▌ **Synthetic Methods**

Catalytic Synthesis of Indolines by Hydrogen Atom Transfer to Cobalt(III)–Carbene Radicals

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Abstract: We report a new method for the synthesis of indolines from *o*-aminobenzylidine *N*-tosylhydrazones proceeding through a cobalt(III)–carbene radical intermediate. This methodology employs the use of inexpensive commercially available reagents and allows for the transformation of easily derivatized benzaldehyde-derived precursors to functionalized indoline products. This transformation takes advantage of the known propensity of radicals to undergo rapid intramolecular 1,5-hydrogen atom transfer (1,5-HAT) to form more stabilized radical intermediates. Computational investigations using density functional theory identify remarkably low barriers for 1,5-HAT and subsequent radical rebound displacement, providing support for the proposed mechanism. We explore the effect of a variety of nitrogen substituents, and highlight the importance of adequate resonance stabilization of radical intermediates to the success of the transformation. Furthermore, we evaluate the steric and electronic effects of substituents on the aniline ring. This transformation is the first reported example of the synthesis of nitrogen-containing heterocycles from cobalt(III)–carbene radical precursors.

Introduction

Identifying new reactivity of well-known functional groups broadens their versatility in organic synthesis. Prior to recent discoveries, the diazo functional group had generally been considered a precursor to discrete carbenes or metallocarbenes. These carbene intermediates have been shown to participate in a variety of two-electron processes including cyclopropanations, 1,2-shifts, and bond insertions.[1] However, the discovery of Co^{II}-metalloradical catalysis, which unlocks radical-type reactivity from carbene precursors, has invalidated the one-dimensional stereotype of carbenes and has enabled carbene precursors to perform a variety of single-electron processes (Figure 1a). In spite of their importance, carbene radicals have thus far not been utilized in the synthesis of nitrogen-containing ring structures. Such reactions would expand the currently still limited synthetic toolbox available for the synthesis of N-heterocyclic motifs.
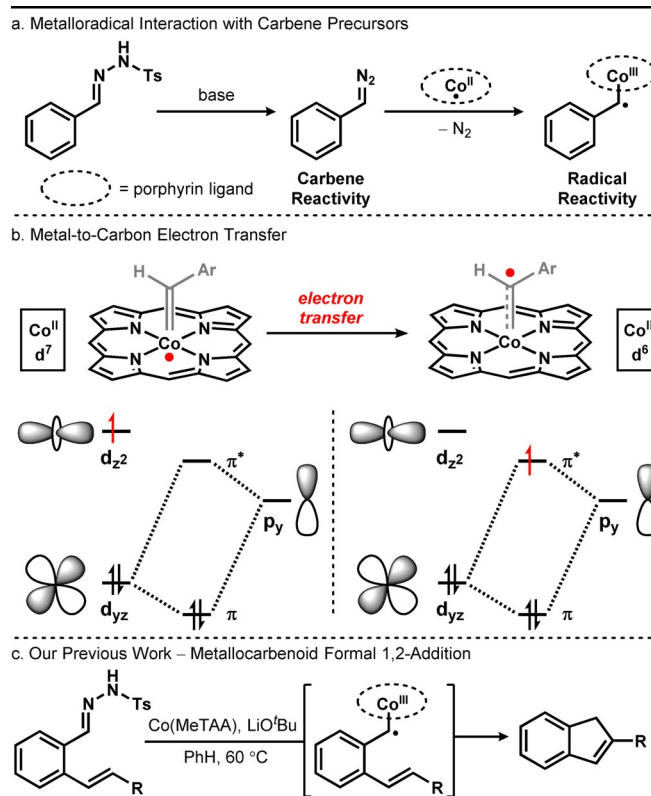
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**Figure 1.** Radical reactivity from carbene precursors.

Planar cobalt(II) complexes exhibit unique catalytic properties that have found niche applications in organic synthesis. These stable metalloradicals contain an open-shell doublet d^7-electronic configuration resulting in a singly occupied electrophilic d_{z^2} orbital. Following coordination of a nucleophilic diazo functional group, these complexes have been found to undergo an intramolecular metal-to-carbon single electron transfer to form a radical carbene intermediate, which is best described as a one-electron reduced Fischer-type carbene (Figure 1 b).[2] These intermediates retain the reactive nature of radicals, but with a decreased susceptibility toward carbene dimerization.[2]

This carbon-centred radical has been shown to participate in various single-electron reactions including 1,2-addition[3] and radical recombination (Figure 1 c).[2b] In a recent example, our group disclosed the formation of indene products from radical carbene precursors which undergo a formal 1,2-addition across a pendant olefin.[4] However, the only reported example in this context of hydrogen atom transfer, a fundamental radical transformation, utilized as a strategy in C—C bond formation is limited to the formation of highly specific sulfolane or sultone derivatives.[5]

