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Electrochemical Total Synthesis of Pyrrolophenanthridone Alkaloids: Controlling the Anodically Initiated Electron Transfer Process

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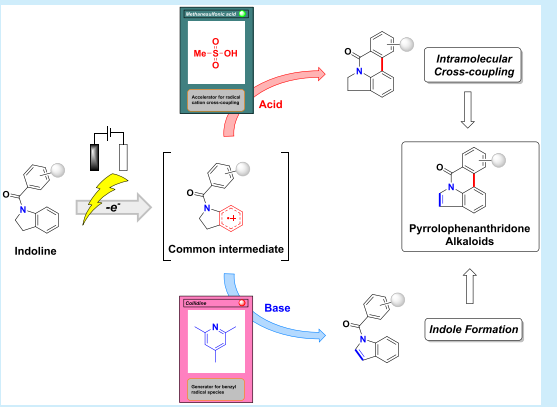
ABSTRACT: Electrochemical intramolecular C(sp^2)−H cross-coupling and dehydrogenative indole synthesis were developed. Both reactions were initiated by anodic oxidation of the same electron-rich indoline moiety, but the product selectivity was controlled by different electron-transfer processes. Intramolecular cross-coupling was achieved by the generation of a strong electrophilic radical cation intermediate in the $MeNO_2$−HFIP−$LiClO_4$ system. Indole formation was accomplished through benzylic oxidation and continuous deprotonation. We applied these reactions to the total synthesis of natural pyrrolophenanthridone alkaloids.



Aryl-aryl cross-coupling is a common strategy in total synthesis and drug discovery.[1a] In the field of medicinal chemistry, palladium-mediated cross-coupling is the most frequently used.[1b] However, Pd catalysts are expensive and cytotoxic; hence, alternative methods are required. An electrochemical method would be a green and clean way to prepare bioactive compounds, because it can generate unique reactive intermediates without any oxidants or reductants.[2] Most electrochemical aryl cross-coupling reactions are "intermolecular" coupling reactions (Figure 1A), because the large oxidation potential (E_{ox}) gap often causes undesired overoxidation or polymerization.[3] Homocoupling reactions are easily handled by electrochemical methods, because of the E_{ox} equivalence. To overcome the E_{ox} difference, a radical cation pool method was developed under cryogenic conditions.

We featured an "intra-molecular" cross-coupling reaction as a key synthetic strategy for naturally occurring alkaloids. Pyrrolophenanthridone alkaloids, isolated from *Amaryllidaceae*, have a heteropolycyclic skeleton containing indole and *N*-benzoyl moieties. Because of this simple fused structure, many researchers have targeted these molecules to demonstrate various synthetic reactions (Figure 1B).[4] For instance, Black and co-workers reported the first total synthesis of hippadine by stoichiometric Pd-mediated intramolecular cross-coupling and continuous 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of an indoline ring. Boger and co-workers accomplished the synthesis of hippadine by a pyridazine-promoted inverse electron-demand Diels−Alder reaction (IEDDA). Kerr and co-workers synthesized hippadine and pratosine by using hypervalent iodine-mediated oxidative intramolecular cross-coupling reaction and the same DDQ treatment. Under these conditions, undesired polymerization was caused by intermolecular reactions. In all cases, a stoichiometric coupling reagent or oxidant (DDQ) was necessary for both the cyclization and indole construction steps.

Another reason for the difficulty in electrochemical intramolecular cross-coupling reactions is the E_{ox} gap between the electron-rich indoline ring and the relatively electron-deficient benzoyl moiety (Figures 1B and 3). We demonstrated a metal-free synthesis of pyrrolophenanthridones by using anodic oxidation.

