Organic LETTERS

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Intramolecular C_{sp^2}–C_{sp^2} Friedel–Crafts Arylation: Substrate- and Condition-Controlled Divergent Synthesis of Fused-β-carbolines

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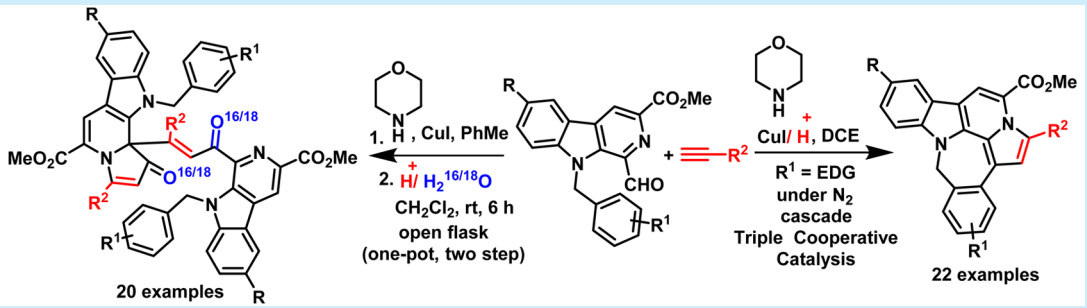
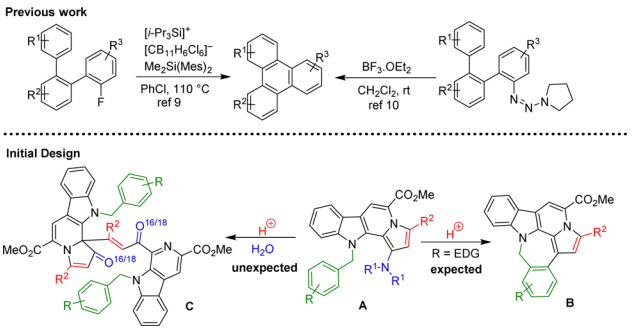
Supporting Information



ABSTRACT: A triple cooperative catalysis-mediated multicomponent reaction between 1-formyl-*N*-substituted-β-carbolines, a terminal alkyne, and a secondary amine allows access to unprecedented polycyclic β-carbolines via sequential A^3-coupling and an intramolecular C_{sp^2}–C_{sp^2} Friedel–Crafts arylation reaction. The reaction is successful in a dry inert atmosphere only with substrates bearing a methoxy-substituted benzyl group at the indole nitrogen. Conversely, treating 3-aminoindolizino[8,7-*b*]indoles (obtained after A^3-coupling) with acid in the presence of H_2O in air offers a general route to natural-alkaloid-like products.

The ubiquity of the β-carboline core in alkaloids and compounds of pharmacological interest provides impetus to develop architectural complexity around it.[1] Strategically, the complexity can be articulated either by placing suitable functional moieties in the indole unit followed by intramolecular cyclization of the resulting intermediates with appropriate reagents or by synthetically decorating the β-carboline-based starting material.[2,3] In one of our research programs, we have been pursuing the latter approach, wherein we employed 1-formyl-9*H*-β-carboline as the advanced intermediate[4] for developing general routes to access annulated β-carbolines which may find utility as anticancer or antiparasitic agents. In this context, recently we reported the synthesis of 2-substituted-2,11-dihydroimidazo[1′,5′:1,2]pyrido-[3,4-*b*]indoles showing antiproliferative and antimetastatic activity against human breast cancer cells and triple cooperative catalysis-mediated enantioselective synthesis of *S*-(−)-5,6-dihydrocanthin-4-ones having moderate antiplasmodial activity.[5,6] Earlier we reported the synthesis of several natural product mimics[7] including Maxonine-like analogues which were prepared via an intramolecular Friedel–Crafts (FC) alkylation involving a C_{sp^2}–C_{sp^3} bond formation from *N*-benzyl protected Morita–Baylis–Hillman adducts of 1-formyl-9*H*-β-carboline.[8] With this background and in continuation of our efforts to prepare fused-β-carboline systems, we envisaged that the A^3-coupling of substituted 1-formyl-9*H*-β-carboline bearing the *N*-benzyl moiety having a phenyl ring with an electron-donating group(s) and a terminal alkyne would furnish 3-aminoindolizino[8,7-*b*]indole (A), which in the presence of a suitable Lewis acid may lose the secondary amine to offer the aromatic carbocation that would undergo intramolecular FC-arylation via C_{sp^2}–C_{sp^2} bond formation to furnish the unprecedented polycyclic β-carboline (B) (Scheme 1). It may be noted that the FC-arylation involving C_{sp^2}–C_{sp^2} bond formation is scarcely reported perhaps due to the instability of the arene carbocation. Siegal et al. activated