The indoline N-heterocycle is commonly observed among both natural products and pharmaceutical scaffolds, and the need to access this important motif has led to a variety of methods by which it can be obtained. Simple indolines can be efficiently prepared from indole precursors in high yields, but this transformation requires the use of strongly acidic, strongly hydridic, or highly pressurized conditions.[6, 7] Several dependable and versatile methods have also been reported employing Pd,[8,9] Cu,[10,11] Ni,[12] Ti,[13] and amines[14] as ring-closing catalysts. Furthermore, a variety of methods to form indolines involving radical ring-closing,[15] alkylation,[16] formal 1,2-addition across olefins,[17–19] benzyne functionalization,[20] and [4+2] cycloadditions[21] each present their own advantages. However, several of these existing methods suffer from functional group intolerance, the necessity of expensive noble transition metal catalysts, harsh reaction conditions, and/or require the use of protecting groups that require tedious conditions for their removal. For this reason, there remains a need for new, efficient, and broadly applicable catalytic routes to expand the currently available methods for indoline synthesis from readily available starting materials.

Although carbene or nitrene precursors have previously been used in the synthesis of indolines,[22] each method has been proposed to proceed by standard two-electron mechanisms commonly observed from these complexes. Cobalt(III) nitrene radicals, which are formed via an analogous decomposition of azide functional groups, have been shown to undergo C—H abstraction in the formation of C—N bonds, but generally have been limited in application to tailor-made starting materials.[23] To date, the only disclosed method for indoline formation via metalloradical catalysis was disclosed by the Che group, in which they invoked a mechanism involving C—H abstraction by the analogous iron(IV) nitrene radical to lead to formation of the key C—N bond (Figure 2 a).[24]
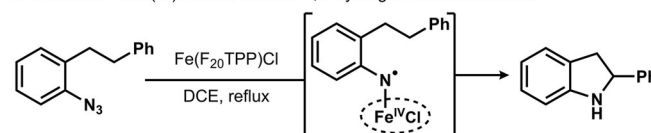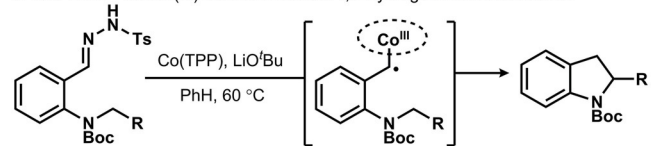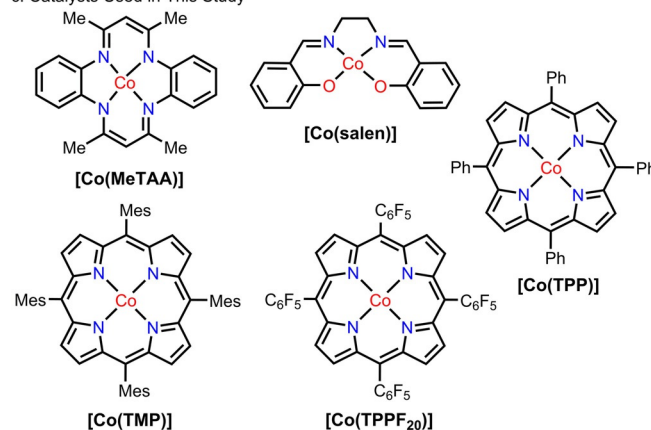

Figure 2. a) Previous method for indoline synthesis by C—N bond formation. b) Our new method for indoline synthesis by C—C bond formation. c) Catalysts tested during reaction optimization in this study.

We herein disclose a method for a complementary synthesis of indolines by exploiting our observation that cobalt radical intermediates undergo 1,5-hydrogen atom abstraction reactions (Figure 2 b). We identified **[Co^{II}(TPP)]** as a cheap, commercially available, air- and moisture-stable catalyst for this transformation, and demonstrated the need for a planar cobalt(II) catalyst through a series of control experiments. The scope of this methodology was investigated through the installation of several functional groups on the carbene precursor, and we examined our proposed mechanism via computational studies. Overall, this method represents the first synthesis of N-heterocycles via a cobalt(III)-carbene radical mediated C—H activation and subsequent radical rebound sequence.
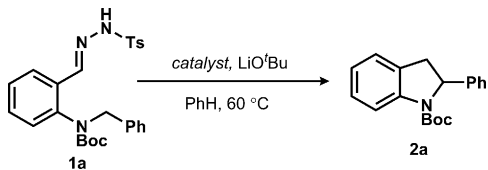
Results and Discussion

Reaction optimization

We began our investigation using the N-benzyl substituted hydrazone **1 a** as a test substrate, designed to facilitate 1,5-hydrogen atom abstraction through stabilization of the intermediate benzylic radical (Table 1).

