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Modular Counter-Fischer–Indole Synthesis through Radical-Enolate Coupling

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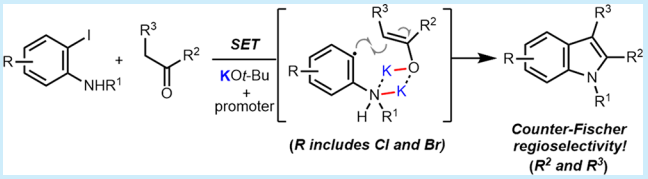
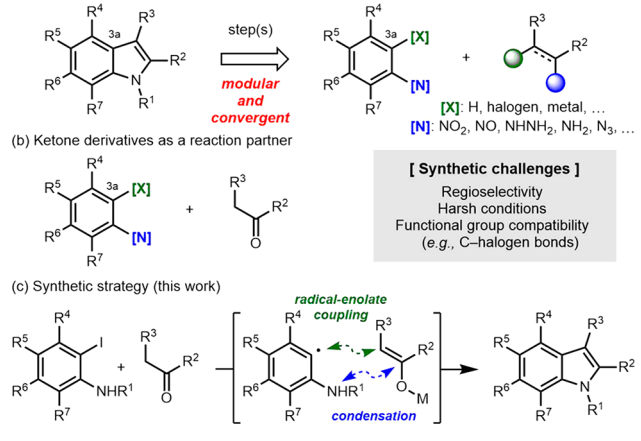
ABSTRACT: A single-electron transfer mediated modular indole formation reaction from a 2-iodoaniline derivative and a ketone has been developed. This transition-metal-free reaction shows a broad substrate scope and unconventional regioselectivity trends. Moreover, important functional groups for further transformation are tolerated under the reaction conditions. Density functional theory studies reveal that the reaction proceeds by metal coordination, which converts a disfavored 5-*endo-trig* cyclization to an accessible 7-*endo-trig* process.



Since their identification in 1869, indoles have become vital structural motifs in a wide range of research areas.[1] Controlled synthesis of substituted indole scaffolds has significantly expanded the accessible chemical space of indoles[2] and is a globally enduring target of investigation.[3] Among the established strategies in this regard, the method utilizing a nitrogenated arene and a two-carbon fragment, which constitutes the C_2 and C_3 positions of the indole backbone, has received special attention because of its modular and convergent nature (Scheme 1, a).[4] Among the numerous two-carbon units available, ketones are particularly attractive because of the widespread availability of building blocks as well as the orthogonal reactivities of the carbonyl and the α carbons, which would be the basis of chemoselective bond formation with the nitrogen and carbon (C_{3a}) atoms, respectively (Scheme 1, b).[4a,5]

Scheme 1. Modular Synthesis of Substituted Indoles



The reported approaches based on the use of ketone derivatives, however, pose significant synthetic challenges originating from regioselectivity issues, extreme reaction conditions, and/or functional group compatibility.[5h−k] For instance, when nitrogenated arenes are identically functionalized at both of the ortho positions[5i,j] (i.e., [X] = R^7) or if two α carbons of the ketone are available to participate in indolization,[5k] regiochemical problems are encountered. In addition, most of the applied reaction conditions involve the introduction of electromagnetic radiation or the use of expensive transition-metal catalysts, which can also lead to complications associated with toxicity.[5l,m] Moreover, the use of transition-metal catalysts obstructs the preservation of valuable functional handles for modification when an oxidative addition to C(sp^2)−(pseudo)halides is involved.[5f]

It was envisaged that the utilization of a radical intermediate originating from 2-iodoaniline derivatives would help overcome these limitations (Scheme 1, c). In 2008, Itami and coworkers disclosed a novel alkaline metal alkoxide mediated activation of aryl iodides.[6] Subsequent studies showed that the process is initiated by single-electron transfer (SET) from either the metal alkoxide species[7] or the downstream intermediates of the iodoarene,[7a−e,8] and the reactivity was further elaborated by the introduction of organic promoters.[7a,b,9] Ultimately, the protocol has been applied to C−C bond formation reactions in the context of arene−arene,[10] arene−alkene,[8b,11] and arene−enolate[12] couplings. We envisioned that

