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Photocatalytic Indole Diels–Alder Cycloadditions Mediated by Heterogeneous Platinum-Modified Titanium Dioxide

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Abstract

Indole alkaloids represent an important class of molecules, with many naturally occurring derivatives possessing significant biological activity. One area that requires further development in the synthesis of indole derivatives is the Diels–Alder reaction. In this work, we expand on our previously developed heterogeneous protocol for the [4+2] cycloaddition of indoles and electron-rich dienes mediated by platinum nanoparticles supported on titanium dioxide semiconductor particles (Pt(0.2%)/TiO₂) with visible-light irradiation. This reaction proceeds with broad scope and is more efficient per incident photon than the previous homogeneous method, and the catalyst can be easily recycled and reused.

Graphical abstract

Keywords

Photoredox catalysis; Heterogeneous catalysis; Indoles; Diels–Alder reactions; Radical-cation cycloadditions

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ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Experimental procedures, reaction optimization, compound characterization and NMR spectra.

The authors declare no competing financial interests.

Introduction

Indole alkaloids represent a large array of complex natural products that exhibit a broad range of chemical diversity and potent biological activity.¹ Many of these structures, including the *Strychnos* alkaloids subfamily, possess tetrahydrocarbazole cores.² Among the most commonly employed, efficient methods for constructing these tetrahydrocarbazole cores involves the Diels–Alder reaction. Indoles are electron-rich dienophiles and have been demonstrated to undergo inverse electron-demand Diels–Alder reactions with electron poor dienes to access tetrahydrocarbazole rings.^{2–3} Indoles have also been demonstrated to undergo normal electron-demand Diels–Alder reactions with electron-rich dienes; however, these reactions typically require the presence of an electron-withdrawing group at the C3 position as well as high temperatures and/or pressures.⁴ Due to the poor tolerance of these conditions towards many common functional groups, the discovery of milder and more efficient protocols is an important goal.

In the early 1990s, Steckhan and coworkers described a method for Diels–Alder cycloadditions that catalyzed by one-electron photooxidation of indole using triphenylpyrillium tetrafluoroborate (TPPT). The resulting indole radical-cation could be trapped by a variety of electron-rich dienes to generate a diverse range of [4+2] cycloadducts (Figure 1A).⁵ While a variety of tetrahydrocarbazoles can be accessed in synthetically useful yields using this protocol, the requirement for UV irradiation from a Xenon arc lamp limits the practicality and functional group compatibility of this method. We hypothesized that developing a visible-light mediated heterogeneous protocol could overcome these limitations by decreasing possible degradation and/or side reactions, and the heterogeneous nature of the photocatalyst would allow for simplified purification and catalyst recyclability. In this context, we were encouraged by previous work by De Mayo and coworkers using CdS, a visible-light-absorbing heterogeneous semiconductor, to promote the radical-cation photodimerization of *N*-vinylcarbazole (Figure 1B).⁶ Based on our previous work employing Pt(0.2%)/TiO₂ for the photoreduction of C–I bonds as well as the photoreductive cyclization of aryl bis(enones)⁷, as well as our previous studies on radical-cation cycloadditions mediated by TiO₂–indole surface interactions⁸, we hypothesized that this relatively inexpensive catalyst could also be used to promote the photooxidative Diels–Alder reaction of indoles with electron-rich dienes to access functionalized tetrahydrocarbazoles under mild reaction conditions and visible-light irradiation.

Herein, we report the use of Pt(0.2%)/TiO₂ and visible-light irradiation to promote the radical-cation Diels–Alder reaction of indoles (Figure 1C). The reaction proceeds with broad scope in moderate to good yields and was found to be more efficient per photon than the previously reported homogeneous protocol. Importantly, the photocatalyst could be easily recovered and reused up to three times, highlighting the benefit of employing heterogeneous catalysts for photoredox transformations.

Results and Discussion

After a screen of the reaction conditions (see section E of SI), we found that indole undergoes a radical-cation Diels–Alder reaction with 1,3-cyclohexadiene (1,3-CHD, 5 equiv.)