We initially found that heating of the tosyl hydrazone in the presence of lithium tert-butoxide as a base resulted exclusively in carbene dimerization products when in the absence of a metal catalyst (Table 1, entry 1). However, the addition of **[Co^{II}(MeTAA)]**, a high-spin metalloradical catalyst with known

Table 1. Optimization of conditions for indoline synthesis.

Entry	Catalyst[a]	Catalyst loading [mol%]	Base [equiv]	t [h]	Yield [%][b]
1	–	–	1.7	18	–
2	[Co(MeTAA)]	5	1.7	18	83
3	[Co(salen)]	5	1.7	18	76
4	**[Co(TPP)]**	**5**	**1.7**	**18**	**>99**
5	[Co(TMP)]	5	1.7	18	>99
6	[Co^{II}(TPPF$_{20}$)]	5	1.7	18	>99
7	CoCl$_2$	25	1.7	18	trace
8	Rh$_2$(OAc)$_4$	25	1.7	18	–
9	Co(TPP)	5	1.2	18	35
10	Co(TPP)	5	3.0	18	65
11	Co(TPP)	5	1.7	6	95
12	Co(TPP)	1	1.7	18	90

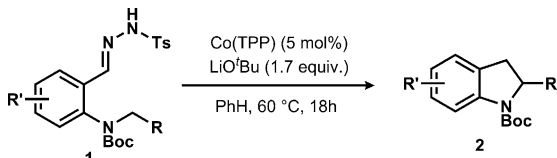[a] Structures of the applied catalysts are shown in Figure 2c. [b] NMR yields.

propensity to form radicals from carbene precursors (for structures of the catalysts, see Figure 2),[4] resulted in conversion to the desired indoline product in 83% yield (entry 2). [Co^{II}(salen)] complexes also facilitated ring-closure, but at reduced and somewhat less reproducible yields (entry 3). After establishing porphyrins as more reliable ligands, we determined commercially available and air- and moisture-stable catalyst [Co^{II}(TPP)] to be superior in this context, leading to quantitative yield of the indoline product (entry 4). More electron rich ([Co^{II}(TMP)]) or electron deficient ([Co^{II}(TPPF$_{20}$)]) cobalt porphyrins gave similar results, and provide no specific advantages over the commercially available [Co^{II}(TPP)] catalyst (entries 4–6). Using CoCl$_2$ as a catalyst led to formation of only trace quantities of the indoline product, suggesting that planar (porphyrin-like) ligands are essential (entry 7). Additionally, introduction of rhodium(II) acetate dimer to facilitate 1,2-carbene insertion[25] resulted in no indoline product, probably because the lithium *tert*-butoxide base necessary to accomplish in situ diazo formation from the tosylhydrazone precursor resulted in catalyst decomposition (entry 8).

The molar ratio of lithium *tert*-butoxide has a significant effect on the yield of this transformation. Decreasing the amount of base to 1.2 equivalents limits the yield to 35%, whereas the addition of three equivalents of base decreases the yield to 65% (entries 9–10). We postulate that this need for superstoichiometric base is related to the low solubility of lithium *tert*-butoxide in benzene. In addition to reagent optimization, we also found that near-quantitative yields could be acquired with shorter reaction times of 6 hours (entry 11), and the catalyst loading could be decreased to 0.01 equivalents with only a slight loss of yield (entry 12).

Scope

To explore the versatility of this transformation, we designed a series of substrates with substituents that might have steric or electronic implications on the proposed reaction mechanism (Table 2). We found that the electron density on the *N*-benzyl

Table 2. Investigation of substituent effects on indoline formation.

Entry	Substrate		Product	Yield [%][a]
1	1a	R=Ph, R'=H	2a	98
2	1b	R=(p-CF$_3$)-Ph, R'=H	2b	92
3	1c	R=(p-OMe)-Ph, R'=H	2c	96
4	1d	R=(o-Me)-Ph, R'=H	2d	97
5	1e	R=2-furanyl, R'=H	2e	95
6	1f	R=2-pyridyl, R'=H	2f	95
7	1g	R=H, R'=H	2g	0
8	1h	R=CH$_3$, R'=H	2h	0
9	1i	R=-CH=CH$_2$, R'=H	2i	80
10	1j	R=Ph, R'=3-Me	2j	80
11	1k	R=Ph, R'=4-OMe	2k	81
12	1l	R=Ph, R'=4-CF$_3$	2l	96

[a] Isolated yields.

ring (entries 1–3) has little effect on the yield of the reaction. Additionally, the introduction of a bulky *ortho* substituent on the benzylic functionality (entry 4) does not prevent the ring-closure. The formed radical is also sufficiently stabilized by both electron-rich and electron-poor heterocycles (entries 5 and 6, respectively). The surprisingly low impact of the electronic environment of the N-substituent supports the proposed single-electron mechanism. Electron donating and electron withdrawing substituents at the aniline moiety are also well tolerated (entries 11 and 12).