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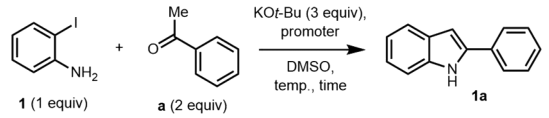
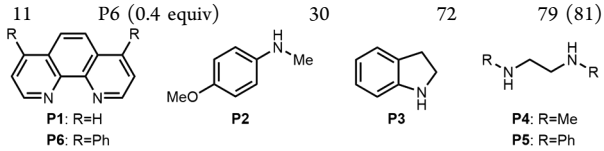
the transition-metal-free approach to generate an aryl radical species, in combination with the established condensation of aniline and ketone species, should serve as an ideal protocol to access diversely substituted indole derivatives in a programmable manner under mild conditions.

To evaluate the hypothesis, we attempted the coupling of 2-iodoaniline (**1**) and acetophenone (**a**) in the presence of 3 equiv of KO*t*-Bu (Table 1). While the unassisted use of KO*t*-Bu was virtually ineffective, the efficiency of the reaction was significantly improved by adding a substoichiometric amount of an organic promoter (entries 1−7). Among the various promoters that were evaluated, 4,7-diphenylphenanthroline (**P6**, bathophenanthroline) was the most potent in terms of product formation, yielding more than 80% of indole product (**1a**). Further optimization of the reaction revealed that the reaction proceeded to completion in 8 h in the presence of 0.2 equiv of **P6** at 60 °C, without notable loss of efficiency (entries 8−10). Of note, the coupling reaction could also be performed near room temperature, although a longer reaction time was required (entry 11).

Table 1. Optimization of Reaction Parameters[a]



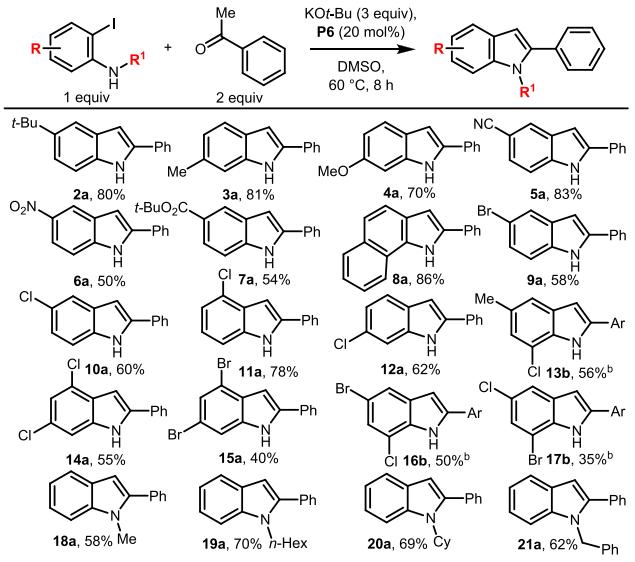
entry	promoter	temp (°C)	time (h)	yield[b] (%)
1		80	18	10
2	P1 (0.4 equiv)	80	18	63
3	P2 (0.4 equiv)	80	18	48
4	P3 (0.4 equiv)	80	18	39
5	P4 (0.4 equiv)	80	18	39
6	P5 (0.4 equiv)	80	18	19
7	P6 (0.4 equiv)	80	18	83
8	P6 (0.2 equiv)	80	18	86
9	P6 (0.2 equiv)	60	18	80
10	P6 (0.2 equiv)	60	8	82 (83)
11	P6 (0.4 equiv)	30	72	79 (81)



[a]Reaction conditions: 2-iodoaniline (0.50 mmol), aceotphenone (1.0 mmol), KO*t*-Bu (1.5 mmol), DMSO (1.5 mL). For more extensive optimization data, see Supporting Information. [b]Yields are determined by GC using dodecane as an internal standard. Yields in parentheses are isolated yields.