First, we screened additives in order to find appropriate conditions for the electrochemical cyclization reaction (Table 1). Interestingly, additive-dependent product selectivity was observed (Table 1, entries 1 and 2). An acid additive gave the desired cyclization (**1a**), but a base additive gave the indole product (**1b**). In the field of energy engineering, electrochemical dehydrogenative transformation of indoline to indole was known as the H_2 gas source.[5a] Herein, we demonstrated

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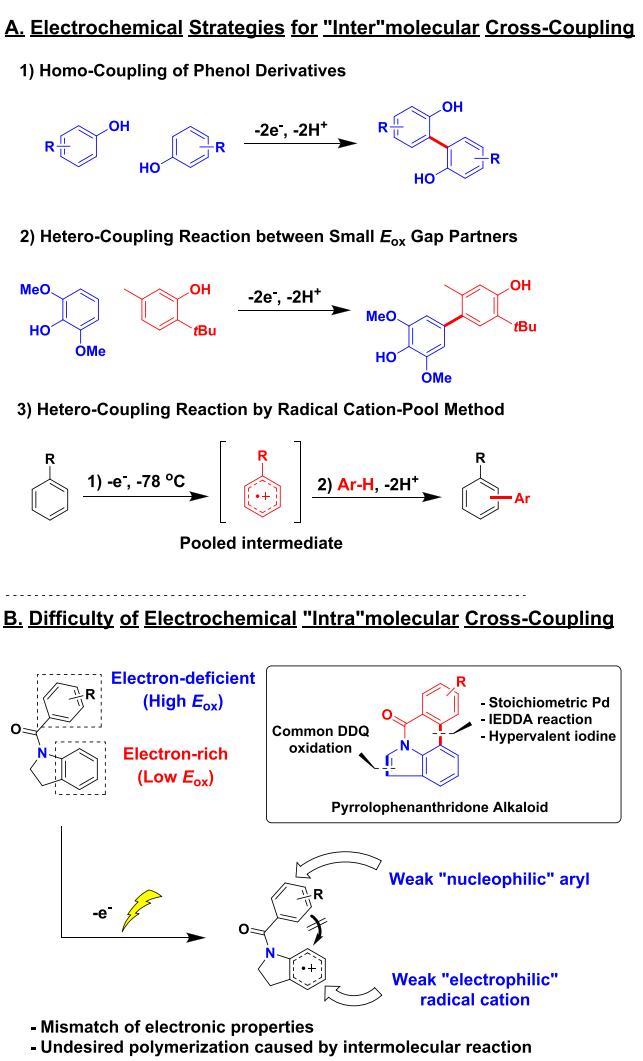
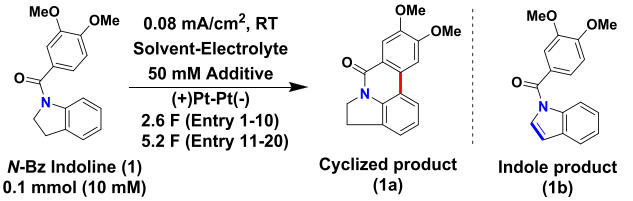


Figure 1. (A) Various approaches for electrochemical cross-coupling. (B) Difficulty of the intramolecular coupling reaction.

practical example of this reaction in organic synthesis. Furthermore, replacement of DDQ oxidation with a greener and cleaner way is a valuable task in indole synthesis;[5] thus, we optimized both reactions.

Next, we optimized the solvent−electrolyte system. In previous studies, we found the nitromethane−lithium perchlorate system was a suitable medium for radical cation-mediated reactions.[6a−c] Raman spectroscopy revealed that the radical cation species was stabilized by the low donor number of $MeNO_2$, and the Lewis acidic lithium cation increased the reactivity of the radical cation by trapping the counteranion species (the perchlorate anion, ClO_4^-) through solvent clustering formation.[6d] 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) was also employed for the oxidative coupling reaction for the same reason.[6e] However, these solvent systems were poorly effective for the cyclization reaction (Table 1, entries 3−5). Recently, we found that the reaction efficacy of electrochemical reactions was affected by an ionic interaction between the radical cation and counteranion species (Figure 2A).[6f] The electrophilicity of the radical cation was decreased by anionic species, such as ClO_4^- derived from $LiClO_4$. The anionic species was trapped by HFIP through strong hydrogen bonding, enhancing the reactivity of the radical cation. Thus, we tried a