A clear limitation of this methodology involves the need for substituents at the nitrogen atom that provide sufficient stabilization of the proposed radical intermediate. We found that a 1,5-hydrogen atom abstraction to form primary (entry 7) and secondary (entry 8) radicals was not possible, suggesting that the carbene radical intermediate is not reactive enough to generate the required N-CH·R radical intermediates in absence of aromatic R-substituents providing resonance stabilization. However, we found the allylic radical to be sufficiently stabilized to provide 80% yield of the desired vinyl indoline product (entry 9).

Functionalization of the aniline ring also provided substituted indoline products in high yields. Introduction of a 5-methyl substituent (entry 10) did not significantly affect reactivity and provided an 80% yield of product. Additionally, we found that electron-rich (entry 11) and electron-poor (entry 12) aniline precursors successfully provided ring-closed products. Substitution on the aniline ring has a more significant effect on product yield as compared to substitution on the benzyl ring (entries 2 and 3). We postulate that the electronics mainly influence the presumed rate-limiting step of converting the tosyl hydrazone substrate into the diazo compound. Substituents on the aniline ring should have a significant influence on this polar two-electron step, as opposed to radical-type steps.

DFT studies

To provide insight into the mechanism, we explored the reaction computationally using DFT methods. In line with similar systems that have previously been studied extensively, we considered a radical-type pathway involving activation of the in situ formed diazo compound by the [Co^{II}(Por)] catalyst. The computations were performed at the BP86 and def2-TZVP level using the non-functionalised [Co^{II}(Por)] system. The choice for this computational method is based on previous realistic mechanistic pathways calculated by us for such systems active as catalysts in related reactions. We further incorporated Grimme's dispersion corrections (DFT-D3) for these systems. For the substrate, we included a full model for the diazo compound formed from substrate S1. Based on the energies obtained from these calculations we propose the mechanistic cycle depicted in Figure 3.

Coordination of the diazo substrate on the catalyst to form a substrate-bound adduct B[27] is exergonic by −4.9 kcal mol^{-1}. From this adduct B, elimination of dinitrogen via TS1 (barrier: $\Delta G^{\ddagger} = +8.8$ kcal mol^{-1}) leads to the formation of carbene-radical intermediate C ($\Delta G^{\circ} = -13.8$ kcal mol^{-1}). From this inter-
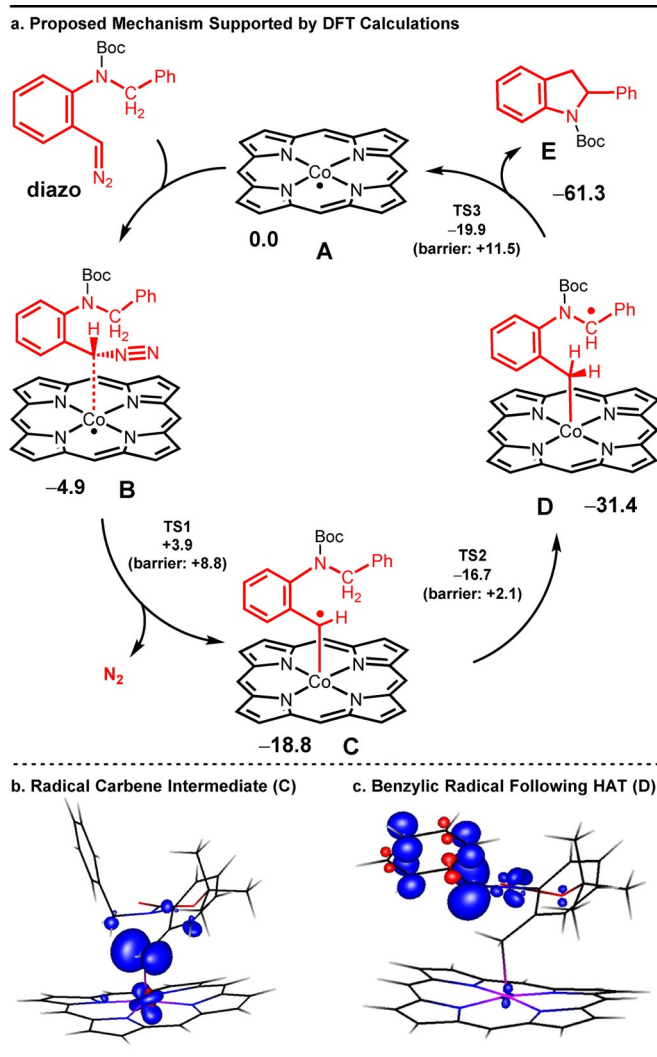
Figure 3. Calculated Mechanism for Indoline Formation. a) DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies (ΔG_{298K}° in kcal mol^{-1}) for the proposed reaction pathway. Energies of all intermediates are reported with respect to species A as the reference point (barriers for the transition states are reported in between brackets). b) Spin density plot of intermediate C showing maximum spin density at the carbene carbon. c) Spin density plot of intermediate D after the 1,5-HAT step showing maximum spin density on the benzylic carbon and some delocalization over the adjacent phenyl ring.

