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**Photocatalysis**

# Dearomative (3+2) Cycloadditions between Indoles and Vinyldiazo Species Enabled by a Red-Shifted Chromium Photocatalyst

*Bradley K. Gall*[+]*, Avery K. Smith*[+]*, and Eric M. Ferreira**

**Abstract:** A direct dearomative photocatalyzed (3+2) cycloaddition between indoles and vinyldiazo reagents is described. The transformation is enabled by the development of a novel oxidizing $Cr^{III}$ photocatalyst, its specific reactivity attributed to increased absorptive properties over earlier Cr analogs and greater stability than Ru counterparts. A variety of fused indoline compounds are synthesized using this method, including densely functionalized ring systems that are feasible due to base-free conditions. Experimental insights corroborate a cycloaddition initiated by nucleophilic attack at C3 of the indole radical cation by the vinyldiazo species.

## Introduction

Photoredox catalysis has emerged as a staple for novel bond-forming transformations.[1] Reactions in this class, originating from an excited-state species generated by light initiation, involve highly active intermediates that are produced via single electron transfer. Chemists now have an arsenal of metal- and nonmetal-based photocatalysts that display ranges of reactivity owing to their respective excited state reduction potentials. Multiple classes of reaction types proceeding by electron transfer can be catalyzed by these species, such as atom-transfer processes, cross-couplings, and cycloadditions. Despite numerous catalysts at our disposal, advancements remain necessary when limitations are encountered in reaction manifolds. Related to our development of synthetic transformations using active metal photocatalysts,[2] emphasizing metals based on the first row,[3] we recently reported a (3+2) cycloaddition between alkenes and vinyldiazo species (Figure 1a).[2f] This transformation initiates via oxidation of the electron rich alkene using either chromium or ruthenium catalysis, and we were enticed by the prospect that this photocatalyzed cycloaddition may translate to heterocycles such as indoles. The densely-substituted fused indoline structure that would result from a cycloaddition is a prevalent structural motif in a variety of natural products and bioactive molecules.[4] A differentiating challenge of this proposed process is that it would necessitate a *dearomatization.*[5] A potentially competing nucleophile addition pathway would involve substitution with rapid rearomatization. In seminal reports, Nicewicz and co-workers showed downhill rearomatization after either *N*-nucleophile[6a] or diazoacetate addition[6b] to arene radical cations (Figure 1b), and Gryko and co-workers described the photoredox C2 alkylation of indoles with α-diazoesters (Figure 1c).[7,8] Photocatalytic intra- and intermolecular dearomative cycloadditions proceeding by energy transfer have been described,[9] as have photoredox dearomative additions featuring intramolecular nucleophiles.[10] Metal-photocatalyzed dearomative cycloadditions *proceeding by electron transfer*, however, are quite rare.[11] Photocatalyzed (4+2) cycloadditions between indoles and dienes have been achieved using either oxidizing triarylpyryliums[12] or heterogeneous metal compositions,[13] which offered

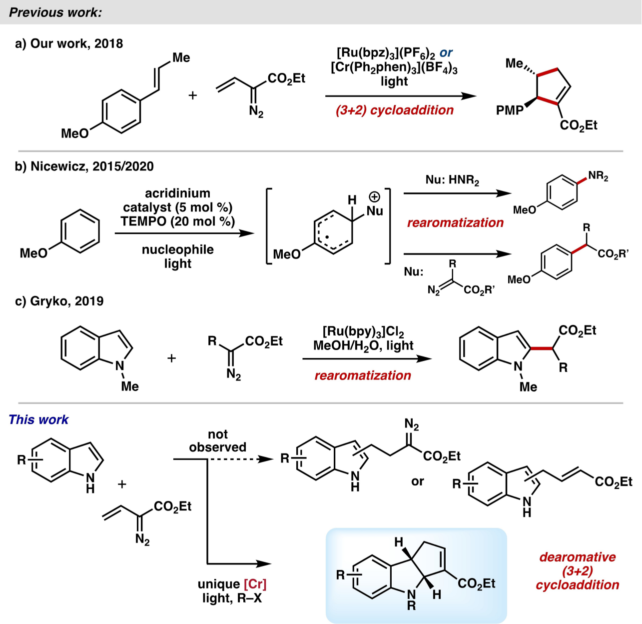

***Figure 1.*** (3+2) cycloadditions expanded to dearomatizations. a) Previous (3+2) cycloaddition with alkenes. b) Photocatalyzed nucleophilic attack on arene radical cation. c) Photocatalyzed diazo addition to indoles with rearomatization.

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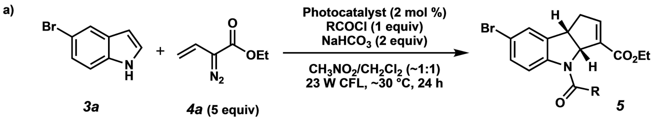
promise that extrapolating to this type of (3+2) cycloaddition was conceivable and would represent a mechanistic complement to carbene-mediated processes by Davies and Doyle.[14,15] Herein, we report the successful realization of this photoredox transformation, specifically enabled by the development of a novel chromium(III) photocatalyst with increased activity.

