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Cyclizations

Visible Light-Mediated Dearomative Hydrogen Atom Abstraction/ Cyclization Cascade of Indoles

*Yang Xiong, Johannes Großkopf, Christian Jandl, and Thorsten Bach**

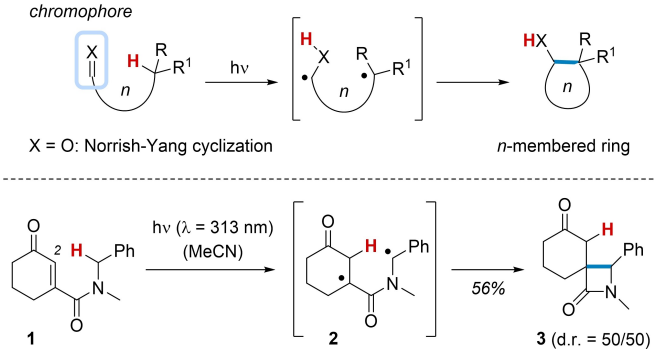
Abstract: The photochemical synthesis of yet unknown 2-oxospiro[azetidine-3,3′-indolines] (17 examples, 80–95 % yield), 2,4-dioxospiro[azetidine-3,3′-indolines] (eight examples, 87–97 % yield), and 1-oxo-1,3-dihydrospiro[indene-2,3′-indolines] (17 examples, 85–97 % yield) is described. Starting from readily accessible 3-substituted indoles, a dearomatization of the indole core was accomplished upon irradiation at λ = 420 nm in the presence of thioxanthen-9-one (10 mol%) as the sensitizer. Based on mechanistic evidence (triplet energy determination, deuteration experiments, by-product analysis) it is proposed that the reaction proceeds by energy transfer via a 1,4- or 1,5-diradical intermediate. The latter intermediates are formed by excited state hydrogen atom transfer from suitable alkyl groups within the C3 substituent to the indole C2 carbon atom. Subsequent ring closure proceeds with pronounced diastereoselectivity to generate a 4- or 5-membered spirocyclic dearomatized product with several options for further functionalization.

Introduction

Upon excitation by a photon, a molecule undergoes significant changes in its electronic structure. If the ground state is a singlet (S_0) and all electrons are pairwise accommodated in molecular orbitals, an electron is promoted from a doubly occupied to a higher unoccupied orbital upon light absorption. As a result, the excited state displays two orbitals which are filled by only one electron (single occupied orbitals, SOMOs). If one electron undergoes a spin flip in the excited singlet state (intersystem crossing, ISC), the electronic situation remains similar and the resulting triplet state also displays the properties of a diradical with two SOMOs.[1] The diradical character of excited states manifests itself in reactions in which one of the radical centers abstracts a hydrogen atom (hydrogen atom transfer, HAT[2]) from a proximal carbon atom. In the C=X chromophore shown in Scheme 1, HAT from the carbon atom in γ-position to the C=X bond is preferred ultimately leading to a four-membered ring ($n = 4$). However, larger rings ($n = 5, 6$) can be formed if there are no γ-hydrogen atoms available. The prototypical reaction of this type is the Norrish–Yang cyclization[3,4] (also referred to as Yang cyclization) in which the chromophore is a carbonyl group. The reaction is a valuable method for the preparation of cyclic tertiary alcohols.[5] Since the carbonyl substrates are mostly ketones which display a high ISC rate, the reaction proceeds typically on the triplet hypersurface.[4]

Based on the basic ideas delineated above, any other C=X chromophore but a carbonyl group could be used for a related HAT/cyclization cascade. Indeed, it has been shown for cyclic α,β-unsaturated carbonyl compounds that their double bond participates in a HAT.[6] An example is the cyclization of cyclohex-2-enone-3-carboxamide **1**, which was initiated by irradiation at λ = 313 nm and which led to β-lactam **3** as a mixture of two diastereoisomers.[6e] Since enones undergo a rapid ISC to a π–π* triplet state[7] it is likely that hydrogen abstraction at the 2-position initiates the reaction and that 1,4-diradical **2** is an intermediate.