Table 1. Additive Effect for Product Selectivity and Optimization for Anodic Cyclization and Indole Synthesis



entry	solvent	electrolyte (concentration)	additive	yield [%][a]
1	MeCN	Bu_4NClO_4 (0.01 M)	MsOH	8 (**1a**)
2	MeCN	Bu_4NClO_4 (0.01 M)	2,6-lutidine	30 (**1b**)
		Cross-Coupling Reaction		
3	$MeNO_2$	$LiClO_4$ (1.0 M)	MsOH	14 (**1a**)
4	HFIP	$LiClO_4$ (0.1 M)	MsOH	20 (**1a**)
5	HFIP	Bu_4NClO_4 (0.1 M)	MsOH	7 (**1a**)
6	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.1 M)	MsOH	65 (**1a**)
7[b]	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.1 M)	MsOH	46 (**1a**)
8[c]	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.1 M)	MsOH	56 (**1a**)
9	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.1 M)	TfOH	44 (**1a**)
10	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.1 M)	MsOH (100 mM)	82 (**1a**)
		Indole Synthesis		
11	TFE	Bu_4NClO_4 (0.01 M)	2,6-lutidine	N.D.
12	DMF	Bu_4NClO_4 (0.01 M)	2,6-lutidine	13 (**1b**)
13	MeCN	Bu_4NClO_4 (0.1 M)	2,6-lutidine	27 (**1b**)
14	MeCN	Bu_4NClO_4 (0.01 M)	Cs_2CO_3	trace (**1b**)
15	MeCN	Bu_4NClO_4 (0.01 M)	*t*-BuOK	N.D.
16[d]	MeCN	Bu_4NClO_4 (0.01 M)	piperidine	2 (**1b**)
17	MeCN	Bu_4NClO_4 (0.01 M)	collidine	50 (**1b**)
18	$MeNO_2$−HFIP (9:1)	$LiClO_4$ (0.01 M)	collidine	25 (**1b**)
19	MeCN	$NaClO_4$ (0.01 M)	collidine	16 (**1b**)
20[e]	MeCN	Bu_4NClO_4 (0.1 M)	collidine-MsOH (200 mM−100 mM)	61 (**1b**)

[a]Determined by ^1H NMR, using pentafluorobenzaldehyde as an internal standard. [b]GC anode was used instead of Pt. [c]Reaction was performed at 0 °C. [d]Polymer-supported piperidine (3−4 mmol/g) was used in a concentration of 1 M. [e]Constant potential (+1.6 V vs Ag) was used.

$MeNO_2$−HFIP mixed solvent, which improved the coupling yield as expected (Table 1, entry 6). Replacement of the Pt anode with glassy carbon (GC) did not improve the yield (Table 1, entry 7). This result indicated that the substrate accumulated on the sp^2 surface of the GC electrode, and an undesired polymerization reaction was promoted.[7] Low temperatures were also ineffective (Table 1, entry 8). Generally, temperature is an important factor for cyclization reactions. For example, it is known that the rotamer population of *N*-benzoyl indoline has a

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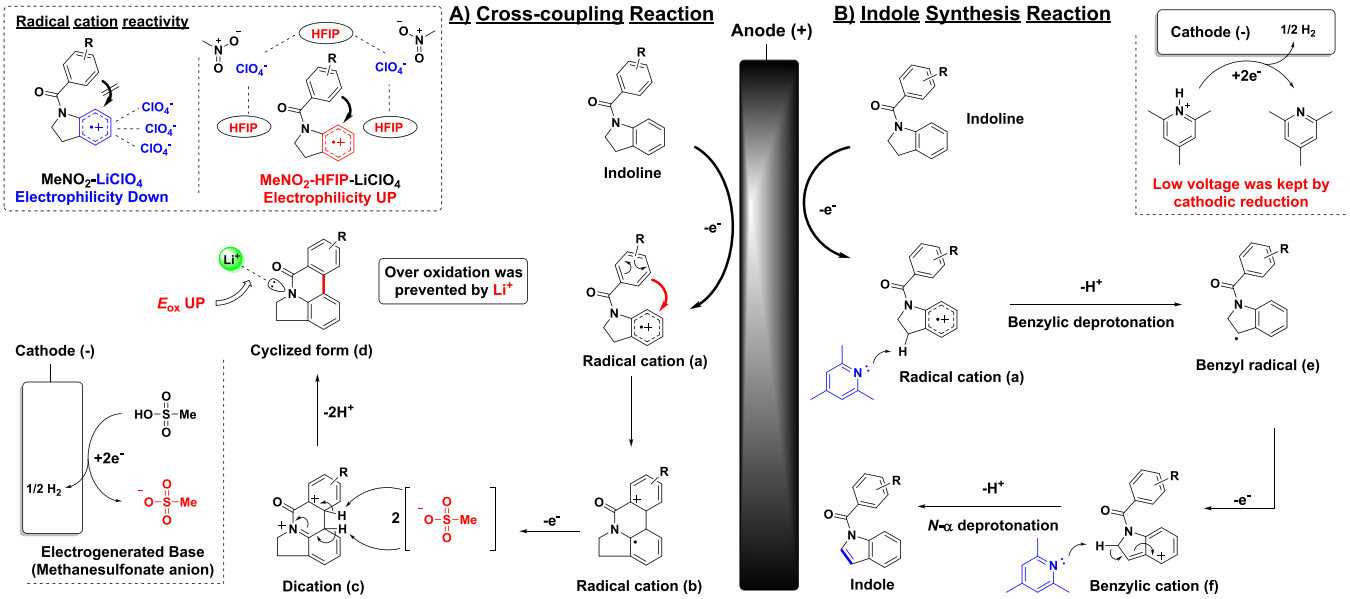