## Results and Discussion

In the aforementioned radical cation (3+2) cycloaddition between alkenes and vinyldiazo species,[2f] both [Cr(Ph$_2$phen)$_3$](BF$_4$)$_3$ (**1a**, $E_{\mathrm{red}} = +1.40$ V in CH$_3$NO$_2$)[16] and [Ru(bpz)$_3$](PF$_6$)$_2$ (**2**, $E_{\mathrm{red}} = +1.45$ V in CH$_3$CN) were active photocatalysts; the Ru catalysts generally afforded faster reactivity, but in select cases Cr was uniquely operative. The reduction potential of N–H indole ($E_{\mathrm{red}} = +1.16$ V in CH$_3$CN)[17] suggested that this oxidative process could be transferable to these heterocycles; a heteroarene oxidation leading to its radical cation would initiate the cycloaddition mechanism. A key aspect in the design of this process is that in situ N-substitution would likely be necessary; the indoline product would otherwise be more susceptible to oxidation than the indole itself, thus suppressing propagation. This principle is consistent with earlier examples of photosensitized (4+2) cycloadditions between indoles and dienes.[12,13] To that end, our initial screening of reactivity is shown in Figure 2a. We treated 5-bromoindole with ethyl vinyldiazoacetate using both the Cr and Ru photocatalysts (entries 1, 2), adding an acid chloride and NaHCO$_3$ for post-cycloaddition acylation. Acetyl chloride afforded modest yields, but more encouraging results were obtained using benzoyl chloride. We were delighted to observe the formation of product **5**—with exclusive regio- and diastereoselectivity—but in somewhat modest yield compared to the previous cycloaddition yields using electron rich alkenes. Other oxidizing photocatalyst systems were examined, both organic and inorganic (see Supporting Information for full catalyst screen), but were met with limited success.[18] [Ru(bpz)$_3$](PF$_6$)$_2$ has been the most broadly successful photocatalyst in inducing radical cation cycloadditions;[2f,19] thus its unexceptional activity here prompted us to probe deeper. The bipyrazine ligands impart improved oxidation capacity over bipyridine ligands (i.e., as in [Ru(bpy)$_3$]$^{2+}$), but we hypothesized that these ligands may also be reactive with the acylating agent.[20] Indeed, when we subjected the Ru catalyst to BzCl and irradiation, a marked change in UV/Vis absorption was observed (Figure 2b), suggesting the catalyst composition had transformed during the reaction.[21]

[Cr(Ph$_2$phen)$_3$](BF$_4$)$_3$ was generally less reactive than [Ru(bpz)$_3$](PF$_6$)$_2$ in radical cation cycloadditions, but we thought this catalyst system framework may offer a path forward. One reason for the lesser reactivity of the Cr complex is its weaker absorption properties; if absorbance could be increased, then it could possibly translate to a more reactive catalyst. Electron-rich substituents are known to have measurable effects on bathochromic shifts in absorbance,[22] and we hypothesized this principle may be applicable to the chromium trisphenanthrolinyl complexes. We found that introducing *p*-OMe substituents on the phenyls of the bathophenanthroline (**1b**, [Cr(PMP$_2$phen)$_3$](BF$_4$)$_3$) led to a complex with a red-shifted, higher absorbance (Figure 3a). A similar experiment with BzCl and irradiation also indicated more promising catalyst stability. To our delight, this complex also led to a significant increase in yield in the (3+2) cycloaddition, affording an improvement to 75 % yield of the desired acylated cycloadduct



| entry | photocatalyst | RCOCl | NMR yield *5* (%)[a] |
|---|---|---|---|
| 1 | [Cr(Ph$_2$phen)$_3$](BF$_4$)$_3$ (*1a*) | AcCl | 8 |
| 2 | [Ru(bpz)$_3$](PF$_6$)$_2$ (*2*) | AcCl | 31 |
| 3 | *1a* | BzCl | 26 |
| 4 | *2* | BzCl | 44 |

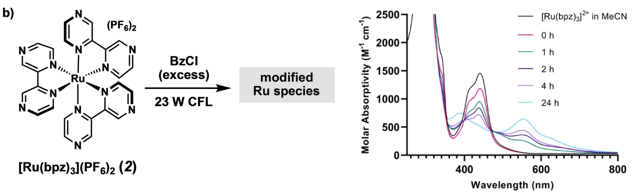
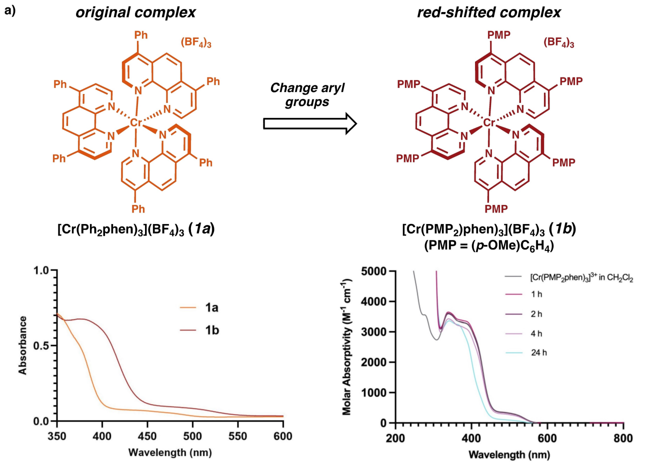
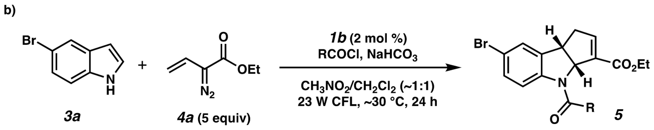


**Figure 2.** a) Initial Ru and Cr catalyst evaluation. b) Time-lapsed UV/Vis evaluation of Ru catalyst stability to BzCl and irradiation. [a] NMR yield determined using CH$_2$Br$_2$ as a standard.





| | RCOCl | NaHCO$_3$ | NMR yield *5* (%)[a] |
|---|---|---|---|
| BzCl | 1 | 2 | 75 |
| BzCl | 3 | 5 | 94 |
| TrocCl | 3 | 5 | 95 |

