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Letter

Metal-Free Synthesis of Indolopyrans and 2,3-Dihydrofurans Based on Tandem Oxidative Cycloaddition

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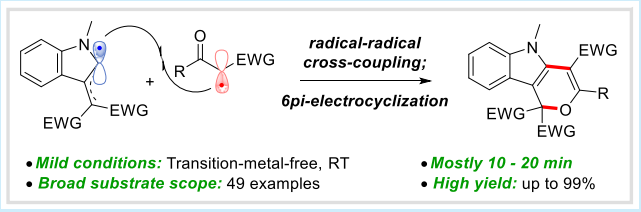
ABSTRACT: The synthesis of versatile scaffold indolopyrans based on C−C radical−radical cross-coupling under metal-free conditions is described. The reaction involving single electron transfer between coupling partners followed by cage collapse allows highly selective cross-coupling while employing only equimolar amounts of coupling partners. Moreover, the mechanistic manifold was expanded for the functionalization of enamines to give the stereoselective synthesis of 2,3-dihydrofurans. This iodine-mediated oxidative coupling features mild conditions and fast reaction kinetics.



Indole derivatives have drawn a great deal of attention owing to their broad biological activity,[1] and numerous elegant syntheses of indoles have been developed.[2] Meanwhile, elaboration of indoles by ring fusion would allow access to unique scaffolds with new biological activities. Especially, the inhibitory activities against various cancer cell lines and hepatitis C NS5B have been reported to be associated with indolopyran scaffolds.[3] As such, intense efforts have been made to develop expedient synthesis of polycyclic indoles.[4] For example, Pd- and Au-catalyzed intramolecular cyclization,[5] ring-closing Friedel−Crafts alkylation,[6] and Pictet−Spengler reaction[7] have been reported.

C−C and C−X bond formation based on cross-dehydrogenative coupling (CDC) has received considerable attention owing to the advantage of obviating prefunctionalization of reactants.[8] While transition-metal-catalyzed reactions comprise an important part of CDCs,[9] metal-free reactions are desirable in that the high cost of transition-metal catalysts and the removal of residual toxic metals could be avoided. Owing to the versatile reactivity and environmental friendliness, hypervalent iodines (λ^3) have attracted great interest from the synthetic community.[10] However, the formation of iodoarenes as the byproducts has been recognized as a drawback.

I_2 is an inexpensive, readily available, inherently nontoxic, and environmentally friendly reagent. In addition, I_2-mediated CDC reactions are operationally simple, and products can be readily purified from residual I_2. Thus, many efficient I_2-mediated reactions have been developed.[11] Generally, I_2 in CDC reactions is used as a radical initiator[12] or directly involved in the formation of X−I (X = C, N, O, etc.).[13]

Bond formation based on radical−radical cross-coupling (RRCC) is challenging owing to the very low activation barrier