With the optimized conditions in hand, we next evaluated the generality of the reaction with substituted (Scheme 1, R^1 and R^4−R^7) 2-iodoanilines (Scheme 2). A wide range of electron-donating and electron-withdrawing substituents, including alkyl, methoxy, cyano, nitro, and carboalkoxy groups, were successfully installed into the products (**2a**−**7a**). Also, an extended π-system was implemented on the indole structure (**8a**). Moreover, halogen substituents, which can be utilized as functional handles for late stage cross-coupling reactions, were introduced at all the four positions of the 6-membered ring of the core structure (**9a**−**13b**). Importantly, the selective installation of a substituent at the 4-position of indole, which is difficult to realize from simple precursors using other methods,[13] were achieved with a synthetically useful yield

Scheme 2. Synthesis of 2-Substituted Indoles[a]



[a]Reaction conditions: iodoaniline (0.50 mmol), ketone (1.0 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.10 mmol), DMSO (1.5 mL), 60 °C, 8 h. Yields of the isolated products. [b]3,4-Dimethoxyacetophenone was used instead of acetophenone because it is more easily isolated.

(**11a**). In addition, substrates possessing two C−Cl or C−Br bonds were successfully employed to provide the corresponding indole products with multiple handles for further elaboration (**14a**−**17b**). Remarkably, alkyl and benzyl substituents at the nitrogen atom of the aniline derivatives were well tolerated under the reaction conditions (**18a**−**21a**).

Subsequently, the scope of the ketone counterpart was assessed by using various methyl ketones to afford 2-substituted indole derivatives (Scheme 3). Both electron-rich and electron-deficient acetophenones were successfully utilized as reaction partners (**1b**−**1g**). In addition, halogen-containing phenyl groups (**1h**−**1k**) as well as polycyclic aromatic hydrocarbons, such as naphthalene (**1l**) and phenanthrene (**1m**), were conserved. Of note, pharmaceutically important heterocyclic moieties were conveniently introduced at the 2-position of the indole system (**1n**−**1s**).[14] Methyl ketones bearing an alkyl substituent such as cyclopropyl (**1t**) and *tert*-butyl groups (**1u**) were also viable substrates for the transformation.

We next attempted to extend this methodology to the preparation of 2,3-disubstitued indoles (Scheme 4). Propiophenone and butyrophenone furnished the corresponding indole products with a C_3 alkyl group in high yields (**1a′** and **1b′**). Tricyclic and tetracyclic indoles were readily prepared from cyclic ketones (**1c′**−**1e′**), and a heteroatom substituent was installed at the 3-position of indole (**1f′**). The use of an aldehyde as a reaction partner, however, led to a significantly diminished yield of the desired 3-phenyl indole (**1g′**). Interestingly, in the case of phenylacetone and benzylacetone, which have two possible positions for enolization, the product originating from thermodynamically more stable enolate was obtained (**1h′** and **1i′**). The regioselectivity trend of **1i′** is consistent with that of the pioneering works of Bunnett and Semmelhack, which cover the regioselectivity for the addition of an aryl radical to an enolate when the formation of multiple regioisomers is possible.[15] Product formation at the methylene side of the enolate is preferred over reaction at the methyl side.

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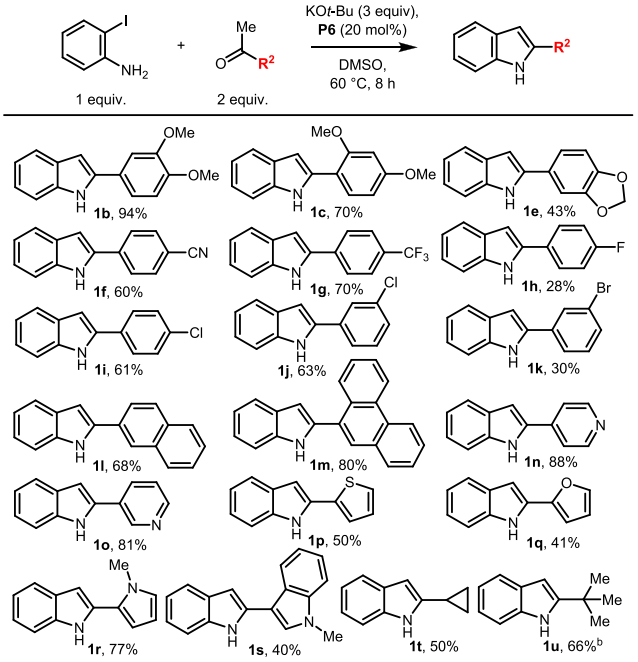
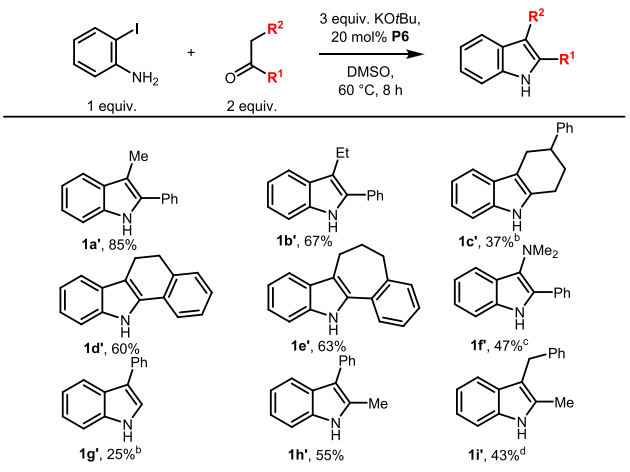
Scheme 3. Synthesis of 2-Substituted Indoles[a]