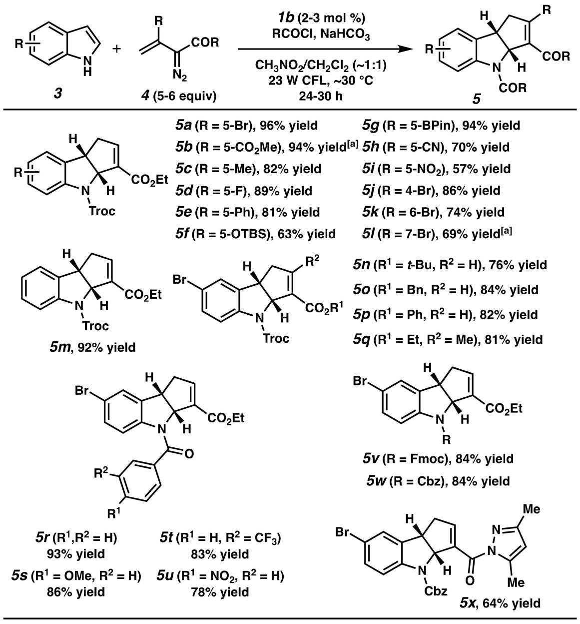
**Figure 3.** a) Implementing a red-shift in the trisphenanthrolinyl Cr complex, and its time-lapsed UV/Vis evaluation to BzCl and irradiation. b) Successful cycloaddition with [Cr(PMP$_2$phen)$_3$](BF$_4$)$_3$. [a] NMR yield determined using CH$_2$Br$_2$ as a standard.

(Figure 3b). Further increasing the amount of BzCl and $NaHCO_3$ to 3 and 5 equiv. respectively was highly beneficial, yielding 94 % of cycloadduct **5**. Chloroformates were equally effective as acylating agents in the transformation; using 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) we obtained an excellent 95 % yield of the cycloadduct.

The scope of this dearomative cycloaddition is depicted in Scheme 1. The reaction tolerated a number of C5-functional groups on the heterocycle, including halides, esters, silyl ethers, boronates, nitriles, and nitro groups (**5a**–**5i**). Silyl ether **5f** and nitro **5i** were afforded in moderate yields, implicating a window of optimal reactivity based on the electronic nature of the indole starting material. Substitutions at C4, C6, and C7 (**5j**–**l**) were all accommodated. In addition to ethyl vinyldiazoacetate, the *tert*-butyl, benzyl, and phenyl esters were effectively reactive (**5n**–**p**). A diazoacetate with β-substitution could also participate in the cycloaddition (**5q**), although γ-substitution was not tolerated.[23] Several acid chlorides and chloroformates could be utilized (**5r**–**w**), generally with the stipulation that there was no α-C–H on the acylating agent.[24] Finally, the reaction was also not limited to diazoesters; the (3+2) cycloaddition was effective using an acylpyrazole-based vinyldiazo species (**5x**, 64 % yield).

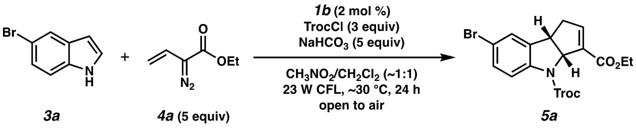
Table 1 highlights the importance of various parameters in this cycloaddition. The choice of base was important; other inorganic and organic bases were not as successful (entries 2–4), sometimes shutting down the cycloaddition altogether. Visible light (23 W CFL) was the optimal light source, although other light sources still promoted reactivity (entries 6,7). Fewer equivalents of the vinyldiazo reagent were tolerated, albeit in modestly diminished yield (entry 8). This reaction can be conveniently set up open to air, although we found the reaction performed equally well in an oxygen or inert atmosphere (entries 9,10), suggesting little to no role for $O_2$. Lower catalyst loading led to a marginal decrease in yield (entry 11). Catalyst and light were essential for cycloaddition to occur (entries 12,13), while acylating agent was critical for the reaction to progress (entry 14). Added TEMPO significantly hampered reactivity, suggesting radical intermediacy in the mechanism (vide infra).

Indoles with C2- and/or C3-substitution proved to be uniquely challenging. Several acylating agents were investigated with indole **6a** (Scheme 2a). Standard conditions utilizing TrocCl with $NaHCO_3$ for acylation proved to be incompatible, as were most other acylating reagents examined (see Supporting Information for full list of reagents).



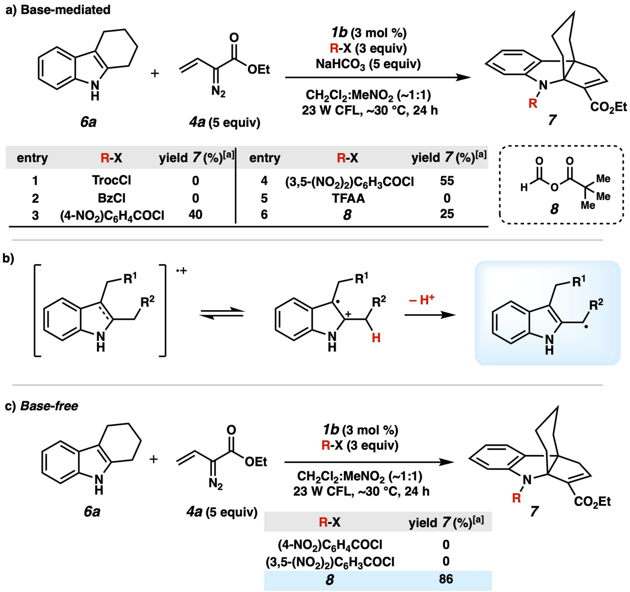
***Scheme 1.*** Photocatalyzed (3+2) cycloaddition - reaction scope. [a] Pyrazole (from diazo rearrangement) present; yield is of cycloadduct only.