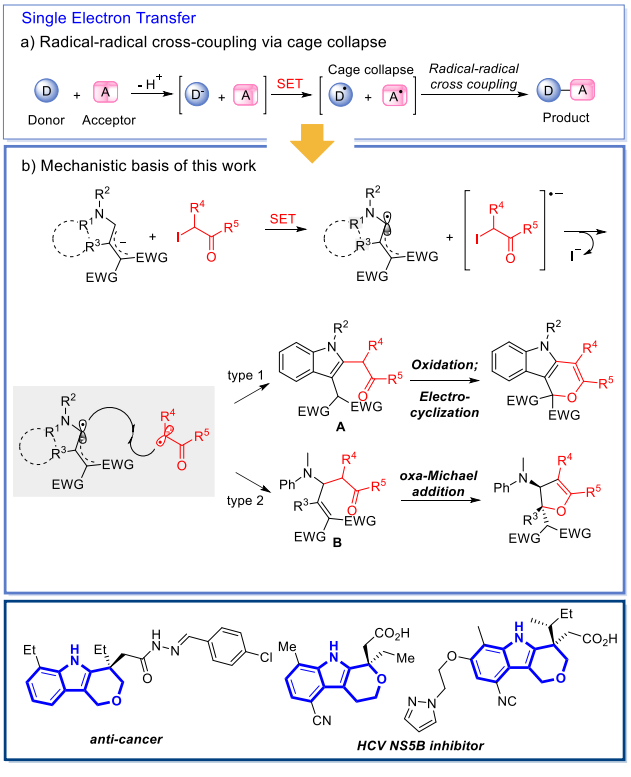


Figure 1. Strategy based on SET for radical−radical cross-coupling.

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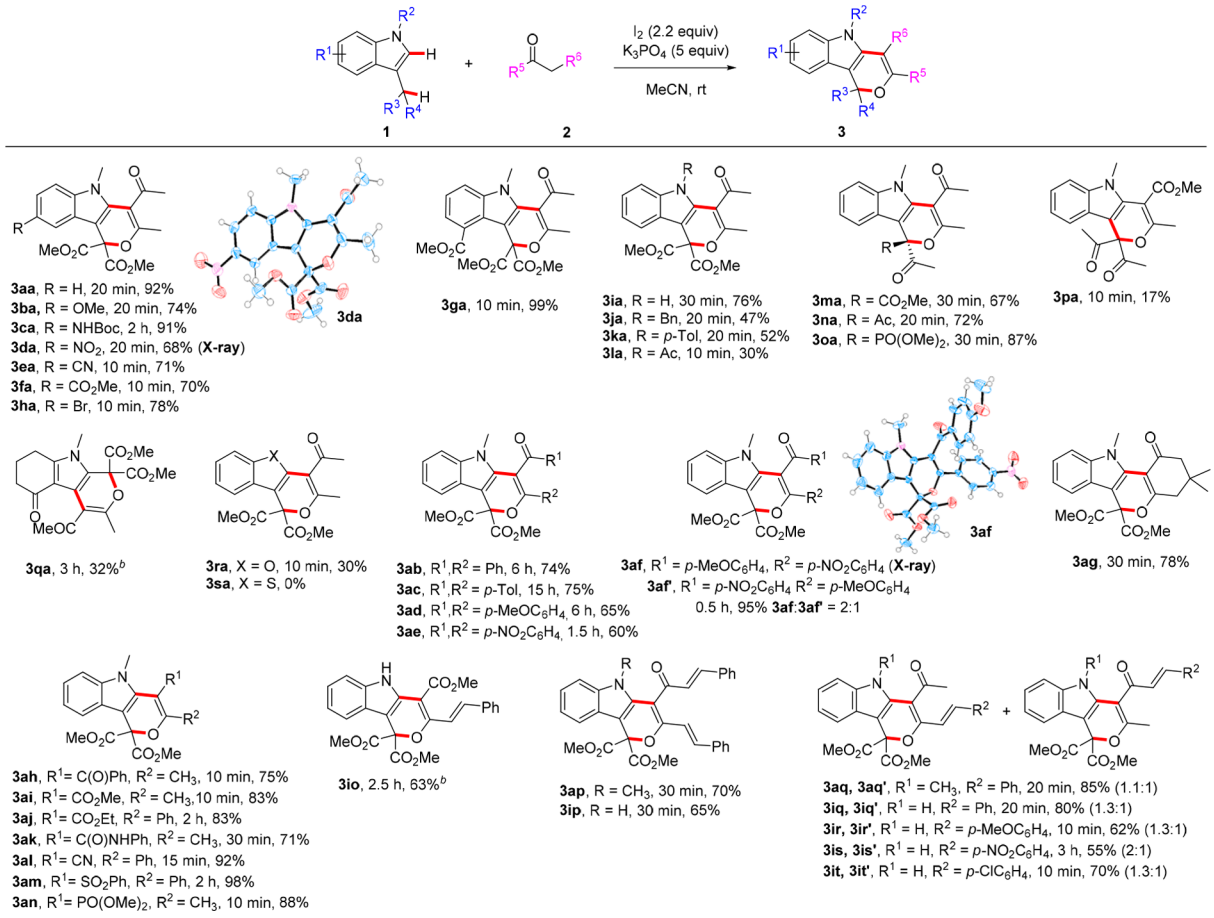
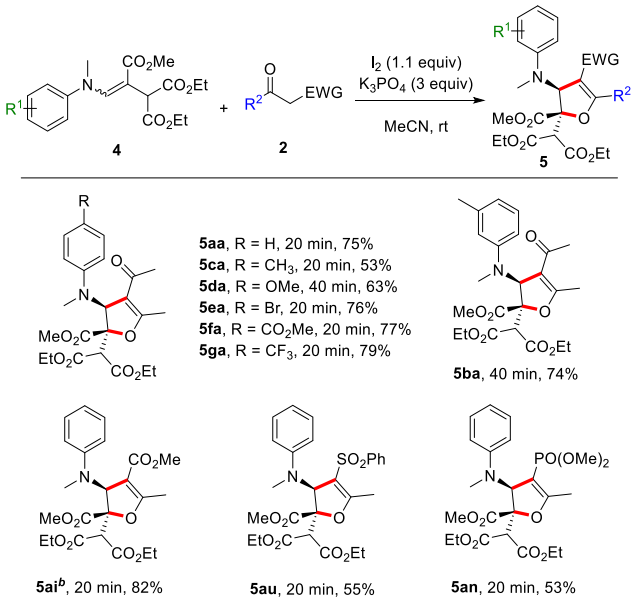
Scheme 1. Substrate Scope for Indolopyrans[a]



