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Synthesis of cyclohepta[b]indoles *via* gold mediated energy transfer photocatalysis†

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Photocatalysis involving energy transfer (EnT) has become a valuable technique for building intricate organic frameworks mostly through [2+2]-cycloaddition reactions. Herein, we report a synthetic method leading to functionalized cyclohepta[b]indoles, an important structural motif in natural products and pharmaceuticals, using gold-mediated energy transfer photocatalysis. The scope of this operationally simple and atom-economical strategy is presented. Density functional theory studies were employed in order to gain insights into the mechanism of formation of the cyclohepta[b]indole core.

During the last few decades, the field of photocatalysis has steadily evolved and is currently experiencing a significant surge in activity.^{1–5} In one of its incarnations, photocatalysis *via* energy transfer (EnT), which is facilitated by light-absorbing photosensitizers, affords the means to access highly active triplet states. As a result, it now permits reactions previously unattainable under thermal activation. Nowadays it is an important tool used in modern organic synthesis for a large variety of reactions.^{2b,6–9} Numerous organic sensitizers^{10–13} and transition metal-based photocatalysts, such as ruthenium,^{14–16} palladium,¹⁷ rhodium,¹⁸ and iridium,^{19–23} have been deployed in EnT photocatalysis. It is known that efficient EnT photosensitizers should possess several key characteristics, namely: (i) high absorption cross-section at the desired wavelength, (ii) efficient intersystem crossing to its triplet state, (iii) significantly long excited triplet state lifetime, and (iv) higher triplet excited-state energy than the targeted substrate.

Recently, we have disclosed two novel photosensitizers [Au(SIPr)(Cbz)] (**PhotAuCat I**) (SIPr = [*N,N*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]; Cbz = carbazolyl) and [Au(IPr)(Cbz)] (**PhotAuCat II**) (IPr = [*N,N*-bis(2,6-

diisopropylphenyl)imidazol-2-ylidene]).²⁴ With high triplet energy values, namely 67.9 kcal mol⁻¹ for **PhotAuCat I** and 67.6 kcal mol⁻¹ for **PhotAuCat II**, these have demonstrated efficiency in diverse [2+2]-photocycloadditions, surpassing state-of-the-art Ir photocatalysts.^{25–27}

Cyclohepta[b]indole serves as a core unit in some natural products as well as in various pharmaceutical compounds.²⁸ For example, arcyriacyanin A isolated from *Arcyria nutans* inhibits protein kinase C and tyrosine kinase and exhibits cytotoxicity against human cancer cells.²⁹ Additionally, a variety of compounds containing the cyclohepta[b]indole scaffold exhibit important pharmacological effects, such as A-FABP inhibition,³⁰ antitubercular properties³¹ and SIRT1 inhibition (Fig. 1).³² It is therefore crucial to identify straightforward synthetic routes to this scaffold considering its remarkable biological properties.

A number of methods exist for the synthesis of the cyclohepta[b]indole core,³³ including cyclization reactions,^{34–36} (*m+n*)-cycloaddition reactions,^{37–40} and Cope rearrangement.⁴¹ However, although these strategies prove viable, most of them involve multi-step routes, high temperature and/or toxic

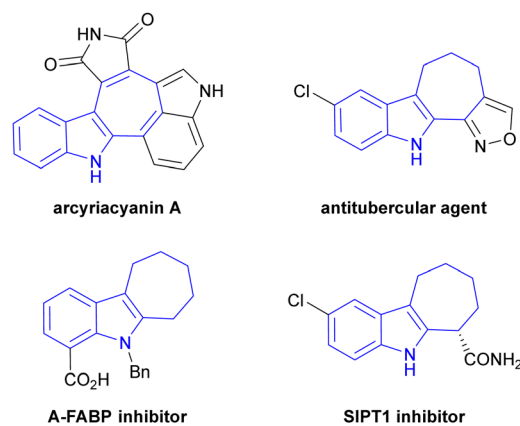


Fig. 1 Representative examples of compounds containing a cyclohepta[b]indole scaffold.