mediate C the key 1,5-HAT step proceeds readily via the low barrier transition state TS2 (barrier: $\Delta G^{\ddagger} = +2.1$ kcal mol^{-1}) to give intermediate D ($\Delta G^{\circ} = -12.6$ kcal mol^{-1}). Ring-closure by radical rebound and homolysis of the Co–C bond proceeds through the low, albeit slightly higher barrier transition state TS3 ($\Delta G^{\ddagger} = +11.5$ kcal mol^{-1}).

The computed barriers of all steps of the catalytic cycle depicted in Figure 3 are surprisingly low. This suggests that formation of the diazo compound from the tosyl hydrazone precursors, which requires heating, is the rate limiting step of the reaction. Once the diazo compound is generated, the next highest electronic barrier in the catalytic reaction is the ring-closing step from species D to liberate the product and regenerate catalyst A. Release of product E with regeneration of catalyst A is strongly exergonic.

We also calculated the spin density distribution of the intermediates **C** and **D** (Figure 3 b and c). Maximum spin-density in intermediate **C** is indeed located on the "carbene carbon" with some further delocalisation in the neighbouring phenyl ring (Figure 3 b). The unpaired electron of intermediate **D** formed after the 1,5-HAT step is delocalised over the benzylic carbon with considerable delocalisation also on the adjacent phenyl ring (Figure 3 c).

Conclusions

In this work, we report a novel route for the synthesis of several substituted indolines which have relevance to both natural product and pharmaceutical scaffolds. The reaction initiates efficiently via a **[Co^{II}(Por)]**-catalysed pathway by activation of an in situ formed diazo compound to form a carbene radical. The ensuing 1,5-hydrogen atom transfer step transforms the reactive carbene radical into a more stabilized conjugated radical, which then liberates the desired N-heterocyclic product with regeneration of the catalyst via a ring-closing radical displacement step. This reaction uses inexpensive, commercially available reagents and allows for the use of tosyl hydrazones as safe, stabile precursors to diazo compounds.[26]

To the best of our knowledge, this is the first example of a cobalt(III)-carbene radical mediated C—H activation/rebound mechanism for the synthesis of N-heterocyclic organic products. The metalloradical catalysed indoline synthesis in this work represents an example of a formal intramolecular carbene insertion reaction into a benzylic C—H bond, but proceeds via a radical mechanism and displays highly controlled reactivity of the key Co^{III}-carbene radical intermediates involved.

Experimental Section

General procedure for indoline formation

To a flame-dried Schlenk tube was added substrate (0.300 mmol) followed by the **[Co(TPP)]** (10 mg, 0.015 mmol, 5.0 mol%). The Schlenk tube was evacuated and back-filled with nitrogen three times, and evacuated prior to transfer to a glove box. Once inside a glove box, the reaction flask was slowly filled with nitrogen, and lithium *tert*-butoxide (40.8 mg, 0.510 mmol, 1.7 equiv) was added. The solids were dissolved in 6 mL of benzene and the reaction flask was removed from the glovebox and transferred to an oil bath preheated to 60 °C. After 18 hours, the reaction mixture was cooled to room temperature, opened to air, and 6 mL of water was added in a single portion. The water layer was extracted 3 times with hexanes (3×6 mL). The organic portions were dried over MgSO$_4$, filtered through cotton, and concentrated in vacuo. The crude residue was then purified via silica gel chromatography to provide the pure indoline product.

See the Supporting Information for further procedures and characterization data.

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbenes · cobalt · indolines · metalloradicals · radicals

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