***Table 1:*** Evaluation of photocatalyzed indole (3+2) cycloadditions with $[Cr(PMP_2phen)_3](BF_4)_3$.



| entry | deviation from standard conditions | yield *5a* (%)[a] | entry | deviation from standard conditions | yield *5a* (%)[a] |
|---|---|---|---|---|---|
| 1 | none | 95 | 9 | inert atmosphere | 88 |
| 2 | $KHCO_3$ | 51 | 10 | $O_2$ atmosphere | 91 |
| 3 | $NaH_2PO_4$ | 52 | 11 | 0.5 mol % catalyst | 76 |
| 4 | $Et_3N$ | 0 | 12 | No catalyst | 0 |
| 5 | $CH_2Cl_2$ only | 86 | 13 | No light | 0 |
| 6 | blue LED (390 nm) | 28 | 14 | No TrocCl | 0[b] |
| 7 | near UV irradiation | 39 | 15 | No $NaHCO_3$ | 45 |
| 8 | 2 equiv *4a* | 73 | 16 | 1 equiv TEMPO added | 19 |

[a] Yields determined by $^1H$ NMR with $CH_2Br_2$ as a standard. [b] < 20 % unprotected cycloaddition product observed.



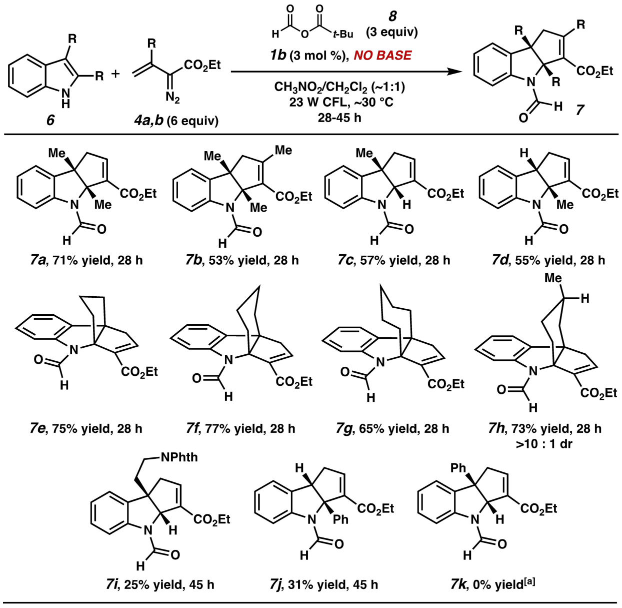
| entry | R-X | yield *7* (%)[a] | entry | R-X | yield *7* (%)[a] |
|---|---|---|---|---|---|
| 1 | TrocCl | 0 | 4 | $(3,5\text{-}(NO_2)_2)C_6H_3COCl$ | 55 |
| 2 | BzCl | 0 | 5 | TFAA | 0 |
| 3 | $(4\text{-}NO_2)C_6H_4COCl$ | 40 | 6 | *8* | 25 |

| R-X | yield *7* (%)[a] |
|---|---|
| $(4\text{-}NO_2)C_6H_4COCl$ | 0 |
| $(3,5\text{-}(NO_2)_2)C_6H_3COCl$ | 0 |
| *8* | 86 |

***Scheme 2.*** Expansion of cycloaddition to C2/C3-substituted indoles. a) Evaluation of base-mediated conditions with acylation agents. b) Facile deprotonation of indole radical cation. c) Base-free conditions in the cycloaddition. [a] Yields determined by $^1H$ NMR with $CH_2Br_2$ as a standard.

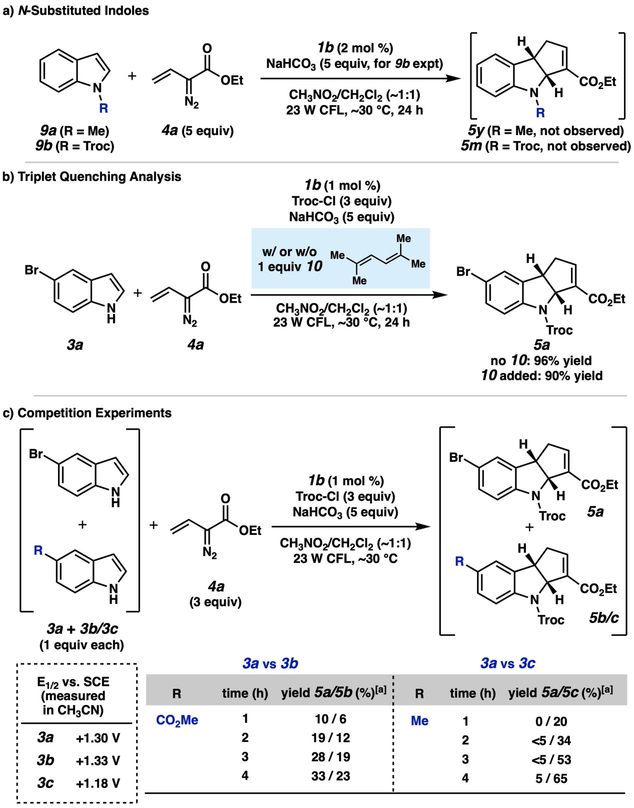
More electron deficient benzoyl chlorides exhibited moderate reactivity (entries 3, 4). We believed a different reagent could be fruitful, perhaps more compact or one that would avoid HCl byproduct generation.[25] TFAA was ineffective, but encouragingly, the infrequently used trimethylacetic formic anhydride (**8**)[26,27] showed measurable activity. Although the modest reactivity across these acylating agents was perhaps predictable due to the increased substitution around the indoline nitrogen, we did not believe that sterics alone could fully explain the reaction failure. We hypothesized that in the presence of the base necessary for N-acylation, the radical cation intermediate could be competitively deprotonated, leading to a radical species that complicates reactivity (Scheme 2b). A *base-free* acylation may circumvent this problem. We thus examined several potential acylation agents without the addition of base on indole **6a** (Scheme 2c). Trimethylacetic formic anhydride was singularly effective, generating *N*-formyl cycloadduct **7** in excellent yield.