Figure 2. Plausible mechanism of (A) intramolecular cross-coupling and (B) indole synthesis.

tendency to favor the *trans*-conformer at low temperature.[8] For this reason, Pd-mediated intramolecular cross-coupling requires a high temperature (120 °C) to form the desired *cis*-conformer. Despite these rotamer problems, our electrochemical cyclization smoothly occurred at room temperature. Changing the MsOH additive to TfOH was also ineffective (Table 1, entry 9). We thought the cathodic-generated base (electrogenerated base, EGB) was important for deprotonation from the dication intermediate (Figure 2A). The acidity of TfOH ($pK_a = -14$) is stronger than that of MsOH ($pK_a = -2.6$), but the basicity of the corresponding anion (TfO^-) is weaker than that of MsO^-. Moderate basicity of EGB is probably needed for deprotonation. Note that AcOH ($pK_a = 4.76$) and trifluoroacetic acid ($pK_a = -0.25$) gave trace yields. This indicates that the reactivity of the radical cation could also be decreased by solvation with the corresponding anion, such as acetate. Methanesulfonate anion is suitable for the cross-coupling reaction, because of its weak, but sufficient, basicity. Finally, we determined that increasing the acid concentration was effective (Table 1, entry 10).

Next, the indole synthesis reaction was optimized (see Table 1). Trifluoroethanol (TFE) and dimethylformamide (DMF) were not suitable for this reaction (Table 1, entries 11 and 12), and increasing the electrolyte concentration was also ineffective (Table 1, entry 13). Inorganic and polymer-supported bases were not suitable (Table 1, entries 14−16). The MeCN−Bu_4NClO_4 system gave the best yield, while the $MeNO_2$−HFIP system and inorganic electrolytes did not work well (Table 1, entries 17−19). Under these conditions, high voltage (between +2.5 V and +6.0 V) and overoxidation of indole were observed. To solve this problem, we used a collidine-MsOH (2:1) mixture (Table 1, entry 20), and the yield was improved. Protonated collidine acted as a sacrificial reagent in the cathodic reduction, and low voltage (+1.6 V) was maintained throughout the electrochemical reaction.

We performed mechanistic studies on both reactions by means of cyclic voltammetry (see Figure 3, as well as Figures S1−S4 in the Supporting Information). The reduction waves of **1a** and **1c** were not observed, indicating that overoxidation and polymerization easily occurred on the electrode surface. The E_{ox} value of cyclized product **1a** was similar to that of substrate **1**, but

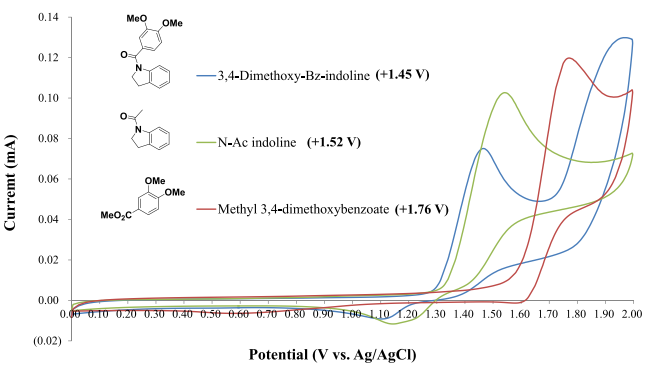

Figure 3. Cyclic voltammogram of **1** and its moieties (2 mM) in MeCN−Bu_4NClO_4 (0.05 M). Scan rate = 10 mV/s.