[a]Reaction conditions: reactions were performed with **1** (0.10 mmol) and **2** (0.11 mmol) in dry MeCN (1.0 mL) under N_2. Isolated yield. [b]Reaction performed at −10 °C.

Scheme 2. Substrate Scope for 2,3-Dihydrofurans[a]



[a]Reaction conditions: Reactions were performed with **4** (0.10 mmol) and **2** (0.11 mmol) in dry MeCN (1.0 mL) under N_2. Isolated yield. [b]Acetoacetate (1.5 equiv), iodine (2 equiv), K_3PO_4 (5 equiv).

of radical couplings, which renders it difficult to control the selectivity for cross-coupling over homocoupling.[14] While I_2-mediated C−X bond formation via the RRCC mechanism has been developed, to the best of our knowledge, the corresponding C−C bond formation under such a mechanistic realm has not been reported. Because of the two congeneric carbon-centered radicals with intrinsically similar reactivity derived from two coupling partners, the selective cross-coupling poses even more challenges.

Our strategy involves the charge-accelerated single electron transfer (SET) between coupling partners followed by cage collapse (Figure 1a), which enables highly efficient coupling to be completed at r.t. within 20 min in many cases, while employing only equimolar amounts of coupling partners. The pair of corresponding radical species formed by SET between the reactants undergoes rapid cross-coupling via cage collapse to give **A** or **B** depending on the substrate type (Figure 1b). Indole-derived **A** undergoes a second oxidation followed by 6π-electrocyclization to give indolopyrans, whereas direct oxa-Michael addition occurs for enamine-derived **B**, resulting in the formation of 2,3-dihydrofurans in a stereoselective manner.