in the presence of Pt(0.2%)/TiO₂ dispersed in MeNO₂ (4 mg/mL) with irradiation from a 10 W blue LED to generate the desired tetrahydrocarbazole in 72% yield (Table 1, Entry 1). The reaction did not proceed in the absence of either Pt(0.2%)/TiO₂ or light (Entries 2 and 3). Consistent with previous observations by Steckhan, the reaction proceeds in low yields in the absence of AcCl and NaHCO₃ (Entry 4) because the unprotected cycloadduct is prone to oxidatively triggered fragmentation.^{5a} Substituting indole for *N*-acetylindole led to no reaction, indicating that acetylation occurs after the [4+2] cycloaddition (Entry 5). Interestingly, a final control experiment with unfunctionalized TiO₂ proceeded with a 60% yield in 5 hours of irradiation even though none of the reaction components absorbed in that region (Entry 6). This control reaction led to the discovery of a visible-light-absorbing complex between indole and the surface of TiO₂. In previously reported work, we confirmed the formation of this complex by FTIR, and we demonstrated using an action spectrum that excitation of this complex is an integral step in the overall mechanism of the transformation.⁸ This complex is also observed with our Pt(0.2%)/TiO₂ catalyst (see section F of SI). In good agreement, irradiating the reaction with a 630 nm LED, where only the Pt nanoparticles absorb, does not result in any reaction (Entry 7), indicating that the observed reactivity with 460 nm LED irradiation is due to the excitation of a TiO₂-indole complex.

Our investigations on the scope of the reaction began with the variation of the indole dienophile (Table 2). For both indole and 5-methoxyindole (Entries 1 and 2), Pt(0.2%)/TiO₂ (72% and 48%, respectively) was found to be a more efficient catalyst than unfunctionalized TiO₂ (60% yield and 31% yield, respectively). For this transformation, the Pt nanoparticles serve as a means to prevent back-electron transfer to indole by trapping the injected electrons, thereby resulting in a more efficient catalytic system (*vide infra*). Since the Pt(0.2%)/TiO₂ catalyst can be easily synthesized in one step, is relatively inexpensive when compared to other popular photoredox catalysts, and provides increased yields, an exploration of the scope was conducted with this catalyst. Overall, the reaction was found to tolerate a variety of electron donating and withdrawing groups at the C5 and C6 positions of indole (Entries 2–10). The reaction was tolerant of both halogen substitution (Entries 3, 4, and 10) and a pinacolatoboron (Bpin) derivative (Entry 6), important substituents for cross-coupling reactions that provide the opportunity for further functionalization of these cycloadducts. Interestingly, when employing 5-iodoindole as the dienophile (Entry 5), no dehalogenation was observed, even though we previously reported that Pt(0.2%)/TiO₂ can be used to promote reductive dehalogenation of iodoarenes.⁷ In this case, the electrons in the CB/Pt nanoparticles are quenched by either O₂ or MeNO₂, preventing reduction of the C-I bond. While arene substitution is well tolerated under our reaction conditions, substitution of the C2 and C3 positions of indole significantly diminished the overall reactivity (Entries 11 and 12). Azaindoles also do not yield [4+2] product, as they are easily deprotonated by NaHCO₃, resulting in *N*-acetylazaindole as the only observed product. Nitro substitution was also not tolerated under our reaction conditions.

Next, the diene scope was examined. In agreement with Steckhan's observations, only dienes that are structurally locked in the *cis* isomer yielded any observable reactivity for the photocatalytic Diels–Alder reaction.⁵ Interestingly, α -terpinene only gave trace amounts of the desired [4+2] product (Entry 14). We hypothesized that if the reaction takes place near

the vicinity of the TiO₂ surface, substitution at the C1 and C4 position of 1,3-CHD could create too large of a steric hindrance for the reaction to proceed efficiently. It was also surprising to observe that cyclopentadiene, which is known to be significantly more reactive than 1,3-CHD in Diels–Alder reactions gave only 19% of the desired [4+2] product (Entry 15). In this case, it is possible that the increased propensity of cyclopentadiene to dimerize resulted in a diminished yield of the productive Diels–Alder cycloadduct. While this protocol has proven effective for a variety of cyclic 1,3-dienes, *cis*-1,3-exocyclic dienes are also well tolerated (Entry 16). This demonstrates that this protocol provides a useful strategy for generating complex indole alkaloids quickly and efficiently, as compound **16** could be accessed after only three synthetic steps, with a total isolated yield of 32%.

Finally, the scope of the acyl group was evaluated. Increasing the bulk of the acetyl chloride was found to have a negative effect on the yield. (Entries 17–19). Chloroformate protecting groups were also examined. While the reaction proceeds poorly with allyl chloroformate (Entry 20) and benzyl chloroformate (Entry 21), both 9-fluorenylmethyl chloroformate (Fmoc chloride, Entry 22) and 2,2,2-trichloroethyl chloroformate (Troc chloride, Entry 23) were found to provide the cycloadduct in moderate yields. In all cases with the exception of Fmoc chloride, a significant loss in yield occurred upon isolation.⁹ Tosyl chloride was also found to be an inefficient protecting group for this reaction (11% yield by ¹H NMR). Other protecting groups commonly employed in organic synthesis such as Boc anhydride (di-*tert*-butyl dicarbonate) and benzyl chloride did not yield any of the desired [4+2] product.