A range of C2/C3 mono- and disubstituted indoles could engage in the cycloaddition using this unique anhydride reagent (Scheme 3). Indoles with fused rings were notably effective (**7e–h**). A substituent on the fused ring induces high diastereoselectivity in the facial addition (**7h**). Nitrogen substituents have been routinely challenging in this class of cycloadditions, but in this case a phthalimide-based tryptamine derivative was tolerated in modest yield (**7i**). A comparison of products **7j** and **7k** is also informative. Based on our previous understanding of this class of reactions, the vinyldiazo acts as a nucleophile to attack the C3 position of the radical cation intermediate. The yields of adducts **7j** and **7k** are consistent with this mechanistic picture, implicating a responsiveness to the steric environment in this nucleophilic attack.[28]



***Scheme 3.*** Photocatalyzed (3+2) cycloaddition with C2/C3-substituted indoles. [a] 2 mol % **1b**, 5 equiv **4a**.

To shed insight on the mechanistic pathway, several experiments were conducted. First, both *N*-Me indole **9a** and *N*-Troc indole **9b** were not viable substrates (Scheme 4a), establishing that the N–H indole species is required for the cycloaddition to proceed.[29] Second, the (3+2) cycloaddition was performed in the presence of 2,5-dimethyl-2,4-hexadiene (**10**, Scheme 4b). This triplet-quenching additive has been shown to inhibit reactivity in photocatalytic intramolecular (2+2) cycloadditions between indoles and alkenes.[9b,e] The (3+2) cycloaddition between indole **3a** and vinyldiazo **4a** is virtually unaffected by this diene; this outcome implicates the lack of an energy transfer pathway.[30] Next, indole competitions are depicted in Scheme 4c. 5-Bromoindole (**3a**) was subjected to the cycloaddition in the presence of an equivalent of either 5-methoxycarbonylindole (**3b**) or 5-methylindole (**3c**). In the former case the cycloaddition preferences are about the same, while in the latter there is a near-exclusive selectivity for cycloaddition with the 5-methylindole. This reaction profile is consistent with reactivity being governed by the indole's electronic properties; the more oxidizable indole preferentially engages. The reduction potential of vinyldiazo **4a** is +1.57 V vs. SCE,[2f] higher than the indoles used in this experiment. This difference suggests photocatalyzed oxidation of the vinyldiazo species is not as likely.



| $E_{1/2}$ vs. SCE (measured in $CH_3CN$) | |
|---|---|
| *3a* | +1.30 V |
| *3b* | +1.33 V |
| *3c* | +1.18 V |

| | **3a vs 3b** | | | **3a vs 3c** | |
|---|---|---|---|---|---|
| R | time (h) | yield *5a/5b* (%)[a] | R | time (h) | yield *5a/5c* (%)[a] |
| $CO_2Me$ | 1 | 10 / 6 | Me | 1 | 0 / 20 |
| | 2 | 19 / 12 | | 2 | <5 / 34 |
| | 3 | 28 / 19 | | 3 | <5 / 53 |
| | 4 | 33 / 23 | | 4 | 5 / 65 |

***Scheme 4.*** Mechanistic studies of the (3+2) dearomative cycloaddition. a) Unreactivity of *N*-substituted indoles. b) Minimal reaction impact by triplet-quenching diene. c) Competition experiments on electronically differentiated indoles. [a] Yields determined by $^1H$ NMR with dodecyl acetate as a standard.

Based on these experiments and the aforementioned indole-diene (4+2) cycloadditions,[12,13] we propose the transformation occurs as depicted in Figure 4. Oxidation of the indole by the $Cr^{III}$ excited state generates radical cation $3^{+\bullet}$. There is significant radical character at C3 in this species,[12c,31] which then combines with the vinyldiazo to yield intermediate **11**.[32] Ring closure and subsequent reduction with either $Cr^{II}$ or indole substrate affords fused indoline **13**. The transformation culminates with an acylation to drive the product outside the oxidation window of the catalyst. In Davies's analogous Rh-catalyzed (3+2) cycloaddition via a carbenoid species, the regioselectivity of the addition was dictated by C2/C3-substitution on the indole.[14a] In this particular photocatalyzed cycloaddition, regioselectivity is exclusive and distinct, governed entirely by the selectivity induced from the indole radical cation intermediate ($3^{+\bullet}$).[33]

A couple of additional pieces of evidence are also consistent with the proposed single electron transfer mechanism. The suppressed reactivity by TEMPO (vide supra, Table 1, entry 16) implicates the intermediacy of radical species. Stern–Volmer quenching studies revealed a strong linear relationship between the concentration of indole **3a** and the emission signal from the Cr complex excited state related to electron transfer (Figure 5). Meanwhile, varying concentrations of vinyldiazo **4a** did not impact the same Cr emission signal whatsoever.[34] These photophysical experiments further point to a reaction mechanism involving initiation by electron transfer.

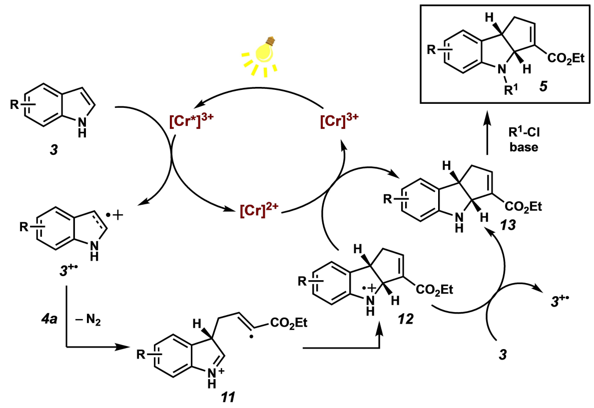


*Figure 4.* Proposed reaction mechanism.