To realize the coupling of indolomalonate **1a** with acetylacetone **2a** under oxidative conditions, we commenced with the examination of several oxidants and bases (see S2). Ultimately, the use of I_2 and K_3PO_4 afforded **3aa** in excellent yield with fast kinetics. Examination of solvent effects revealed acetonitrile as an optimal solvent. Under the optimized

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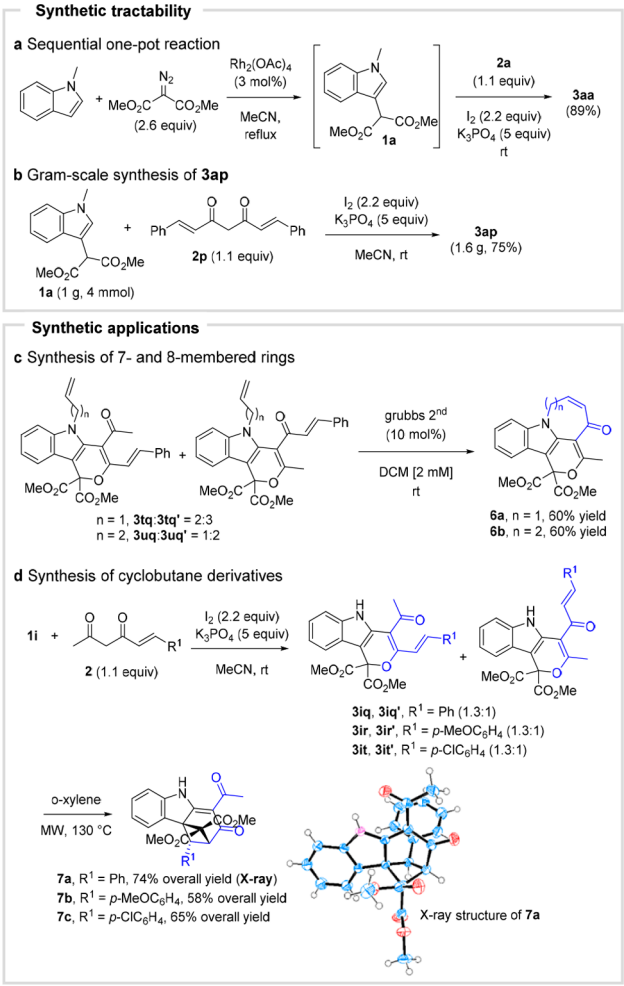

Figure 2. Synthetic tractability and applications.

conditions employing equimolar amounts of **1a** and **2a**, the reaction proceeded to completion in 20 min with a quantitative yield.

With the optimized conditions in hand, we examined the scope of the reaction (Scheme 1). It turned out that the electronic effect of the indole ring was insignificant, as observed by the highly efficient conversions regardless of the electronic nature of the substituents (**3aa**−**3ha**, X-ray strucure of **3da**). The examination of several N-substitutions on the indole revealed that while the N−H indole substrate **1i** produced **3ia** with a good yield those containing benzyl and aryl groups **3ja** and **3ka** afforded diminished yields. In addition to the malonate, various electron-withdrawing groups including ketoester, diketone, and ketophosphonate were well tolerated to yield the corresponding products in good to excellent yields (**3ma**−**3oa**). Notably, **1p** bearing ketoester at position C2 of indole, in which the corresponding enolate anion is in cross-conjugation with the indole nitrogen atom, afforded **3pa** in poor yield. We speculated that the cross-conjugation results in attenuation of the ability for electron transfer. Likewise, the reaction of C2-substituted pyrrole **1q** produced **3qa** in moderate yield. In a similar context, the heterocycles lacking a nitrogen atom, benzofuran **1r** and benzothiophene **1s**, afforded either low or no conversion (**3ra** and **3sa**).

Next, we investigated the scope of the coupling partner **2**. The reaction tolerated well both electron-rich and -deficient ketones to provide indolopyrans in good yields (**3ab**−**3ae**). To examine the regioselectivity of the cyclization, diketone **2f** bearing two electronically disparate carbonyl groups was subjected to the reaction. A moderate selectivity of 2:1 was observed with the electron-deficient carbonyl group participating in the cyclization (X-ray structure of **3af**). Aliphatic cyclic diketone **2g** and aryl alkylketone **2h** reacted smoothly with **1a** to produce the corresponding products **3ag** and **3ah** in high yields (78% and 75%, respectively). Notably, complete regiocontrol was observed with **2h**.