[a]Reaction conditions: iodoaniline (0.50 mmol), ketone (1.0 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.10 mmol), DMSO (1.5 mL), 60 °C, 8 h. Yields of the isolated products. [b]Ketone (1.5 mmol), **P6** (0.20 mmol), 80 °C.

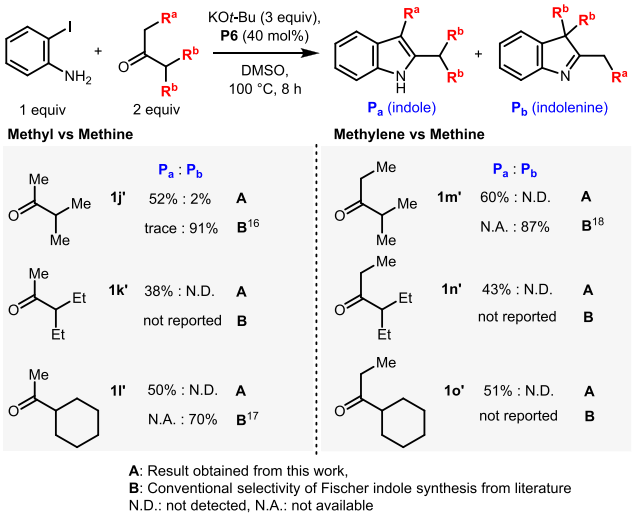
Scheme 4. Synthesis of 2,3-Disubstituted Indoles[a]



[a]Reaction conditions: iodoaniline (0.50 mmol), ketone (1.0 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.10 mmol), DMSO (1.5 mL), 60 °C, 8 h. Yields of the isolated products. [b]**P6** (0.20 mmol), 100 °C, ketone (1.5 mmol). [c]Ketone (1.5 mmol). [d]21% of 2-phenethyl-*1H*-indole was obtained as a side product. The yield and ratio of the product were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

To gain better insight into the regioselectivity of the method, the indole formation reaction was attempted with ketone derivatives that can potentially provide an indolenine, a frequently observed product in existing protocols (e.g., Fischer indole synthesis) (Scheme 5).[5b] Although a preference arising from the formation of thermodynamic enolate has been observed when both of the possible products are indoles (Scheme 4, **1h′** and **1i′**), a propensity to counteract that of

Scheme 5. Regioselectivity Trend of the Reaction[a]



[a]Reaction conditions: iodoaniline (0.50 mmol), ketone (1.5 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.20 mmol), DMSO (1.5 mL), 100 °C, 8 h. Yields of the isolated products. The ratio of products was determined by GC.

conventionally approaches has been identified. Cyclization on the methine side of the ketone, which furnishes an indolenine product, was generally disfavored under the developed condition. Instead, the ring-formation event occurred preferentially on the methyl or methylene side of the ketone to provide the corresponding indole products (Scheme 5, **1j′**,[16] **1k′**, **1l′**,[17] **1m′**,[18] **1n′**, and **1o′**). The corresponding regioselectivity is also analogous to Semmelhack and Bunnett's works, although a small amount of products originating from the reaction at the methine side of ketone was formed in their works.[15] To our knowledge, these are the first examples of single-step indolization with such a regiochemical trend under transition-metal-free conditions.[19]

Two possible mechanisms have been hypothesized for this reaction (Scheme 6, a). The first route involves SET of a metalloenamine generated from condensation of aniline **1** and ketone **a** (path 1, **I**) to provide an aryl radical enamine intermediate **II**. This can lead to a 5-*endo-trig* intramolecular cyclization, and subsequent oxidation forms the observed indole product **1a**. Alternatively, aryl radical **VII-b** can complex with an enolate, and the resulting complex **IV** can in turn add in a 7-*endo-trig* fashion (path 2). Subsequent SET, protonation, and condensation can form the desired indole product.