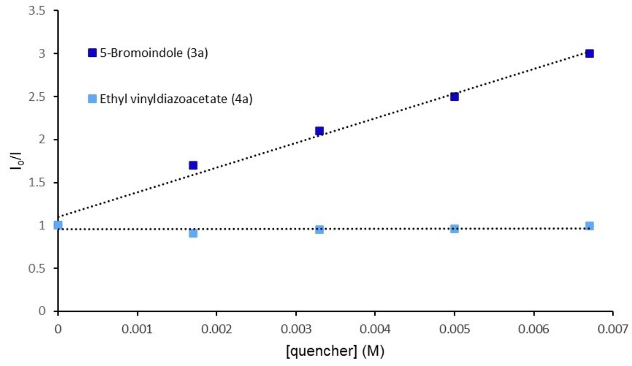
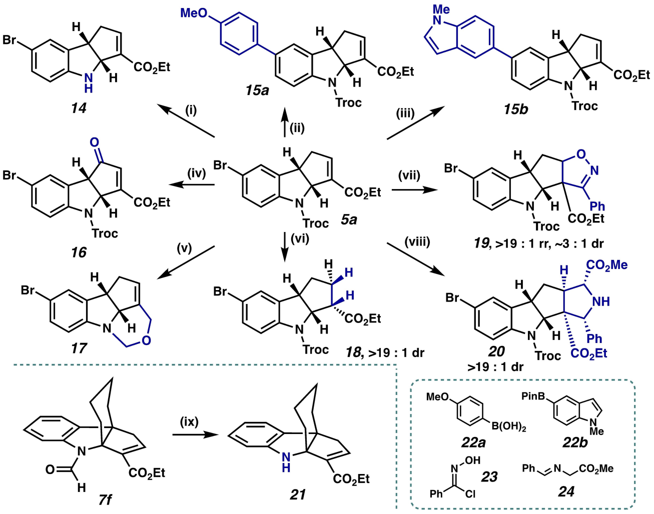


*Figure 5.* Stern–Volmer analysis.

The indoline cycloadducts can be readily diversified, as shown by the transformations of indoline **5a** (Scheme 5). Removal of the trichloroethoxycarbonyl proceeds in excellent yield (**14**). Cross couplings with the aryl bromide moiety can be achieved with aryl or heteroaryl boron reagents (**15a,b**). Allylic oxidation affords enone **16**,[35] while DIBAL reduction generates hemiaminal ether **17**.[36] The fused 5,5-ring system allows for diastereoselective transformations. Conjugate reduction using $NaBH_4$/Fe(tpp)Cl generates the exclusive saturated ester diastereomer (**18**).[37] The enoate is also poised for subsequent cycloadditions. Nitrile oxide addition[38] affords isoxazoline **19** with excellent regioselectivity and moderate dr, while Ag-catalyzed glycine-imine (3+2) cycloaddition[39] yields pyrrolidine **20** featuring six stereogenic centers. For formylated derivatives, the removal of the N-protecting group is also straightforward under acidic conditions (**7f**→**21**). The synthetic handles generated via this cycloaddition present a breadth of options for subsequent manipulations, offering promise for wide applications.

## Conclusion

The development of catalysts based on earth abundant metals is an important endeavor toward sustainable chemistry. These catalysts also present the possibility of discovering unique transformations altogether. We have described herein the development of an increased-activity first row metal photocatalyst, $[Cr(PMP_2phen)_3](BF_4)_3$, and



*Scheme 5.* Indoline product diversification. (i) Zn, AcOH, 23 °C, 98 % yield. (ii) **22a**, cat. Pd(dppf)$Cl_2$, $K_3PO_4$, $H_2O$, 1,4-dioxane, 100 °C, 68 % yield. (iii) **22b**, cat. Pd(dppf)$Cl_2$, $K_3PO_4$, $H_2O$, 1,4-dioxane, 100 °C, 64 % yield. (iv) PDC, *t*-BuOOH, PhH/$H_2O$, 0 to 23 °C, 63 % yield. (v) DIBAL, $CH_2Cl_2$, 0 °C, 64 % yield. (vi) $NaBH_4$, cat. Fe(tpp)Cl, THF/MeOH, 23 °C, 83 % yield. (vii) **23**, $Et_3N$, EtOAc/$CH_2Cl_2$, 23 °C, 82 % yield. (viii) **24**, cat. AgOAc, cat. $PPh_3$, $Et_3N$, $PhCH_3$, 23 °C, 92 % yield. (ix) HCl, MeOH/$H_2O$, 23 °C, 65 % yield.

demonstrated its efficacy in dearomative (3+2) cycloadditions with indoles. Densely functionalized indolines are accessible via this extremely mild transformation, with synthetic handles poised for further manipulation. Further characterization of this new catalyst and derivatives, mechanistic studies, and applications in additional transformations and bioactive indoline syntheses are underway.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

**Keywords:** Chromium · Cycloaddition · Dearomatization · Indoles · Photocatalysis

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[1] For select reviews and perspectives, see: a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; c) T. P. Yoon, *ACS Catal.* **2013**, *3*, 895; d) R. A. Angnes, Z. Li, C. R. D. Correia, G. B. Hammond, *Org. Biomol. Chem.* **2015**, *13*, 9152; e) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075; f) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898; g) J. D. Bell, J. A. Murphy, *Chem. Soc. Rev.* **2021**, *50*, 9540.

[2] a) S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 6506; *Angew. Chem.* **2015**, *127*, 6606; b) R. F. Higgins, S. M. Fatur, S. G. Shepard, S. M. Stevenson, D. J. Boston, E. M. Ferreira, N. H. Damrauer, A. K. Rappé, M. P. Shores, *J. Am. Chem. Soc.* **2016**, *138*, 5451; c) S. M. Stevenson, R. F. Higgins, M. P. Shores, E. M. Ferreira, *Chem. Sci.* **2017**, *8*, 654; d) F. J. Sarabia, E. M. Ferreira, *Org. Lett.* **2017**, *19*, 2865; e) R. F. Higgins, S. M. Fatur, N. H. Damrauer, E. M. Ferreira, A. K. Rappé, M. P. Shores, *ACS Catal.* **2018**, *8*, 9216; f) F. J. Sarabia, Q. Li, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2018**, *57*, 11015; *Angew. Chem.* **2018**, *130*, 11181.