the yield of the intramolecular cross-coupling reaction was high. The basicity of the nitrogen lone pair was increased by structural strain-induced delocalization breakage of the sp^2 amide plane,[9] and it was indicated by the R_f value on TLC (see Figure S5 in the Supporting Information). This suggests that the interaction of the amide nitrogen of **1a** with the Lewis acid is stronger than that of **1**. The Lewis acidity of the Li cation derived from $LiClO_4$ is stronger than the tetrabutylammonium cation. A Lewis acidic lithium cation is an important factor to increase the E_{ox} value of the cyclized product and suppress undesired overoxidation. To support this hypothesis, the coupling yield is dramatically affected by supporting electrolytes (Table 1, entries 4 and 5). For indole synthesis, a neutral benzyl radical (**e**) is generated from radical cation (**a**) via base-mediated deprotonation (Figure 2B). Continuous anodic oxidation and a second deprotonation from the *N*-α position give the corresponding indole.

We applied these reactions to the total synthesis of pyrrolophenanthridone alkaloids (see Scheme 1). The simple pyrrolophenanthridones—oxoassoanine (**1a**), pratosine (**1c**), anhydrolycorinone (**2a**), and hippadine (**2b**)—were synthesized from the corresponding 3,4-dimethoxy or 3,4-methylenedioxybenzoyl indolines in one or two steps.

Pratorinine (**1d**) and pratorimine (**1e**) were isolated from the *Crinum* species.[10a,b] These compounds exhibit cytotoxic activity

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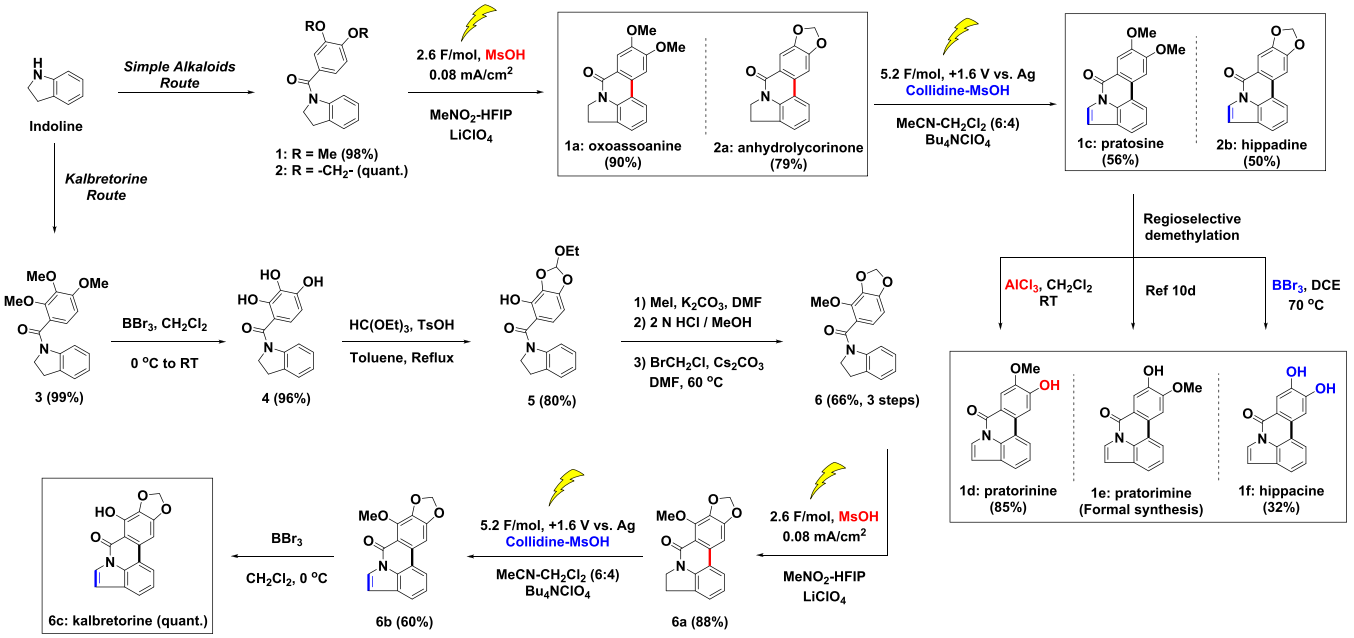
Scheme 1. Total Synthesis of a Series of Pyrrolophenanthridone Alkaloids