We investigated both mechanisms by density functional theory (DFT) with several monomeric as well as complexed SET promoters that may be present in the solution (see the Supporting Information).[20] Of those investigated, the (**KO*t*-Bu**)$_4$**/P6** complex was the most thermodynamically favored SET promoter. The resulting reaction coordinate diagram is shown in Scheme 6b. DFT results revealed a substantial barrier of 36.1 kcal/mol for the intramolecular cyclization (path 1, **TS-X**). This is more than 10 kcal/mol higher than the expected experimental barrier of ∼26 kcal/mol (estimated for the case of Table 1, entry 10 with 83% yield, 60 °C, 8 h, assuming 4 half-lives). This was in contrast to the addition route of path 2 leading to **TS-IV** with a barrier of 14.6 kcal/mol for the C−C formation of the metal aryl radical and the metal enolate. Most notably, the dipotassium coordination in **TS-IV** changed the

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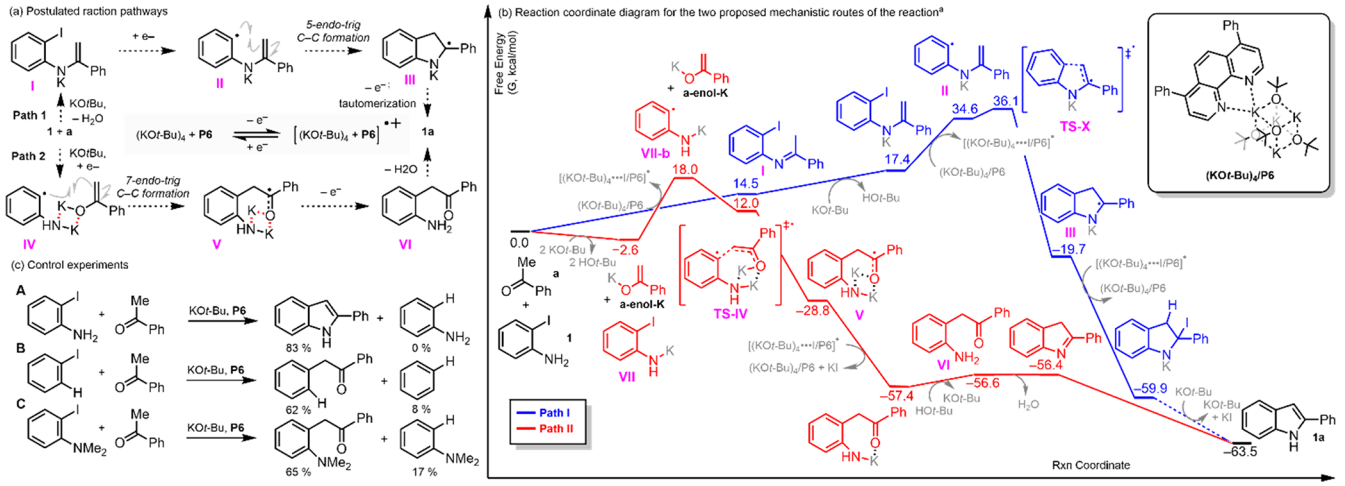
Scheme 6. (a) Postulated Reaction Pathways. (b) Reaction Coordinate Diagram for the Two Proposed Mechanistic Paths for the Reaction of 2-Iodoaniline and Acetophenone with KO*t*-Bu$_4$/P6 Complex. (c) Control Experiments with 2-Iodoaniline, Iodobenzene, and 2-Iodo-*N*,*N*-dimethylaniline