[3] For a recent perspective, see: C. B. Larsen, O. S. Wenger, *Chem. Eur. J.* **2018**, *24*, 2039.

[4] a) J. E. Saxton in *The Alkaloids: Chemistry and Biology, Vol. 51* (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, chap. 1; b) T.-S. Kam, K.-H. Lim in *The Alkaloids: Chemistry and Biology, Vol. 66* (Ed.: G. A. Cordell), Elsevier, Amsterdam, **2008**, chap. 1; c) M. Cuendet, J. M. Pezzuto in *Modern Alkaloids: Structure, Isolation, Synthesis and Biology* (Eds.: E. Fattorusso, O. Taglialatela-Scafati), Wiley-VCH, Weinheim, **2008**, chap. 2; d) J. D. Podoll, Y. Liu, L. Chang, S. Walls, W. Wang, X. Wang, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 15573; e) X.-Y. Liu, Y. Qin, *Acc. Chem. Res.* **2019**, *52*, 1877.

[5] For reviews on indole dearomatization and applications in synthesis, see: a) S. P. Roche, J.-J. Youte Tendoung, B. Tréguier, *Tetrahedron* **2015**, *71*, 3549; b) G. Huang, B. Yin, *Adv. Synth. Catal.* **2019**, *361*, 405; c) C. Zheng, S.-L. You, *Nat. Prod. Rep.* **2019**, *36*, 1589; d) H. Abou-Hamdan, C. Kouklovsky, G. Vincent, *Synlett* **2020**, *31*, 1775.

[6] a) N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326; b) N. Holmberg-Douglas, N. P. R. Onuska, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2020**, *59*, 7425; *Angew. Chem.* **2020**, *132*, 7495.

[7] Ł. W. Ciszewski, J. Durka, D. Gryko, *Org. Lett.* **2019**, *21*, 7028.

[8] For a review on visible light-mediated indole functionalization, see, A. A. Festa, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2019**, *48*, 4401.

[9] Select intramolecular examples: a) M. J. James, J. L. Schwarz, F. Strieth-Kalthoff, B. Wibbeling, F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 8624; b) M. Zhu, C. Zheng, X. Zhang, S.-L. You, *J. Am. Chem. Soc.* **2019**, *141*, 2636; c) M. Zhu, X. Zhang, C. Zheng, S.-L. You, *ACS Catal.* **2020**, *10*, 12618; d) A. B. Rolka, B. Koenig, *Org. Lett.* **2020**, *22*, 5035; e) Z. Zhang, D. Yi, M. Zhang, J. Wei, J. Lu, L. Yang, J. Wang, N. Hao, X. Pan, S. Zhang, S. Wei, Q. Fu, *ACS Catal.* **2020**, *10*, 10149; f) M. Zhu, H. Xu, X. Zhang, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2021**, *60*, 7036; *Angew. Chem.* **2021**, *133*, 7112; g) M. Zhu, X.-L. Huang, S. Sun, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2021**, *143*, 13441; Select intermolecular examples: h) N. Hu, H. Jung, Y. Zheng, J. Lee, L. Zhang, Z. Ullah, X. Xie, K. Harms, M.-H. Baik, E. Meggers, *Angew. Chem. Int. Ed.* **2018**, *57*, 6242; *Angew. Chem.* **2018**, *130*, 6350; i) J. Ma, S. Chen, P. Bellotti, R. Guo, F. Schäfer, A. Heusler, X. Zhang, C. Daniliuc, M. K. Brown, K. N. Houk, F. Glorius, *Science* **2021**, *371*, 1338; j) W. Zhuang, Y.-Z. Cheng, X.-L. Huang, Q. Huang, X. Zhang, *Org. Chem. Front.* **2021**, *8*, 319.

[10] a) E. C. Gentry, L. J. Rono, M. E. Hale, R. Mastuura, R. R. Knowles, *J. Am. Chem. Soc.* **2018**, *140*, 3394; b) Y.-Z. Cheng, Q.-R. Zhao, X. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2019**, *58*, 18069; *Angew. Chem.* **2019**, *131*, 18237.

[11] For recent examples of electrochemcial dearomative indole annulations, see: a) K. Liu, W. Song, Y. Deng, H. Yang, C. Song, T. Abdelilah, S. Wang, H. Cong, S. Tang, A. Lei, *Nat. Commun.* **2020**, *11*, 3; b) C. Song, K. Liu, X. Jiang, X. Dong, Y. Weng, C.-W. Chiang, A. Lei, *Angew. Chem. Int. Ed.* **2020**, *59*, 7193; *Angew. Chem.* **2020**, *132*, 7260; c) J. Wu, Y. Dou, R. Guillot, C. Kouklovsky, G. Vincent, *J. Am. Chem. Soc.* **2019**, *141*, 2832; d) K. Liu, S. Tang, P. Huang, A. Lei, *Nat. Commun.* **2017**, *8*, 775.

[12] a) A. Gieseler, E. Steckhan, O. Wiest, *Synlett* **1990**, 275; b) A. Gieseler, E. Steckhan, O. Wiest, F. Knoch, *J. Org. Chem.* **1991**, *56*, 1405; c) O. Wiest, E. Steckhan, F. Grein, *J. Org. Chem.* **1992**, *57*, 4034; d) O. Wiest, E. Steckhan, *Tetrahedron Lett.* **1993**, *34*, 6391; e) T. Peglow, S. Blechert, E. Steckhan, *Chem. Commun.* **1999**, 433; f) U. Haberl, E. Steckhan, S. Blechert, O. Wiest, *Chem. Eur. J.* **1999**, *5*, 2859.

[13] S. P. Pitre, J. C. Scaiano, T. P. Yoon, *ACS Catal.* **2017**, *7*, 6440.

[14] a) Y. Lian, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 440; b) C. Jing, Q.-Q. Cheng, Y. Deng, H. Arman, M. P. Doyle, *Org. Lett.* **2016**, *18*, 4550.