Importantly, the observed reactivity and *endo:exo* ratios of these tetrahydrocarbazole products were similar to those observed by Steckhan and coworkers, indicating that the heterogeneous nature of the reaction did not impart any negative effects on the reaction efficiency or stereoselectivity.

Having established the scope for the heterogeneous photocatalytic Diels–Alder reaction, we were interested in how this protocol compared to the seminal example by Steckhan and coworkers with TPPT.^{5a} Typically, quantum yields are used to compare the amount of chemical change per photon absorbed in a given period of time in photochemical reactions.¹⁰ However, in heterogeneous reactions some of the photons are scattered off the surface of the catalyst, making it difficult to determine the exact number of photons absorbed by the sample over a given period of irradiation. Therefore, to overcome these intrinsic problems in comparing these two systems, the number of photons *absorbed* at a given wavelength per units of time and volume (*I_a*) is replaced by *I₀*, the number of photons of a given wavelength per time and volume *arriving* at the sample.¹¹ This apparent quantum yield is more formally known as photonic efficiency (ζ_p) and can be described as equation (1).

$$\zeta_p = \frac{\text{Rate}}{I_0} \quad (1)$$

In order to calculate *I₀*, we employed our recently developed Ru(bpy)₃Cl₂ visible-light actinometer¹², where we were able to calculate that the *I₀* for the 460 nm LED set-up

employed was $4.7 \pm 0.1 \times 10^{-7} \text{ mol h}\nu \text{ s}^{-1}$ (see section H of SI). In order to calculate the ζ_p , initial reaction rates after 1 hour of irradiation were determined (Figure 2). By employing equation (1), the ζ_p for Steckhan's protocol was calculated to be 0.035, while the ζ_p for the heterogeneous protocol mediated by Pt(0.2%)/TiO₂ was calculated to be 0.074. However, any direct comparison of the homogeneous and heterogeneous protocols should be made cautiously, as the reaction conditions differ for both protocols and it is difficult to determine the exact number of active catalytic sites on the semiconductor. However, from this work, it is clear that we were successfully able to develop a heterogeneous protocol for the photocatalytic Diels–Alder reaction of indoles, and after further optimization of the reaction conditions, we were able to further improve the overall ζ_p .

An important aspect of any heterogeneous photocatalyst is the ability to easily separate and reuse the catalyst. In this regard, the reusability of the Pt(0.2%)/TiO₂ catalyst was examined. After irradiation, the reaction was centrifuged to separate the catalyst from the reaction mixture, and the catalyst was dried overnight under vacuum in an attempt to remove any volatile organic compounds from the catalyst surface. As seen in Figure 3, it was observed that the catalyst activity decreases sharply on its third and fourth use. The loss in activity is hypothesized to be due to surface poisoning from organics, which in this case is presumably derived from indole. This is evidenced by the diffuse reflectance spectrum taken of a TiO₂ catalyst after only one use (see section J of SI).

The proposed mechanism of this transformation is outlined in Scheme 1. Indole first adsorbs to the surface of TiO₂, yielding a complex with an absorption that extends into the visible region. This complex can then be excited by a 460 nm LED light source, resulting in the injection of an electron into the conduction band (CB) of TiO₂.⁸ The electron is first trapped by the Pt nanoparticles on the TiO₂ surface,¹³ minimizing the occurrence of problematic back-electron transfer, and then quenched by either MeNO₂ ($E_{1/2} = -0.91 \text{ V vs. SCE}$) or O₂ ($E_{1/2} = -0.73 \text{ V vs. SCE}$).¹⁴ Since the injected electrons are in equilibrium between the Pt nanoparticles and the TiO₂ CB, quenching of these electrons by MeNO₂ or O₂ is a strategy to further decrease the probability of back-electron transfer. Upon forming the indole radical-cation, it can then undergo a [4+2] radical cyclization with 1,3-CHD. After cyclization, an electron from the Pt(0.2%)/TiO₂ catalyst can then reduce the tetrahydrocarbazole radical-cation. Intermittent illumination experiments revealed no dependence between the yield of the reaction and the temporal profile of the irradiation, suggesting that chainpropagation mechanisms involving oxidation of the indole substrate by the tetrahydrocarbazole radical-cation are not operative (see section G of SI).¹² Finally, the tetrahydrocarbazole is rapidly acylated, preventing the over-oxidation and cycloreversion of the reaction products ($E_{1/2} = 0.46 \text{ vs SCE}$) that are somewhat easier to oxidize than the starting indole ($E_{1/2} = 1.07 \text{ V vs. SCE}$).^{5a}