toward T-cell leukemia and sarcoma cell lines.[10e,f] (Please note that the authors of refs 10e and 10f confuse pratorinine with pratorimine.) Pelletier and co-workers revised the early suggested structures of these compounds and accomplished the synthesis of pratorimine via Pschorr cyclization.[10c,d] Since these compounds have phenolic OH groups at vanillyl or isovanillyl moieties, we first screened *O*-protecting groups to prevent anodic generation of reactive phenoxonium cation species (compounds **S1d** and **S1e**). When using benzyl (Bn) and acetyl (Ac) protection, these were easily decomposed under electrochemical conditions before cyclization. Unfortunately, electrochemical cyclization of nonprotected *N*-vanillyl indoline gave a poor yield. Finally, we tried regioselective demethylation of pratosine to synthesize the phenolic pyrrolophenanthridones. Treatment with $AlCl_3$ worked well for *para*-selective demethylation,[11] and the first synthesis of pratorinine was accomplished. Hippacine (**1f**)[10g] was also synthesized via BBr_3-mediated full demethylation for the first time.

Kalbretorine (**6c**) was isolated from *Haemanthus kalbreyeri*. It possesses antitumor activity toward mouse sarcoma cell line (S-180).[10h] We originally planned a formal total synthesis, followed by Miki group synthesis.[10i] However, detailed experimental procedures were not provided in their report, so we designed our own synthetic route to kalbretorine from 2,3,4-trimethoxybenzoyl indoline (**3**). After full demethylation of **3**, regioselective protection of the trihydroxy benzoyl group was accomplished by triethyl orthoformate. Note that direct methylenation failed because of low regioselectivity and difficulty of isomer separation. Subsequent *O*-methylation, deprotection, and methylene protection were smoothly achieved, and kalbretorine precursor **6** was prepared. Continuous anodic cyclization and indole formation gave *O*-methyl kalbretorine (**6b**). After final demethylation, the desired kalbretorine was synthesized in a total of nine steps from indoline.

In conclusion, we established metal-free electrochemical intramolecular cross-coupling reactions by using the $MeNO_2$–HFIP–$LiClO_4$ system as a strong enhancer for radical cation reactivity. A DDQ-free dehydrogenative anodic indole synthesis was also achieved through a different base-mediated reaction pathway. Seven naturally occurring alkaloids were synthesized via these reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01082.

General experimental procedure and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (b) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. Factors determining the selection of organic reactions by medicinal chemists and the use of these reactions in arrays (small focused libraries). *Angew. Chem., Int. Ed.* **2010**, *49*, 8082−8091.

(2) (a) Lipp, A.; Ferenc, D.; Gutz, C.; Geffe, M.; Vierengel, N.; Schollmeyer, D.; Schafer, H. J.; Waldvogel, S. R.; Opatz, T. A Regio- and Diastereoselective Anodic Aryl-Aryl Coupling in the Biomimetic Total Synthesis of (−)-Thebaine. *Angew. Chem., Int. Ed.* **2018**, *57*, 11055−11059. (b) Nakamura, H.; Yasui, K.; Kanda, Y.; Baran, P. S. 11-Step Total Synthesis of Teleocidins B-1−B-4. *J. Am. Chem. Soc.* **2019**, *141*, 1494−1497. (c) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. Total Synthesis of Dixiamycin B by Electrochemical Oxidation. *J. Am. Chem. Soc.* **2014**, *136*, 5571−5574. (d) Mihelcic, J.; Moeller, K. D. Anodic Cyclization Reactions: The Total Synthesis of Alliacol A. *J. Am. Chem. Soc.* **2003**, *125*, 36−37. (e) Sumi, T.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. Anodic Oxidation on a Boron-Doped Diamond Electrode Mediated by Methoxy Radicals. *Angew. Chem., Int. Ed.* **2012**, *51*, 5443−5446. (f) Chiba, K.; Arakawa, T.; Tada, M. Synthesis of euglobal-G3 and -G4. *Chem. Commun.* **1996**, *15*, 1763−1764.