[15] Indole dearomatization via (3+2) cycloaddition can also be achieved through alternative methods, including by opening strained rings or by conjugate addition into an electron deficient C2–C3 π bond. Select examples: a) H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 7851; b) A. Awata, T. Arai, *Angew. Chem. Int. Ed.* **2014**, *53*, 10462; *Angew. Chem.* **2014**, *126*, 10630; c) Z. Chai, Y.-M. Zhu, P.-J.

Yang, S. Wang, S. Wang, Z. Liu, G. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 10088; d) H. Wang, J. Zhang, Y. Tu, J. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 5422; *Angew. Chem.* **2019**, *131*, 5476.

[16] Reduction potentials are reported vs. the saturated calomel electrode (SCE). $\mathrm{Ph_2phen}$: 4,7-diphenyl-1,10-phenanthroline.

[17] H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2015**, *27*, 714.

[18] Running experiments for longer did not increase the yield; vinyldiazo reagents will slowly convert to pyrazoles under the reaction conditions.

[19] S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 19350.

[20] For an interesting example of photocatalyst modification during the course of a reaction, see, J. J. Devery III, J. J. Douglas, J. D. Nguyen, K. P. Cole, R. A. Flowers II, C. R. J. Stephenson, *Chem. Sci.* **2015**, *6*, 537.

[21] Acylation of the bipyrazine ligand(s) is likely occurring, leading to complex combinations of acylated species.

[22] K. Bowden, E. A. Braude, E. R. H. Jones, *J. Chem. Soc.* **1946**, 948.

[23] A γ-Ph vinyldiazo reagent was tested; see the Supporting Information for details. This reagent is prone to rapid pyrazole formation under irradiation.

[24] When enolizable acylating agents were used, we observed fast decomposition of the vinyl diazo reagent.

[25] The indole functionalization with diazo reagents in ref. [7] was impacted by protic sources.

[26] E. J. Vlietstra, J. A. Zwikker, R. J. M. Nolte, W. Drenth, *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 460.

[27] For recent examples of use, see: a) K. C. Nicolaou, Q. Chen, R. Li, Y. Anami, K. Tsuchikama, *J. Am. Chem. Soc.* **2020**, *142*, 20201; b) L. S. Kovacevic, C. Idziak, A. Markevicius, C. Scullion, M. J. Corr, A. R. Kennedy, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2012**, *51*, 8516; *Angew. Chem.* **2012**, *124*, 8644; c) D. D. Caspi, H. Zhang, S. C. Virgil, F. M. Piller, B. M. Stoltz, *Heterocycles* **2012**, *86*, 1003.

[28] C2,C3-unsubstituted indoles were also competent under these conditions; the cycloaddition product from 5-bromoindole was obtained in 80 % yield. See the Supporting Information.

[29] N-Substitution of indole with Troc-Cl is slow under the reaction conditions in the absence of vinyldiazo **4a** (≈10 % yield after 24 h).

[30] Relatedly, it has been reported that α-carbonyl radicals—derived photocatalytically from ethyl diazoacetate—will add to N–H indoles at C2. See Ref. [7]. When this reaction was tested as a competition experiment between 5-bromoindole and 5-methylindole, both indoles reacted with similar rates. In a proposed (3+2) cycloaddition mechanism initiated by energy transfer with the vinyl diazoacetate (e.g., **4a**→**4a***), it is expected that **4a*** would have radical-type behavior. In the competition experiment herein, the observed lack of indole selectivity and the C2-regioselective radical addition are both incongruous with this proposed mechanism.

[31] a) S. E. Walden, R. A. Wheeler, *J. Chem. Soc. Perkin Trans. 2* **1996**, 2663; b) L. J. Kettle, S. P. Bates, A. R. Mount, *Phys. Chem. Chem. Phys.* **2000**, *2*, 195.

[32] One could envision the vinyldiazo acting as either a 1-electron nucleophile or a 2-electron nucleophile in attacking the radical cation intermediate. Single electron addition would be more consistent with the radical character at C3 of $\mathbf{3^{+\bullet}}$.

[33] An intramolecular example was attempted where the indole and diazo were proximal and regioselective orientation would be favorable; however, only small amounts of an intermolecular cycloaddition product were observed. The failed cycloaddition is consistent with the entropic difficulties of a 9-*endo* radical cyclization.

[34] The excitation of $\mathrm{[Cr(PMP_2Phen)_3](BF_4)_3}$ produces two main emission signals. The lower energy emission at 752 nm represents the 2E state, which is responsible for electron transfer. There is a higher energy emission in the 400–500 nm range. We observed less pronounced linear Stern–Volmer quenching by both the indole and the vinyldiazoacetate. These $\mathrm{Cr^{III}}$ species are capable of energy transfer; we attribute this quenching to non-productive outcomes (e.g., pyrazole formation, non-productive relaxation). See the Supporting Information.

[35] L. Guandalini, S. Dei, F. Gualtieri, M. N. Romanelli, S. Scapecchi, E. Teodori, K. Varani, *Helv. Chim. Acta* **2002**, *85*, 96.

[36] For a similar observation of this intramolecular cyclization/reduction, see, A. M. Baylis, M. P. H. Davies, E. J. Thomas, *Org. Biomol. Chem.* **2007**, *5*, 3139.

[37] S. Sakaki, T. Kojima, T. Arai, *J. Chem. Soc. Dalton Trans.* **1994**, 7.

[38] V. Jäger, P. A. Colinas in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, chap. 6.

[39] a) D. A. Barr, R. Grigg, H. Q. N. Gunaratne, J. Kemp, P. McMeekin, V. Sridharan, *Tetrahedron* **1988**, *44*, 557; b) J. Casas, R. Grigg, C. Nájera, J. M. Sansano, *Eur. J. Org. Chem.* **2001**, 1971.

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