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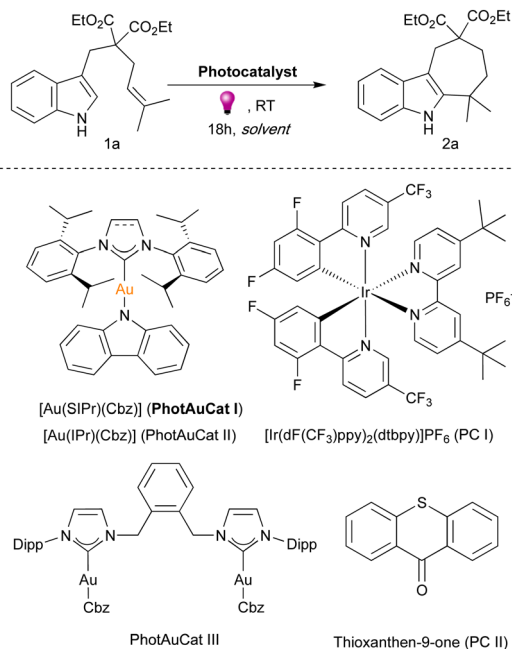


Fig. 2 Model reaction studied and photocatalysts tested.

solvents. Noteworthy, there is currently only one example of photochemical synthesis of cyclohepta[*b*]indole-type scaffolds using direct irradiation in quartz tubes with harsh 254 nm UV light.⁴²

Recently, while exploring the intermolecular [2+2]-cycloaddition of indoles *via* gold-mediated EnT photocatalysis, we discovered the unexpected formation of cyclohepta[*b*]indole.²⁷ Considering the great interest in this scaffold, we now further explore this initial observation and report on an efficient protocol for its synthesis *via* gold-mediated energy transfer photocatalysis from functionalized indoles.

We initiated our investigations with the model substrate, dimethyl-substituted indole **1a**. Previously, we found that cyclohepta[*b*]indole **2a** was formed upon irradiation with 365 nm light in the presence of dinuclear gold sensitizer **PhotAuCat III** (Fig. 2) in a 64% yield in EtOAc after 18 hours (see ESI† for complete optimization studies, Table S1).²⁷ **PhotAuCat I**, being an efficient and easily accessible gold sensitizer, was tested under identical conditions, providing a 74% yield of **2a**. An even higher yield (84%) was obtained by using *i*PrOAc as the solvent. Various solvents, such as EtOAc, Et₂O, MTBE, 2-MeTHF, THF, MeOH, and MeCN, were also examined, but afforded the desired product in slightly lower 73–78% yields (see ESI†, Table S1). Noteworthy, when THF was used as a solvent only 8% of the desired product **2a** was observed. *i*PrOAc was found to be the optimum solvent and was used in the screening of other photosensitisers. **PhotAuCat II**, which has a slightly lower E_T value than **PhotAuCat I** yielded 61% of **2a** under the same reaction conditions. Interestingly, when we tested commonly used iridium and organic photosensitisers, namely, [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**PC I**) and thioxanthen-9-one (**PC II**), in both cases no reaction occurred. These results highlight the importance of gold photocatalysts for

applications in energy transfer photocatalysis. When utilizing 2 mol% of **PhotAuCat I**, a noticeable decrease in the product yield was observed, affording a mere 37% of **2a** compared to the 84% achieved with 4 mol% catalyst. Control experiments in the absence of photocatalyst and in the absence of irradiation were also conducted and, in both cases, no reaction occurred, indicating the need for both the photocatalyst and light.

Having optimized the reaction conditions, we next explored the reaction scope with various unprotected indoles (Fig. 3). The presence of two terminal methyl groups on the alkene appears essential for this type of reactivity. We began the exploration of the reaction scope by varying the ester groups on the linker. Noteworthy, ethyl (**2a**), methyl (**2b**), bulky *tert*-butyl (**2c**), isopropyl (**2d**) and benzyloxy (**2e**) ester groups were well tolerated and the desired products were obtained in high yields, 60–95%. Interestingly, changing R from ester to cyano groups led to a lack of reactivity under the optimized reaction conditions. The same result was observed when introducing a *p*-toluenesulfonamide group (–NTs) in the linker (see ESI†). We then explored various substituents on the indole ring. 3-Methoxy substituted indole proceeded to the cyclized product **2f** smoothly in 80% yield as well as indole bearing 4-methoxy