Our interest in a HAT/cyclization cascade of indoles was kindled by studies on their intra- and intermolecular [2+2] photocycloaddition reaction. Although cyclobutane formation at the C2 and C3 atoms by intermolecular addition of olefins had been known to occur upon direct excitation of



Scheme 1. Schematic reaction pathway of a photochemical cyclization via hydrogen atom transfer (HAT) by a given chromophore C=X (top) and example for a HAT/cyclization cascade[6e] of enone **1** to product **3** via 1,4-diradical intermediate **2** (bottom).

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suitably protected indoles,[8] recent work focused on the dearomative photocycloaddition under visible light irradiation in the presence of a sensitizer.[9,10] In these reactions, triplet states are involved which are localized at the C2/C3 indole double bond, and we hypothesized that it should be possible to employ the triplet reactivity of indoles for an unprecedented dearomative HAT/cyclization cascade. Upon judicious choice of a sensitizer, visible light might drive the C–H bond activation by energy transfer and via a reactive triplet intermediate. We have now undertaken a study which aimed to identify conditions and possible substituents at the 3-position of indole and which would deliver products of a dearomative cyclization. We have found that both four- and five-membered ring formation is possible depending on the substituent. Visible light irradiation drives the reaction and gives access to a variety of products with a spiro[azetidine-3,3′-indoline][11] and a 1,3-dihydrospiro[indene-2,3′-indoline] skeleton. Mechanistic studies support the hypothesis that the reaction occurs by energy transfer via a 1,n-diradical intermediate.

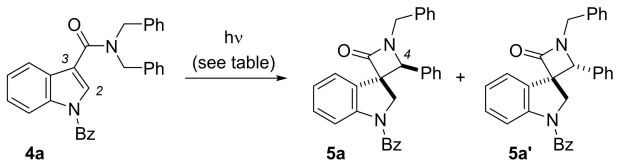
Results and Discussion

Oxo- and Dioxospiro[azetidine-3,3′-indolines]

Our first experiments focused on indole-3-carboxamides as a potential class of substrates. Since preliminary work with unprotected indoles was not successful, an electron withdrawing group was attached to the indole nitrogen atom. Relying on the previously employed benzoyl group,[8] we performed optimization reactions with indole-3-carboxamide **4a** (Table 1) which presents two benzylic methylene groups at the nitrogen atom for a possible HAT. Based on its UV/Vis spectrum the compound invited irradiation at $\lambda =$ 350 nm. To our delight, clean product formation was observed in dichloromethane solution upon excitation at this wavelength (entry 1). Two diastereomeric products **5a** and **5a′** were formed whose constitution and relative configuration was tentatively assigned based on NMR and NOESY data. The assignment was later corroborated by single crystal X-ray crystallography of separable diastereoisomeric products (see below). The major diastereoisomer displays the phenyl group at C4 of the azetidinone ring *cis* to the indoline CH_2 group and *trans* to the benzo ring. The reaction could also be performed in other solvents (entries 2, 3) with acetonitrile providing the highest simple diastereoselectivity.[12] Since thioxanthones have been shown in recent work to be outstanding triplet sensitizers,[13,14] we attempted a catalytic version of the cyclization cascade with parent thioxanthen-9-one (TXT). Although the desired reaction proceeded in several solvents (entries 4–7) upon irradiation at $\lambda = 420$ nm, acetonitrile remained superior as it rendered the reaction both chemoselective (86 % yield) and diastereoselective (d.r. = 83/17). The reaction did not proceed at $\lambda = 420$ nm in the absence of the sensitizer (entry 8). An iridium catalyst could also be used but failed to deliver any improved results (entry 9).