To investigate the feasibility for introducing various functional groups on the pyran ring, we performed the reaction with various active methylene compounds (AMCs) including ketoesters **2i** and **2j**, ketoamide **2k**, ketonitrile **2l**, ketosulfone **2m**, and ketophosphonate **2n** (**3ai**−**3an**). In all the cases, coupling successfully proceeded in excellent yields. Moreover, the introduction of vinyl groups on diketones (**2o**−**2t**) as functional handles was tolerated to afford the corresponding products in good yields (**3ap**, **3aq**, and **3io**−**3it**).

To broaden the scope of the method, we investigated the cross-coupling of enamines and AMCs (Scheme 2). Under the standard reaction conditions, 2,3-dihydrofuran **5aa** was obtained in 75% yield as a single diastereomer (NOESY experiment, SI Figure 4). Examination of the electronic effect of the aryl groups revealed that the reaction with the enamines bearing both electron-rich and -deficient aryl groups proceeded smoothly to give good to excellent yields of 2,3-dihydrofurans (**5aa**−**5ga**). Also, various AMCs smoothly participated in the reaction to give **5ai**, **5au**, and **5an**.

Next, we explored the synthetic application of the method (Figure 2a). The reaction could be performed as a two-step one-pot reaction by combining the carbene- and iodine-mediated steps (89% overall). Also, a gram-scale reaction proceeded without loss of efficiency (Figure 2b).

We demonstrated that the indolopyrans are a versatile scaffold, which can be elaborated into complex polycyclic compounds. Thus, additional 7- and 8-membered rings could be readily introduced by ring-closing metathesis (RCM) to give **6a** and **6b** in good yields by employing *N*-allyl or *N*-butenyl (Figure 2c). Thermal rearrangement can be promoted to produce highly complex architectures with cyclobutane formation when pendant vinyl groups are introduced on the substrates (Figure 2d). The reaction appears to involve the interconversion of the two regioisomers under the reaction conditions since identical products were obtained from both isomers (**7a**−**7c**).

As part of our mechanistic studies, we first focused on the identification of reaction intermediates along the reaction pathway. It was established that **3′aa** is an intermediate in the pyran formation based on the observation that a nearly quantitative amount of pyran **3aa** was obtained when **3′aa** was treated with 1.1 equiv of iodine (Figure 3a-i). With the speculation that the conversion of **3′aa** to **3aa** might involve the formation of oxa-triene **3″aa**, we performed an alternative oxidation of **3′aa** with MnO_2 to afford **3aa** (Figure 3a-ii). This led us to conclude that 6π-electrocyclization of **3″aa** is responsible for the formation of **3aa**. Next, the intermediacy of **8a** was confirmed by the formation of **3ab** in 91% yield when **8a** was reacted with **1a** in the presence of 1.1 equiv of iodine (Figure 3a-iii).

To probe the reaction mechanism, we performed a series of control experiments. The ability of the intermediate **8a** to form