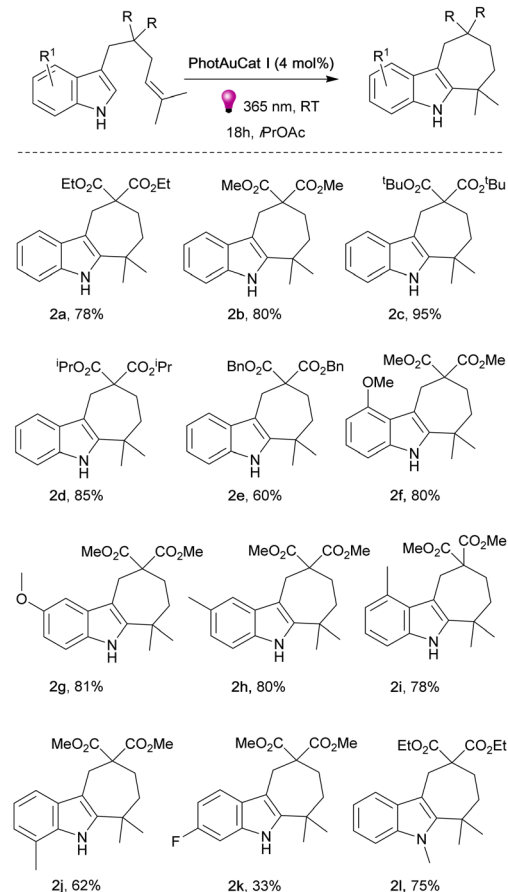


Fig. 3 Substrate scope of indole derivatives. Unless otherwise noted, standard reaction conditions: **1a** (0.10 mmol) and catalyst (0.004 mmol, 4 mol%) in solvent (2 mL) with 365 nm LEDs at rt for 18 h; yields are of isolated products.



group **2g** in 81% yield. Different methyl-substituted indoles afforded the desired products **2h–2j** in good yields of 62–81%.

The corresponding product **2k** with the 5-fluoro-substituted indole was obtained in 33% yield. 5-Bromo and 6-benzyloxy congeners did not react even by increasing the catalyst loading and prolonging the reaction time (see ESI†). This fact is consistent with previously observed reactivity for bromo-substituted indoles.²⁶ In order to establish whether the absence of an N–H proton can affect the reaction outcome, we synthesized *N*-methyl indole and performed the reaction with this substrate. The product **2l** was isolated with 75% yield showcasing that the presence of an N–H proton is not essential for the transformation to proceed. When an indole with a lone methyl group at the terminal position of the alkene was tested under the same conditions, no reaction occurred (see ESI†). Our earlier observation of the [2+2]-photocycloaddition product formation in cases where the alkene attached to the indole lacks methyl groups serves as compelling evidence for the significant impact of substitution on the terminal position on the product formation.²⁶

Intrigued by the unexpected formation of the cyclohepta[*b*]indole core instead of the (originally expected) classical [2+2]-cycloaddition product, further mechanistic studies were performed. The absorption spectra of **1a** and **PhotoAuCat I** show that only the latter absorbs light at 365 nm (see Fig. S4 in ESI†). To support the involvement of the triplet-triplet energy transfer mechanism, we performed quenching studies. The reaction was completely suppressed in the presence of TEMPO. However, the formation of an adduct of TEMPO was not detected. Based on these observations and previously reported data for gold photocatalysts and for similar

indole substrates,²⁶ we hypothesized that the energy transfer proceeds between the excited state photosensitizer and the substrate. However, the reason for the formation of the unexpected ringed product instead of cyclobutane-fused indole remained unclear.

To investigate the reaction mechanism, we employed density functional theory (DFT). An alternative mechanism of cyclization of **Ind-1**, involving intramolecular hydrogen atom transfer (HAT), was proposed, and analysed to explain the unexpected reactivity (Fig. 4). The analysis begins with the activation of **Ind-1** from its singlet spin state to the triplet state ^T**Ind-1**. This activation is achieved through triplet-triplet energy transfer from the excited triplet state of [Au(SIPr)(Cbz)], facilitated by the higher energy of the triplet state of [Au(SIPr)(Cbz)] ($\Delta G_T = 67.9$ kcal mol⁻¹) compared to that of substrate **Ind-1** ($\Delta G_T = 62.2$ kcal mol⁻¹). The reaction involves a two-step mechanism: (i) C–C bond formation, and (ii) H-atom transfer (HAT). The first step takes place in ^T**Ind-1** on the triplet surface *via* ^T**TS**₁₋₂ with an activation free energy of 10.9 kcal mol⁻¹. This step is energetically feasible due to a moderate barrier and exergonicity ($\Delta G = -14.5$ kcal mol⁻¹). The resulting triplet intermediate ^T**Ind-2** undergoes a thermoneutral inter system crossing (ISC) to the open-shell singlet biradical ^{OS}**Ind-2**. In the next step, a 1,3-HAT leads to another open-shell intermediate ^{OS}**Ind-3**, and eventually to the closed-shell product **2a**. This HAT step needs to overcome an energy barrier of 18.6 kcal mol⁻¹ *via* transition state ^{OS}**TS**₂₋₃. Considering this moderate energy barrier, and the high exergonicity ($\Delta G = -64.0$ kcal mol⁻¹), this step is facile and irreversible. Alternatively, the HAT step in ^T**Ind-2** along the triplet surface requires a noticeably higher