Conclusion

In this work, we have successfully developed a heterogeneous photocatalyzed protocol for the Diels–Alder reaction of indoles, which takes place under mild conditions and visible-light irradiation. The reaction proceeds with broad scope with a variety of indoles and *cis*-1,3-dienes. Furthermore, chloroformates can also be employed instead of acetyl chloride

as protecting groups, albeit in decreased yields. The reaction was found to be over twice as efficient per photon compared to the seminal homogeneous work, and the heterogeneous catalyst could be easily recycled and reused up to three times.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A. Previous Work: Steckhan and coworkers. **B. Previous Work: De Mayo and coworkers.** **C. Our Work.**

Figure 1. Previous work and our work on the photocatalytic radical-cation cycloaddition reactions of *N*-heterocycles.^{5a,6}

Figure 2.
Initial photonic efficiency comparison of the homogeneous and heterogeneous protocols.

Figure 3. Recyclability of Pt(0.2%)/TiO₂ for the photocatalytic Diels-Alder reaction of indole and 1,3-CHD.

Scheme 1.

Proposed mechanism for the photocatalytic Diels–Alder reaction of indole with 1,3-CHD mediated by Pt(0.2%)/TiO₂.

Table 1

Control reactions for the heterogeneous photocatalyzed Diels–Alder reaction of indole and 1,3-CHD.

Entry	Modifications from Standard Conditions	Yield
1	None	72%
2	No Pt(0.2%)/TiO ₂	N.R.
3	Reaction performed in dark	N.R.
4	No AcCl/NaHCO ₃	11%
5	<i>N</i> -Acetylintole instead of indole	N.R.
6	TiO ₂ instead of Pt(0.2%)/TiO ₂	60%
7	630 nm LED instead of 460 nm LED	N.R.

Standard Conditions: Indole (0.3 mmol), 1,3-CHD (1.5 mmol), AcCl (0.3 mmol), NaHCO₃ (0.6 mmol), and MeNO₂ (3 mL) were irradiated under air with a 10 W 460 nm LED. Yields are reported based on ¹H NMR using trimethyl(phenyl)silane as an external standard.

Table 2

Reaction scope for the photocatalytic Diels–Alder reaction of indoles.

1: X = H	72% (5 h); <i>Endo:Exo</i> = 3.6:1
	2: X = OMe	48% (5 h); <i>Endo:Exo</i> = 3.9:1
	3: X = Br	62% (5 h); <i>Endo:Exo</i> = 3.3:1
	4: X = I	52% (5 h); <i>Endo:Exo</i> = 3.9:1
	5: X = CO ₂ Me	59% (5 h); <i>Endo:Exo</i> = 3.4:1
	6: X = Bpin	52% (5 h); <i>Endo:Exo</i> = 3.4:1
	7: X = CN	40% (7 h); <i>Endo:Exo</i> = 3.2:1
	8: X = Me	55% (5 h); <i>Endo:Exo</i> = 3.8:1
	9: X = Et	52% (5 h); <i>Endo:Exo</i> = 3.9:1
10: 56% (5 h) <i>Endo:Exo</i> = 3.2:1
11: 11% (5 h) <i>Endo:Exo</i> = 2.7:1
12: Trace (5 h)
13: 52% (5 h) <i>Endo:Exo</i> = 2.1:1
14: Trace (18 h)
15: 19% (5 h) <i>Endo:Exo</i> = 1.2:1
16: 67% (5 h)
17: 49% (5 h) <i>Endo:Exo</i> = 3.1:1
18: 45% (5 h) <i>Endo:Exo</i> = 3.2:1
19: 16% (5 h) ^a <i>Endo:Exo</i> = 2.9:1
20: 16% (5 h) (29%) ^a <i>Endo:Exo</i> = 4.8:1
21: 14% (5 h) (30%) ^a <i>Endo:Exo</i> = 3.5:1
22: 29% (5 h) <i>Endo:Exo</i> = 2.7:1
23: 32% (7 h) (50%) ^a <i>Endo:Exo</i> = 4.6:1	

Standard Conditions: Indole (0.3 mmol), diene (1.5 mmol), R-Cl (0.3 mmol), NaHCO₃ (0.6 mmol), and MeNO₂ (3 mL) were irradiated under air with a 10 W 460 nm LED. Yields are reported as isolated yields. *Endo:exo* ratios were determined by ¹H NMR analysis of crude reaction mixture.

^aYield determined by ¹H NMR using trimethyl(phenyl)silane as an external standard.