(3) (a) Atobe, M.; Tateno, H.; Matsumura, Y. Applications of Flow Microreactors in Electrosynthetic Processes. *Chem. Rev.* **2018**, *118*, 4541−4572. (b) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying Organic Synthesis. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594−5619. (c) Kirste, A.; Nieger, M.; Malkowsky, I. M.; Stecker, F.; Fischer, A.; Waldvogel, S. R. *ortho*-Selective Phenol-Coupling Reaction by Anodic Treatment on Boron-Doped Diamond Electrode Using Fluorinated Alcohols. *Chem. - Eur. J.* **2009**, *15*, 2273−2277. (d) Dahms, B.; Kohlpaintner, P. J.; Wiebe, A.; Breinbauer, R.; Schollmeyer, D.; Waldvogel, S. R. Selective Formation of 4,4'-Biphenols by Anodic Dehydrogenative Cross- and Homo-Coupling Reaction. *Chem. - Eur. J.* **2019**, *25*, 2713−2716. (e) Morofuji, T.; Shimizu, A.; Yoshida, J. Metal- and chemical-oxidant-free C-H/C-H cross-coupling of aromatic compounds: the use of radical-cation pools. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259−7262.

(4) (a) Black, D. C.; Keller, P. A.; Kumar, N. A direct synthesis of pyrrolophenanthridone alkaloids. *Tetrahedron Lett.* **1989**, *30*, 5807−5808. (b) Boger, D. L.; Wolkenberg, S. E. Total Synthesis of *Amaryllidaceae* Alkaloids Utilizing Sequential Intramolecular Heterocyclic Azadiene Diels-Alder Reactions of an Unsymmetrical 1,2,4,5-Tetrazine. *J. Org. Chem.* **2000**, *65*, 9120−9124. (c) Ganton, M. D.; Kerr, M. A. A Domino Amidation Route to Indolines and Indoles: Rapid Syntheses of Anhydrolycorinone, Hippadine, Oxoassoanine, and Pratosine. *Org. Lett.* **2005**, *7*, 4777−4779.

(5) (a) Rainka, M. P.; Peters, A.; Soloveichik, G. Base effects on electrochemical oxidation of indoline. *Int. J. Hydrogen Energy* **2013**, *38*, 3773−3777. (b) Li, B.; Wendlandt, E.; Stahl, S. S. Replacement of Stoichiometric DDQ with a Low Potential *o*-Quinone Catalyst Enabling Aerobic Dehydrogenation of Tertiary Indolines in Pharmaceutical Intermediates. *Org. Lett.* **2019**, *21*, 1176−1181. (c) Reisberg, S. H.; Gao, Y.; Walker, A. S.; Helfrich, E. J. N.; Clardy, J.; Baran, P. S. Total synthesis reveals atypical atropisomerism in a small-molecule natural product, tryptorubin A. *Science* **2020**, *367*, 458−463.

(6) (a) Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. Electrocatalytic Intermolecular Olefin Cross-Coupling by Anodically Induced Formal [2 + 2] Cycloaddition between Enol Ethers and Alkenes. *J. Am. Chem. Soc.* **2001**, *123*, 11314−11315. (b) Miura, T.; Kim, S.; Kitano, Y.; Tada, M.; Chiba, K. Electrochemical Enol Ether/Olefin Cross-Metathesis in a Lithium Perchlorate/Nitromethane Electrolyte Solution. *Angew. Chem., Int. Ed.* **2006**, *45*, 1461−1463. (c) Okada, Y.; Chiba, K. Redox-Tag Processes: Intramolecular Electron Transfer and Its Broad Relationship to Redox Reactions in General. *Chem. Rev.* **2018**, *118*, 4592−4630. (d) Shida, N.; Imada, Y.; Okada, Y.; Chiba, K. Mechanistic Insights on Concentrated Lithium Salt/Nitroalkane Electrolyte Based on Analogy with Fluorinated Alcohols. *Eur. J. Org. Chem.* **2020**, *2020*, 570−574. (e) Schulz, L.; Waldvogel, S. R. Solvent Control in Electro-Organic Synthesis. *Synlett* **2019**, *30*, 275−286. (f) Shida, N.; Imada, Y.; Nagahara, S.; Okada, Y.; Chiba, K. Interplay of arene radical cations with anions and fluorinated alcohols in hole catalysis. *Commun. Chem.* **2019**, *2*, 24.