Scheme 1. Comparison with known C_{sp^2}–C_{sp^2} Friedel–Crafts Arylation



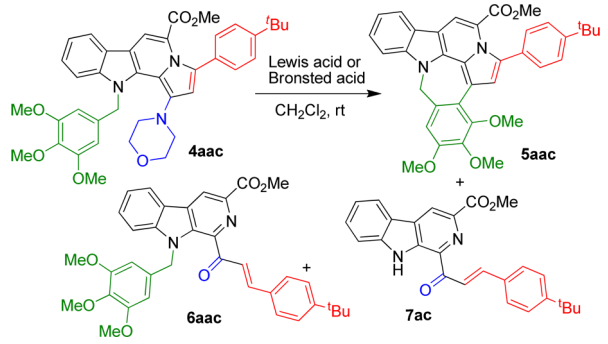
Received: September 16, 2016

DOI: 10.1021/acs.orglett.6b02794
Org. Lett. XXXX, XXX, XXX–XXX

fluoroarenes via silyl cations for the intramolecular FC-reaction leading to arene−arene coupling.[9] Ren et al. used aryltriazene as an aryl cation precursor for achieving intramolecular FC-arylation to prepare polycyclic aromatics.[10] Working toward the envisaged strategy, we have successfully developed a triple cooperative catalysis mediated cascade protocol wherein the polycyclic *β*-carboline scaffold **B** is readily prepared from 1-formyl-9-(substituted benzyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate and a terminal alkyne. Interestingly, we discovered that the phenyl group of the *N*-benzyl unit bearing a methoxy group(s) in the phenyl ring follows the protocol under dry inert conditions. However, if the reaction is performed in two steps, i.e., initial formation of 3-aminoindolizino[8,7-*b*]indole followed by treatment with acid in the presence of water in air, it results in unexpected product **C** containing two *β*-carboline units. Herein, we disclose the details of the results of this interesting substrate- and condition-controlled divergent synthesis of new *β*-carboline derivatives.

To test the success of our design, in the first phase we prepared a suitable starting material **4aac** starting from the aldehyde **1a** following the reported strategy (see Supporting Information (SI) for details).[11] Next to induce intramolecular C_{sp^2}−C_{sp^2} FC-arylation, **4aac** was treated with $BF_3{\cdot}Et_2O$ for 12 h in dichoromethane as reported,[10] but the reaction was unsuccessful. Hence we were invoked to assess the reaction in the presence of different Lewis and Bronsted acids (Table 1 in the SI). The reaction was completed in 12 h in the presence of $Sc(OTf)_3$, $Bi(OTf)_3$, and $In(OTf)_3$ to afford the chalcone **6aac** instead of the anticipated **5aac** but failed with $AlCl_3$ or $FeCl_3$ (Scheme 2).

Scheme 2. Synthesis of polycyclic *β*-carboline via intramolecular C_{sp^2}−C_{sp^2} Friedel−Crafts Arylation

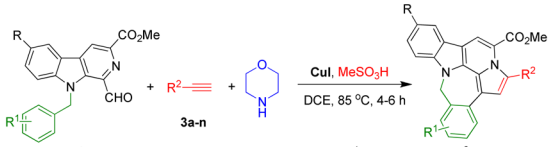


Subsequently, Bronsted acids were investigated for their effectiveness in the transformation. Whereas pTSA produced the chalcone **6aac**, HCl and AcOH were inert in the reaction. Formation of **6aac** may be attributed to preferential attack of the hydroxy group onto the generated arene carbocation rather than intramolecular FC-arylation (vide infra). The reaction in TFA completed within 1 h to offer two products which were isolated and spectroscopically characterized. We were delighted to discover that the major product (35%) was established as **5aac** while the minor product (16%) was the chalcone **7ac**. Altering TFA with trifluoromethanesulfonic acid (TFMS) though completed the reaction in 2 h, increasing the yield of **5aac** to 52% together with a minor amount (12%) of **7ac**. The reaction with methanesulfonic acid (MSA) pleasingly improved the yield of **5aac** to 62% without any trace of **7ac** in 3 h. Enhancing the loading of MSA from 1.0 to 1.5 equiv furnished **5aac** in 86% yield, but further loading of MSA was found to be detrimental for reaction. During the process we also evaluated substrates carrying pyrrolidine or piperazine in place of morpholine, but in both cases yields of the product were inferior (see SI). Thus, the conditions best suited for intramolecular C_{sp^2}−C_{sp^2} FC-arylation included treating substrate **4aac** (1.0 equiv) with MSA (1.5 equiv) in dichloromethane at rt for 3 h.