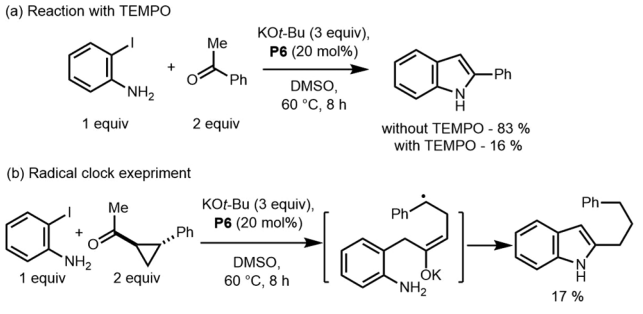


[a]DFT results computed using PBE[21]/6-31G*[22] and LANL2DZ[23] geometries with SMD[24] solvation corrections in DMSO. [b]Reaction conditions: iodoarene (0.50 mmol), ketone (1.0 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.10 mmol), DMSO (1.5 mL), 60 °C, 8 h. The yields were determined by GC using dodecane as an internal standard.

coupling event from the disfavored 5-*endo-trig* cyclization of path 1 to the 7-*endo-trig* addition of path 2 with a much more favorable orbital alignment for the addition process. Alternatively, we also considered pathways that involve all the different protonation states of the aniline and enolate reactants which were found to be higher in energy (see Supporting Information). Interestingly, control experiments (Scheme 6, c-**B** and c-**C**) revealed that the product formation is less efficient—while the decrease in yield was ∼20%, substantial quantities of the proto dehalogenation products were detected. The fact that change in the nature of iodoarene's substituents leads to substantial changes in reaction efficiency suggested that metal coordination may contribute to increase the reaction efficiency as suggested by the DFT.

Further control experiments were conducted to support the single electron pathway of the reaction. When the reaction of 2-iodoaniline and acetophenone was set up in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), the yield of the reaction was dramatically reduced (Scheme 7, a). In addition, a ketone precursor with a radical clock furnished the corresponding ring-opening indole product (Scheme 7, b).

Scheme 7. Verification of Single Electron Pathway[a]

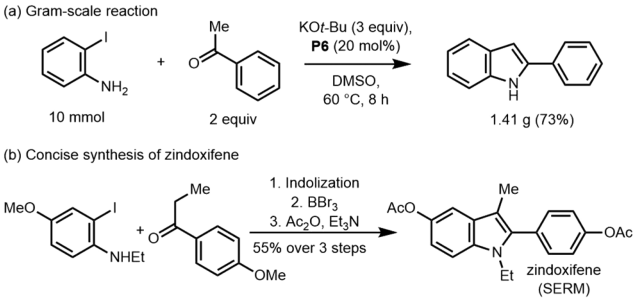


[a]Reaction conditions: iodoaniline (0.50 mmol), *trans*-2-phenylcyclopropyl methyl ketone (1.0 mmol), KO*t*-Bu (1.5 mmol), **P6** (0.10 mmol), DMSO (1.5 mL), 60 °C, 8 h.

Combined, these results support the participation of the ketyl radical in the reaction.[25]

Finally, the synthetic utility of the protocol was assessed. The reaction was conducted on a gram scale to provide an indole product in practically effective yield (Scheme 8, a).

Scheme 8. Synthetic Utility of the Reaction



Moreover, the process was successfully applied to the concise synthesis of a nonsteroidal selective estrogen receptor modulator (SERM), zindoxifene (Scheme 8, b). The targeted drug molecule was prepared in the most efficient manner to date from readily available precursors.[26]

In conclusion, we have developed an efficient transition-metal-free KO*t*-Bu-mediated protocol for indole synthesis. This method is advantageous in that no transition metal or light irradiation is required and it provides easy access to indoles bearing various functional groups, including C(sp^2)−halogen bonds for further functionalization. Additionally, the developed strategy exhibits unconventional regioselectivity, which is rarely observed in other transition-metal-free conditions. DFT studies suggest that metal-coordinated radical−enolate coupling is essential: this coordination enables the key C−C bond-forming event to occur via a favored 7-*endo-trig* cyclization rather than the forbidden 5-*endo-trig* process. All in all, the first counter Fischer-indole regiocontrol was achieved through a metal-chelated radical enol coupling synthetic platform.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00003.

Experimental procedures, mechanistic studies, compound characterization, NMR spectra, and computation section (PDF)

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Notes

The authors declare no competing financial interest.

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