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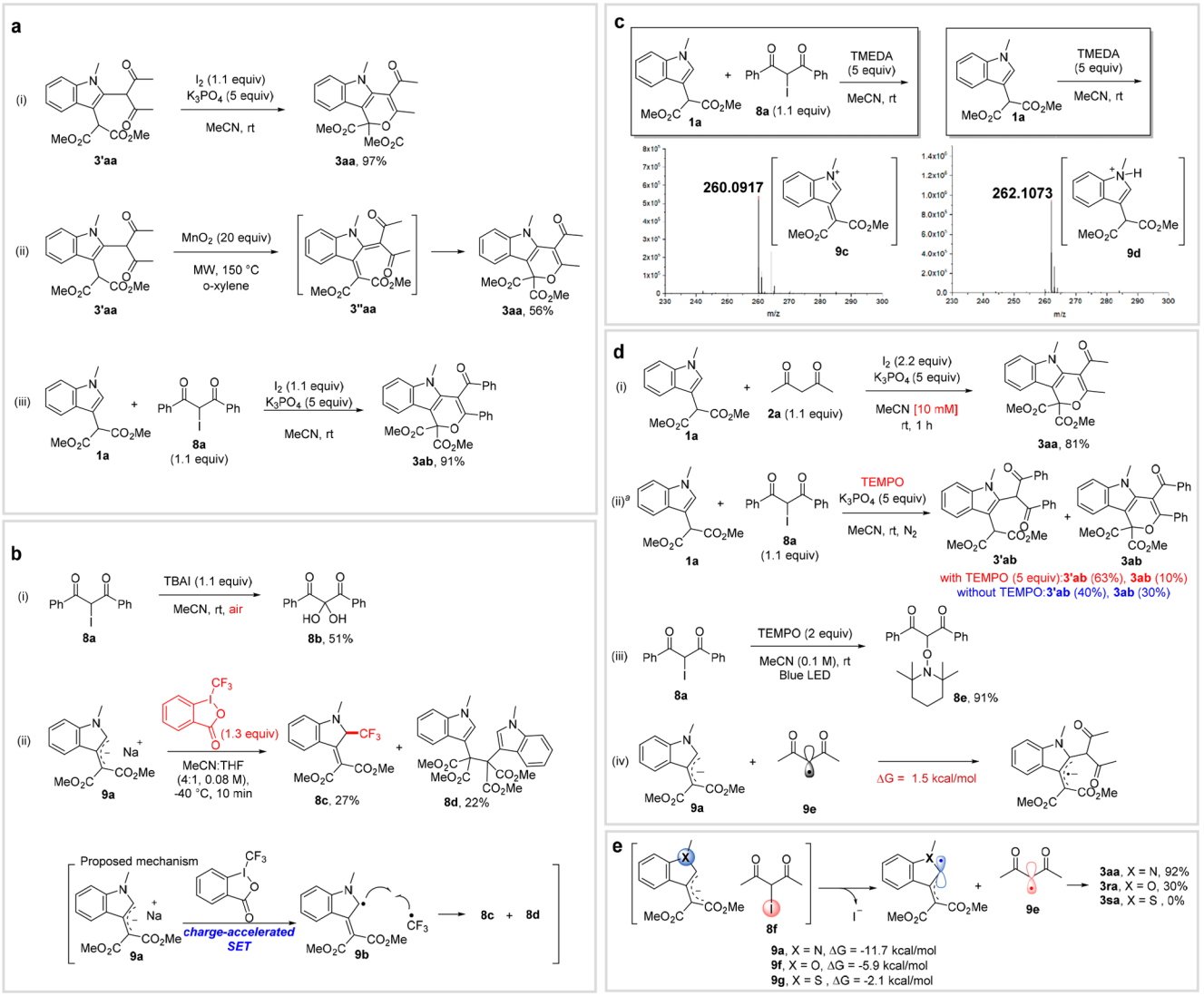

Figure 3. (a) Identification of the intermediates along the reaction pathway. (b) Probing the presence of radical species derived from the reactants. (c) HRMS analysis by direct injection of the reaction mixtures of **1a** and **8a** compared to **1a** alone sampled at 10 min. (d) RRCC vs $S_{RN}1$ mechanism: effect of reaction concentration and radical scavenger; ΔG for $S_{RN}1$ pathway. (e) Gibbs free energy changes for the SET calculated at the B3LYP-D3/6-31+G(d,p)/LANL2DZdp level in MeCN (SMD) and the corresponding yields. [a]NMR yield.

radical species has been confirmed by the formation of the tricarbonyl compound **8b** when iododiketone **8a** was treated with nBu$_4$NI in the presence of air, which may form via the corresponding peroxy intermediate (Figure 3b-i). The formation of a radical species on the indolomalonate was evidenced by reacting indolomalonate anion **9a** with Togni reagent II, a well-known electron acceptor (Figure 3b-ii).[15] The reaction was completed at −40 °C in 10 min to produce trifluoromethylated **8c** and dimer **8d** in 27% and 22% yield, respectively, both of which strongly suggest the presence of indolomalonate radical **9b**.

