and the combined extracts were washed successively with $NaHCO_3$ and brine before being dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether–EtOAc) to afford 34.8 mg of **6** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.44 (m, 1 H), 7.35–7.27 (m, 6 H), 7.23–7.17 (m, 3 H), 4.45 (d, J = 5.9 Hz, 1 H), 4.40 (s, 1 H), 4.15 and 4.07 (d of ABq, J_{AB} = 14.2 Hz, ^3J = 1.2 Hz, 2 H), 3.69 (s, 2 H), 2.46–2.16 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 146.0, 145.8, 138.1, 137.1, 132.4, 129.1, 128.5, 127.8, 127.5, 127.2, 126.0, 123.2, 76.3, 64.8, 60.1, 56.2; IR (KBr) 3533–3167 (br), 1685, 1456, 727 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ (M + H) 292.1332, found 292.1330.

Compound 7. To a solution of **2a** (52.1 mg, 0.2 mmol) in 0.5 mL of Et_2O was added ethyl diazoacetate (42 μL, 0.4 mmol, caution!), and the solution was stirred at room temperature for 3 days. The excess ethyl diazoacetate was destroyed by addition of HOAc. The mixture was diluted with EtOAc and water. Layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc) to afford 51 mg of **7** as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 6.9 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.36–7.19 (m, 9 H), 6.75 (s, 1 H), 4.89 (d, J = 1.6 Hz, 1 H), 4.27 (s, 1 H), 4.14–4.04 (m, 2 H), 3.84 (d, J = 11.1 Hz, 1 H), 3.67 and 3.60 (ABq, J = 13.0 Hz, 2 H), 3.57 (dd, J = 11.1, 1.9 Hz, 2 H), 1.28 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 161.8, 144.1, 137.6, 137.0, 129.4, 128.8, 128.5

(overlap), 128.4, 127.4, 124.8, 123.8, 73.7, 63.7, 63.4, 61.0, 57.0, 51.7, 14.0; IR (KBr) 1729, 1692, 1112 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}N_3O_3$ (M + H) 376.1656, found 376.1660.

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