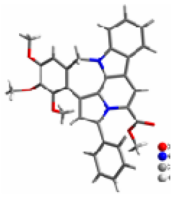
The successful synthesis of 5,6-dihydrocanthin-4-ones via triple cooperative catalysis provided impetus to test the cooperativity of the catalyst system for synthesizing polycyclic *β*-carboline starting from the *N*-protected aldehyde. Therefore, in a pilot experiment the aldehyde **2aa** (1.0 equiv) was treated with **3c** (1.1 equiv) in the presence of CuI (10 mol %), morpholine (35 mol %), and MSA (1.5 equiv) in toluene at 85 °C to furnish the product in 72% yield which was identical to **5aac**. In order to improve the yield of **5aac**, an optimization study was undertaken where an improved yield (82%) of **5aac** was observed when the reaction is performed in the presence of CuI using DCE as the medium (Table 2 in the SI). Other catalysts though successful afforded product in inferior yields. Thus, the best conditions for the synthesis of the polycyclic *β*-carboline via triple cooperative catalysis were **2aa** (1.0 equiv), **3a** (1.1 equiv), morpholine (35 mol %), CuI (10 mol %), and MSA (1.5 equiv) in DCE at 85 °C for 4 h.

With the optimized conditions in hand, the scope of the protocol was tested for its generality with respect to alkynes (**3**) and *N*-protected aldehydes (**2**). Initially, the scope was examined by reacting the aldehyde **2aa** with different alkynes **3**. In the first set of reactions the aromatic alkynes (**3a**−**n**) were treated with **2aa** under the optimized conditions. It was discovered that except for the alkyne **3i** and **3n** all substrates afforded the corresponding products (**5aaa**−**5aah**, **5aaj**−**5aam**) in 64−84% yields (Scheme 3). It was observed that the electronic character of the

Scheme 3. Scope of the Triple Cooperative Catalysis Mediated Synthesis of Polycyclic *β*-Carbolines[a]



2aa R = H, R^1 = 3,4,5-$(OMe)_3$
2ab R = H, R^1 = 3,4-$(OMe)_2$
2ac R = H, R^1 = 3,5-$(OMe)_2$
2ad R = H, R^1 = 3-OMe
2ba R = Cl, R^1 = 3,4,5-$(OMe)_3$



X-ray crystal structure of **5aaa**

5aaa R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = Ph (72%)
5aab R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-Me-C_6H_4 (78%)
5aac R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-^{t}Bu-C_6H_4 (82%)
5aad R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-^{n}Bu-C_6H_4 (69%)
5aae R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-F-C_6H_4 (82%)
5aaf R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-Br-C_6H_4 (79%)
5aag R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-OMe-C_6H_4-C_6H_4 (82%)
5aah R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-OPh-C_6H_4 (64%)
5aai R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 4-NMe_2-C_6H_4 (0%)
5aaj R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 3-Me-C_6H_4 (72%)
5aak R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 3-F-C_6H_4 (74%)
5aal R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 3,5-F_2-C_6H_3 (76%)
5aam R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 2,4,5-Me_3-C_6H_2 (84%)
5aan R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = 6-OMe-naphth-2-yl (0%)
5aao R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = cyclopropyl (42%)
5aap R = H, R^1 = 3,4,5-$(OMe)_3$, R^2 = CO_2Me (66%)
5aba R = H, R^1 = 3,4-$(OMe)_2$, R^2 = Ph (72%)
5aca R = H, R^1 = 3,5-$(OMe)_2$, R^2 = Ph (92%)
5acc R = H, R^1 = 3,5-$(OMe)_2$, R^2 = 4-^{t}Bu-C_6H_4 (90%)
5ada R = H, R^1 = 3-OMe, R^2 = Ph (86%)
5baa R = Cl, R^1 = 3,4,5-$(OMe)_3$, R^2 = Ph (75%)