To further examine the presence of the radical species derived from indolomalonate **1a**, high-resolution mass spectrometry (HRMS) was obtained by direct sampling from the reaction of **1a** with **8a** (Figure 3c). The HRMS analysis indicated a peak corresponding to iminium ion **9c** (m/z = 260.0917). To identify the source of the iminium ion **9c**, we performed a control experiment. When the mixture lacking **8a** was subjected to HRMS, a peak corresponding to the protonated **9d** was detected (m/z = 262.1073), thus indicating that the species corresponding to the peak of m/z = 260.0917 is a unique species forming only when both reactants are present. Based on the observation, we reasoned that the oxidation of radical species **9b** in the mass spectrometer is responsible for the species at m/z = 260.0917.

We performed several control experiments to distinguish the mechanism in operation between solvent-caged RRCC and SRN1. First, the cross-coupling proceeded with similar efficiency even under 10-fold dilution (Figure 3d−i, 92%, 0.1 M vs 81%, 0.01 M, see S14). Second, the effect of a radical scavenger was examined (Figure 3d-ii, see S14), in which the presence of TEMPO did not interrupt the cross-coupling, affording a similar combined yield (73%) of **3′ab** and **3ab** compared to that without the scavenger (70%). This observation led us to examine the intrinsic reactivity of the radical species derived from **8a** toward TEMPO (Figure 3d-iii);[16] the trapping turned out to be highly efficient (91%). Based on the two experiments (Figure 3d-ii and -iii), the $S_{RN}1$ mechanism could be ruled out, the chain nature of which would have been interrupted by TEMPO (Figure 3d-ii). The

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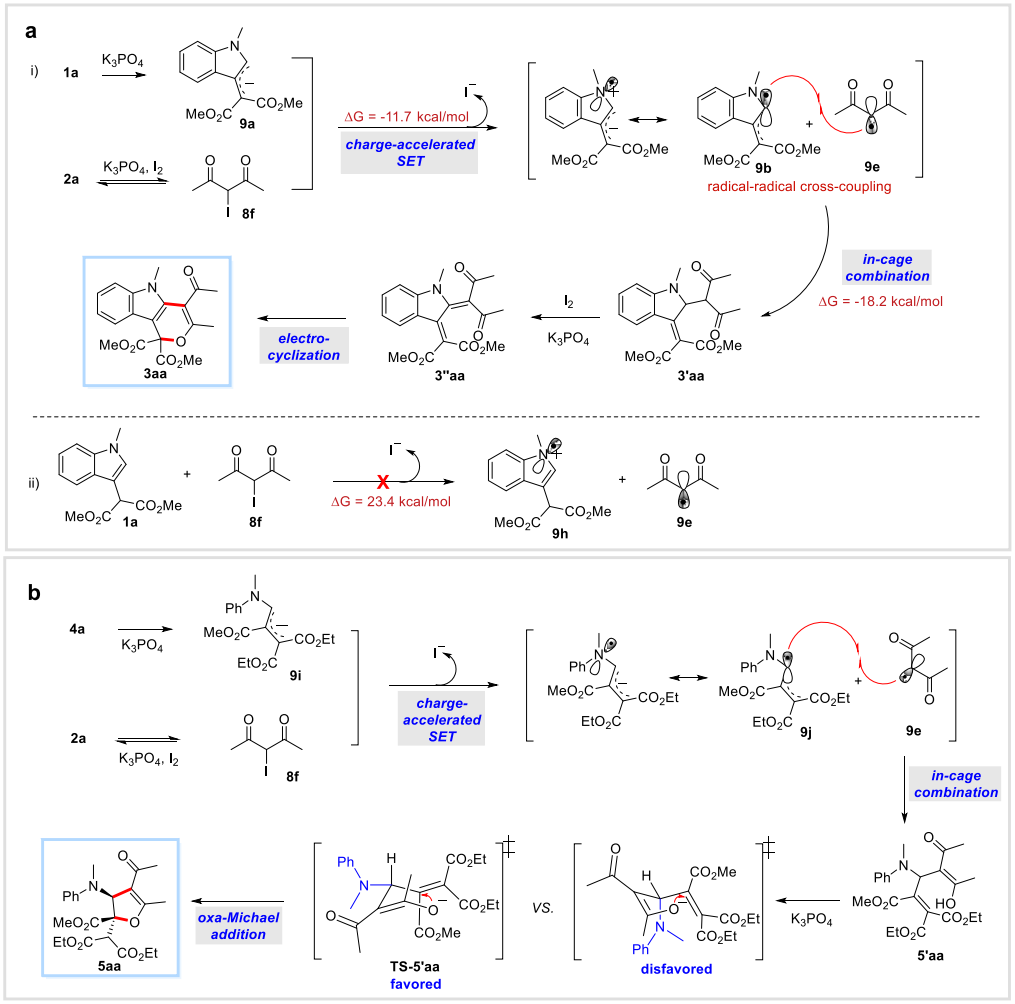