(7) Imada, Y.; Okada, Y.; Noguchi, K.; Chiba, K. Selective Functionalization of Styrenes with Oxygen Using Different Electrode Materials: Olefin Cleavage and Synthesis of Tetrahydrofuran Derivatives. *Angew. Chem., Int. Ed.* **2019**, *58*, 125−129.

(8) Feilcke, R.; Goddard, R.; Imming, P.; Seidel, R. W. A structural study of seven *N*-acylindolines and their Pd(II)-mediated intramolecular oxidative coupling reactions for the synthesis of pyrrolophenanthridone alkaloids. *J. Mol. Struct.* **2019**, *1178*, 341−351.

(9) (a) Tani, K.; Stoltz, B. M. Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate. *Nature* **2006**, *441*, 731−734. (b) Clayden, J.; Moran, W. J. The Twisted Amide 2-Quinuclidone: 60 Years in the Making. *Angew. Chem., Int. Ed.* **2006**, *45*, 7118−7120.

(10) (a) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. Alkaloids of *Crinum pratense*. *Phytochemistry* **1981**, *20*, 2003−2007. (b) Ghosal, S.; Saini, K. S.; Frahm, A. W. Alkaloids of *Crinum latifolium*. *Phytochemistry* **1983**, *22*, 2305−2309. (c) Maddry, J. A.; Joshi, B. S.; Ali, A. A.; Newton, M. G.; Pelletier, S. W. Revised structures of pratorinine and pratorimine. *Tetrahedron Lett.* **1985**, *26*, 4301−4302. (d) Joshi, B. S.; Desai, H. K.; Pelletier, S. W. Synthesis of Pratorimine. *J. Nat. Prod.* **1986**, *49*, 445−448. (e) Abd el Hafiz, M.; Ramadan, M. A.; Jung, M. L.; Beck, J. P.; Anton, R. Cytotoxic Activity of *Amaryllidaceae* Alkaloids from *Crinum augustum* and *Crinum bulbispermum*. *Planta Med.* **1991**, *57*, 437−439. (f) Min, B. S.; Gao, J. J.; Nakamura, N.; Kim, Y. H.; Hattori, M. Cytotoxic Alkaloids and a Flavan from the Bulbs of *Crinum asiaticum var*. *Chem. Pharm. Bull.* **2001**, *49*, 1217−1219. (g) Ramadan, M. A.; Kamel, M. S.; Ohtani, K.; Kasai, R.; Yamasaki, K. Minor phenolics from *Crinum bulbispermum* bulbs. *Phytochemistry* **2000**, *54*, 891−896. (h) Ghosal, S.; Lochan, R.; Kumar, A. Y.; Srivastava, R. S. Alkaloids of *Haemanthus kalbreyeri*. *Phytochemistry* **1985**, *24*, 1825−1828. (i) Miki, Y.; Umemoto, H.; Dohshita, M.; Hamamoto, H. Synthesis of pyrrolophenanthridone alkaloid kalbretorine from indolecarboxylic acids via hypervalent iodine(III) mediated halodecarboxylation and reduction. *Tetrahedron Lett.* **2012**, *53*, 1924−1927.

(11) Negi, A. S.; Chattopadhyay, S. K.; Srivastava, S.; Bhattacharya, A. K. A Simple Regioselective Demethylation of *p*-Aryl Methyl Ethers Using Aluminum Chloride-Dichloromethane System. *Synth. Commun.* **2005**, *35*, 15−21.

https://dx.doi.org/10.1021/acs.orglett.0c01082
Org. Lett. XXXX, XXX, XXX−XXX