[a]All reactions were performed using 0.2 g of **2**. Isolated yields after column chromatography. X-ray structure of **5aaa** at 35% probability level

substituents on the phenyl ring did not impact the output, but reactions of the substrates bearing phenyl ring with multiple substituents required 6 h for completion. The terminal alkyne **3i** with the phenyl ring bearing the *N*,*N*-dimethyl group afforded only the corresponding chalcone **7ai** whereas **2aa** reacted with 2-ethynyl-6-methoxynaphthalene (**3n**) to yield **1a** instead of **5aan**. The X-ray diffraction analysis of a single crystal of **5aaa** confirmed

DOI: 10.1021/acs.orglett.6b02794
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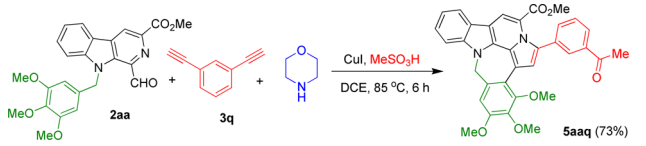
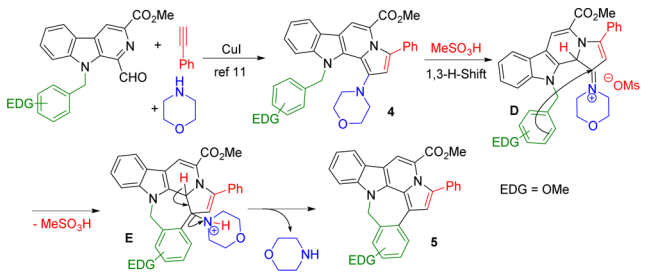
the assigned structure. Next, reactions of aliphatic terminal alkynes **3o–p** with **2aa** were examined, and though successful, the corresponding products (**5aao–5aap**) were isolated only in moderate yields together with several unidentifiable products. Subsequently, the reaction was attempted with different aldehydes bearing a methoxy-substituted *N*-benzyl group (**2ab**, **2ac**, and **2ad**) which were reacted with **3a** and **3c** to smoothly obtain **5aba**, **5aca**, **5acc**, and **5ada** in excellent yields. To enhance the scope, we conducted the reaction of **2ba** with **3a** to obtain the product **5baa** in 75% yield. Similarly, use of 1,3-diethynylbenzene (**3q**) resulted in the formation of the product **5aaq** inferring that only one alkyne group participated in the reaction while the other alkyne group was transformed to the acetyl group (Scheme 4). It may be noted that very recently Li et al. have disclosed acid-promoted conversion of terminal alkynes to acetophenones in HFIP but their protocol failed in DCE.[12]

Scheme 4. Scope of Reaction with 1,3-Diethynylbenzene (3q)



Based on our previous work,[11] a plausible mechanism for the synthesis of **5** is outlined in Scheme 5. Initially, the aldehyde **2**

Scheme 5. Plausible Mechanism for the Formation of 5

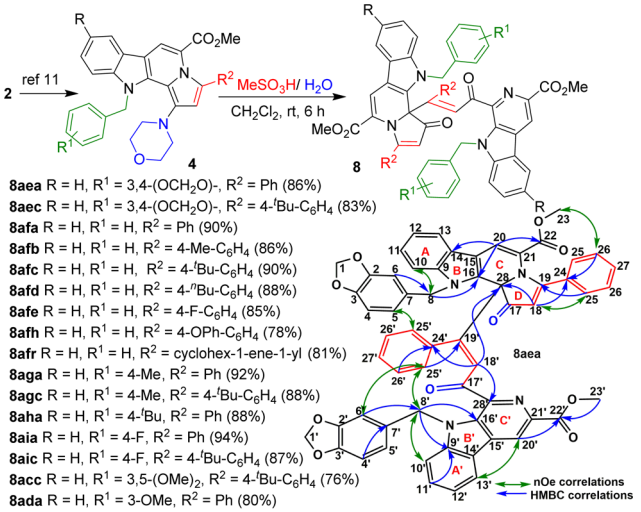


reacts with morpholine and **3** in the presence of CuI to form **4**. Successively, acid protonates the nitrogen of the morpholine followed by a 1,3-H-shift to offer the intermediate imine **D**, which then undergoes intramolecular C_{sp^2}–C_{sp^2} FC-reaction to produce **E** which loses morpholine to furnish **5**.