Figure 4. Proposed reaction mechanism. (a) Formation of **3′aa** via cage-collapse radical−radical cross-coupling followed by a second oxidation and electrocyclization to provide **3aa**. Gibbs free energy changes were calculated at the B3LYP-D3/6-31+G(d,p)/LANL2DZdp level in MeCN (SMD). (b) Mechanism for the formation of 2,3-dihydrofurans.

mechanistic rationale was further corroborated by the DFT calculations, where the $S_{RN}1$ pathway turned out to be endergonic in contrast to the highly exergonic RRCC pathway (Figures 3d-iv vs 4a-i).

Of note is the crucial role of the nitrogen-conjugated unsaturation in the reaction (Figure 3e). We reasoned that the stability of the radical species resulting from SET accounts for the efficiency of the reaction, in which the formation of **9a** is highly favorable as opposed to those for **9f** and **9g**. The Gibbs free energy changes calculated by DFT calculations are consistent with the experimental results (Scheme 1, **3ra** and **3sa**).

The proposed mechanism for indolopyrans based on the mechanistic studies and DFT calculations is shown in Figure 4a. The SET between **8f** and **9a** results in the formation of **9b** and **9e** with a Gibbs free energy change of −11.7 kcal/mol (Figure 4a-i; see SI Figure 3). Subsequently, the resulting radical species **9b** and **9e** undergo RRCC via cage collapse to afford **3′aa** with a free energy change of −18.2 kcal/mol, indicating an overall highly exergonic process. Moreover, the delocalized negative charge in **9a** is shown to be crucial in SET as suggested by the unfavorably high free energy change in SET between the neutral **1a** and **8f** (23.4 kcal/mol, Figure 4a-ii). Finally, oxidation of **3′aa** provides **3″aa**, which spontaneously undergoes 6π-electrocyclization to give **3aa**.

On the other hand, the formation of 2,3-dihydrofuran proceeds through RRCC to afford **5′aa** via the SET between **8f** and **9i**, and subsequent oxa-Michael addition of the enolate **TS-5′aa** affords **5aa** (Figure 4b). The formation of single diastereomers could be rationalized by the chairlike transition state (TS).

In conclusion, we have developed an efficient synthesis of indolopyrans and 2,3-dihydrofurans based on radical−radical cross-coupling. Extensive mechanistic studies allowed us to conclude that the coupling proceeds through *solvent-caged radical−radical cross-coupling* mediated by *charge-accelerated SET*, in which cage collapse plays an important role to achieve high selectivity for cross-coupling over homocoupling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01896.

Full experimental details, characterization data, and copies of ^{1}H and ^{13}C spectra and HRMS data (PDF)

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Accession Codes

CCDC 1881731, 1881736, and 1881740 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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