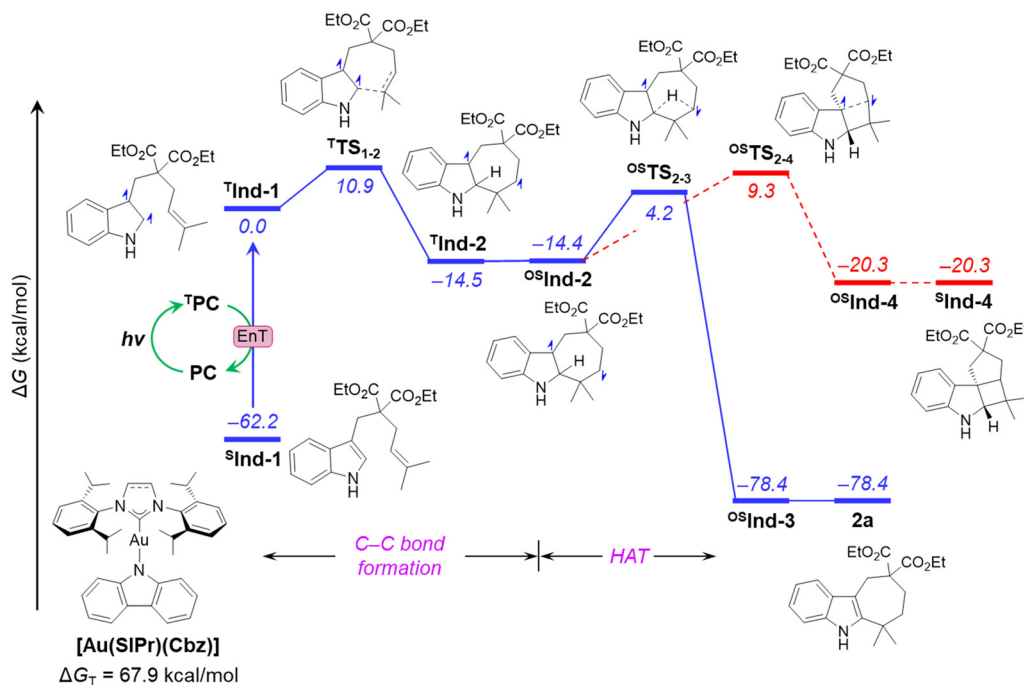


Fig. 4 Computed free energy profile of the cyclization reaction. Energy values (in kcal mol⁻¹) are reported at the ω B97X-D(SMD-EtOAc)/def2-TZVPP// ω B97X-D/def2-SVP level of theory. T, triplet; OS, open-shell singlet; S, closed-shell singlet.



energy barrier of 39.9 kcal mol⁻¹ (Fig. S5 in ESI[†]), and thus can be discarded. We have also computed the reaction pathway for the formal [2+2]-cycloaddition product from ^{OS}Ind-2. The process involves a gradual approach of two radical centres to each other, resulting in ^{OS}Ind-4. This step requires an energy barrier of 23.7 kcal mol⁻¹, which is 5.1 kcal mol⁻¹ higher than the HAT step. Moreover, ^SInd-4 is 58.1 kcal mol⁻¹ less stable than ^{OS}Ind-3. Therefore, the higher barrier and the significant destabilization of the product, in line with the experimental observations, reinforce the conclusion that the formal [2+2]-cycloaddition pathway is unproductive.

We report on the use of [Au(SIPr)(Cbz)] (**PhotAuCat I**) as a photosensitizer for intramolecular cycloaddition of indoles leading to cyclohepta[*b*]indoles. A wide scope for this transformation was explored, where the desired products were obtained in good to excellent yields. DFT calculations were conducted and highlight an initial C–C bond formation followed by a hydrogen atom transfer (HAT) step. The method provides a new route to cycloheptane-fused indoles, replacing lengthy and complex protocols. This contribution adds to the reported uses of these gold catalysts as a versatile tool in energy transfer chemistry and catalysis where HAT is now shown to be a compatible process. Further studies aimed at probing the versatility of **PhotAuCats** are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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