Next we assessed the reaction of aldehyde **2ae** wherein the indole nitrogen carried a (3,4-methylenedioxyphenyl)methyl group. Treating **2ae** with alkyne **3a** under the optimized conditions resulted in a complex mixture from which the major product was only in 18% isolated yield. Based on detailed spectroscopic analysis the structure was established as **8aea** bearing *E* stereochemistry (refer to SI). Since a single crystal for the compound could not be obtained, molecular dynamics for the energy minimized structure of **8aea** was assessed to arrive at the assigned structure. Efforts to induce FC-arylation in **4aea** under different conditions were unsuccessful.

Nonetheless, close analogy of one unit of **8aea** with fascaplysin prompted us to optimize conditions for improving its yield. After initial assessment, we discovered that performing the reaction in two steps improves the yield of **8aea** to 48%. Under the process, the initial formation of **4aea** in toluene is followed by removal of solvent and treatment of the residue with MSA in dichloromethane in the same pot. Mechanistically the formation of **8aea** is suggested to involve a hydrolysis step (vide infra), and therefore, we added water which to our satisfaction improved the yield of **8aea** (86%). An identical reaction of **4aec** with MSA resulted in the formation of **8aec** (Scheme 6).

Scheme 6. Scope for the Acid-Mediated Synthesis of 8[a]



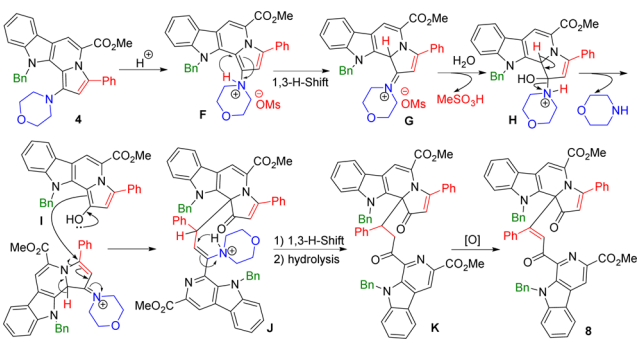
8aea R = H, R^1 = 3,4-(OCH_2O)-, R^2 = Ph (86%)
8aec R = H, R^1 = 3,4-(OCH_2O)-, R^2 = 4-^{t}Bu-C_6H_4 (83%)
8afa R = H, R^1 = H, R^2 = Ph (90%)
8afb R = H, R^1 = H, R^2 = 4-Me-C_6H_4 (86%)
8afc R = H, R^1 = H, R^2 = 4-^{t}Bu-C_6H_4 (90%)
8afd R = H, R^1 = H, R^2 = 4-^{n}Bu-C_6H_4 (88%)
8afe R = H, R^1 = H, R^2 = 4-F-C_6H_4 (85%)
8afh R = H, R^1 = H, R^2 = 4-OPh-C_6H_4 (78%)
8afr R = H, R^1 = H, R^2 = cyclohex-1-ene-1-yl (81%)
8aga R = H, R^1 = 4-Me, R^2 = Ph (92%)
8agc R = H, R^1 = 4-Me, R^2 = 4-^{t}Bu-C_6H_4 (88%)
8aha R = H, R^1 = 4-^{t}Bu, R^2 = Ph (88%)
8aia R = H, R^1 = 4-F, R^2 = Ph (94%)
8aic R = H, R^1 = 4-F, R^2 = 4-^{t}Bu-C_6H_4 (87%)
8acc R = H, R^1 = 3,5-$(OMe)_2$, R^2 = 4-^{t}Bu-C_6H_4 (76%)
8ada R = H, R^1 = 3-OMe, R^2 = Ph (80%)
8aja R = H, R^1 = 3-Me, R^2 = Ph (84%)
8bfa R = Cl, R^1 = H, R^2 = Ph (85%)
8bfc R = Cl, R^1 = H, R^2 = 4-^{t}Bu-C_6H_4 (86%)
8bfe R = Cl, R^1 = H, R^2 = 4-F-C_6H_4 (89%)

[a]All reactions were performed using 0.2 g of **4**. The yields are the isolated yield after column chromatography.

Buoyed by the success of the protocol we considered evaluating its scope with substrates (**4**) bearing different substituted benzyl groups. As mentioned above, products **4** were not isolated but reacted further with MSA in dichloromethane as medium in the same pot. Accordingly, in the first set, **4afa–4afe**, **4afh**, and **4ahl** were treated with MSA in the presence of water for 6 h resulting in respective products **8afa–8afe**, **8afh**, and **8afl** in excellent yields. Next, substrates **4aga**, **4agc**, **4aha**, **4aia**, and **4aic** were reacted with MSA under the standardized conditions to obtain **8aga**, **8agc**, **8aha**, **8aia**, and **8aic** in 83–94% yields. Subsequently, reactions of **4acc**, **4ada**, and **4aja** were conducted, and they too complied affording **8acc**, **8ada**, and **8aja**, respectively. Finally, to broaden the substrate scope **4bfa**, **4bfc**, and **4bfe** prepared from 6-chloro-*β*-carboline aldehyde **1b** were investigated, and they too followed the protocol to efficiently afford **8bfa**, **8bfc**, and **8bfe**.

To explain the formation of the observed products a plausible mechanism is proposed in Scheme 7. Initially, in the presence of

Scheme 7. Plausible Mechanism for the Formation of 8



DOI: 10.1021/acs.orglett.6b02794
Org. Lett. XXXX, XXX, XXX–XXX

acid, **4** undergoes protonation to form intermediate **F** which is transformed into **G** via a 1,3-H-shift. Subsequent nucleophilic attack of water onto **G** yields the hydroxyl intermediate **I**, which reacts with **G** to produce intermediate **J** via a concerted mechanism. A second 1,3-H-shift followed by hydrolysis transforms **J** to the intermediate **K**, which undergoes oxidation leading to product **8**. In order to provide support for the proposed mechanism a few potential control experiments were performed. To ascertain the oxidation of the intermediate **H**, a control experiment was conducted under an inert atmosphere, and as expected the yield of **8afa** dropped to 32% only. To unequivocally provide evidence that water is the source of oxygen, compound **8afa** was treated with MSA in dry methylene chloride in the presence of $H_2{}^{18}O$ (97%). On completion the reaction mixture was directly subjected to mass spectral analysis which displayed the presence of a mixture of ^{16}O (891 amu) and ^{18}O (895 amu) **8afa**. We have previously reported that the reaction of pyridine-2-aldehyde with terminal alkyne in the presence of secondary amine furnishes the substituted indolizine.[11] As a result, in another control experiment, we treated pyridine-2-carbaldehyde with **3aa** in the presence of CuI, morpholine, and MSA which resulted in the formation of chalcone **9ac** (see SI for details).

In summary, we have developed a triple cooperative catalysis-mediated cascade approach for the synthesis of unprecedented polycyclic β-carbolines via an intramolecular $C_{sp^2}-C_{sp^2}$ FC-arylation. The success of the protocol relies on the presence of electron-donating substituents (methoxy) on the phenyl ring of the *N*-benzyl group and inert conditions. Mechanistically, the protonation of tertiary amine followed by a 1,3-H-shift offers an imine intermediate which undergoes nucleophilic attack of the $C_{sp^2}-H$ of the electron-rich arene system in a highly concerted manner to produce polycyclic β-carboline. Conversely in the presence of water in air the imine intermediate undergoes nucleophilic attack by the water to yield a hydroxyl intermediate that reacts with the imine intermediate in situ resulting in the formation of an unusual β-carboline system via sequential 1,3-H-shift, hydrolysis, and oxidation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02794.

Experimental details, spectroscopic data, X-ray analysis data of **5aaa**, and copies of ^1H and ^{13}C NMR data (PDF)
Crystallographic data for **5aaa** (CIF)

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Author Contributions

⊥S.U.D. and V.D.Y. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.U.D., V.Y., and R.M. gratefully acknowledge financial support from CSIR, New Delhi in the form of fellowships. The SAIF Division of CDRI is acknowledged for providing spectroscopic data. Prof. Sandeep Verma and his student Mr. B. Mohapatra, IIT Kanpur are acknowledged for carrying out the X-ray diffraction analysis of **5aaa**. The work was carried out via partial funding to S.B. from DST, New Delhi and Ministry of Earth Sciences, New Delhi.

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DOI: 10.1021/acs.orglett.6b02794
Org. Lett. XXXX, XXX, XXX−XXX