The scope of the reaction was tested under optimized conditions with a variety of substituted indole-3-carboxamides **4** (Scheme 2). The starting materials were synthesized from commercially available indole-3-carboxylic acids by amide bond formation and subsequent *N*-benzoylation (see the Supporting Information for details). Initially, the substituent R^1 was varied at the respective *N*-benzyl substituted substrates (R = phenyl). Several diastereomeric products could be separated and some of them produced crystalline solids.[15] Single crystal X-ray crystallography confirmed the previously mentioned assignment for the minor diastereoisomer **5m′** and for the major diastereoisomer **5o**. An improved selectivity was observed when replacing the reactive nitrogen substituent from benzyl to arylmethyl (R = aryl).

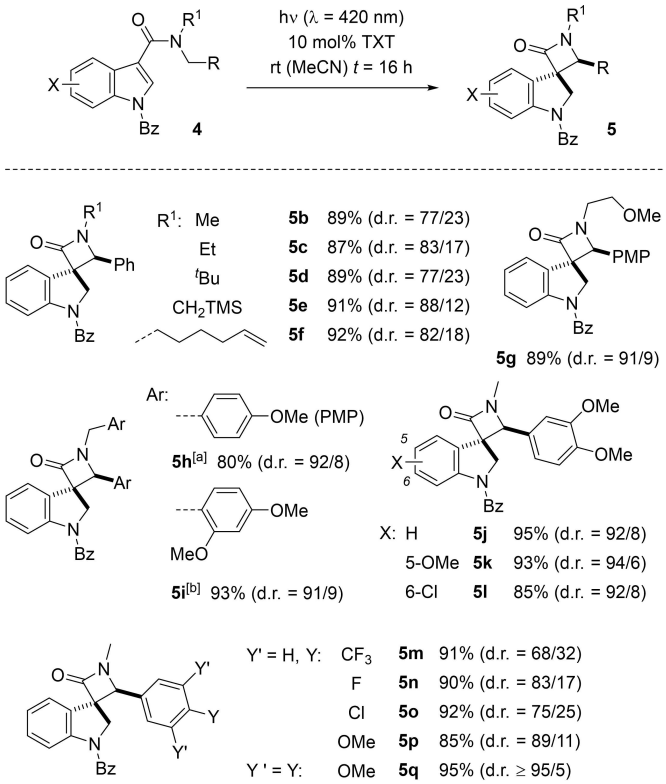
Table 1: Screening of reaction conditions for the HAT/cyclization cascade of indole **4a** to the diastereomeric products **5a** and **5a'**.



4a **5a** **5a'**

Entry[a]	λ[b] [nm]	t[c] [h]	Solvent	Sens.[d]	Yield[e] [%]	d.r.[f] [%]
1	350	16	CH_2Cl_2	–	92	71/29
2	350	16	MeCN	–	92	83/17
3	350	16	$PhCF_3$	–	91	80/20
4	420	24	CH_2Cl_2	TXT	92	71/29
5	420	20	Et_2O	TXT	55	67/33
6	420	16	$PhCH_3$	TXT	61	71/29
7	420	16	MeCN	TXT	86[g]	83/17
8	420	20	MeCN	–	–	–
9	420	24	MeCN	$Ir(ppy)_3$	43	72/28

[a] Reactions were performed in the respective solvent by irradiation at the indicated wavelength ($c = 10$ mM) at room temperature. [b] Emission maximum of the respective lamp (for detailed emission spectra, see the Supporting Information). [c] Irradiation time. [d] Sensitizer, TXT = thioxanthen-9-one (10 mol%), $Ir(ppy)_3$ (4 mol%) (ppy = 2-phenylpyrdine). [e] The yield was determined by ^{1}H NMR . [f] Diastereomeric ratio (d.r.) **5a**/**5a′** as determined by ^{1}H NMR integration. [g] Yield of isolated product.



Scheme 2. Synthesis of 2-oxospiro[azetidine-3,3′-indolines] **5** from *N*-benzoyl protected indole-3-carboxamides **4** by a visible light-mediated photochemical cyclization (PMP = *para*-methoxyphenyl). [a] The reaction was performed on 1 mmol scale. [b] The reaction was performed in $MeCN/CH_2Cl_2 = 10/1$ (v/v).

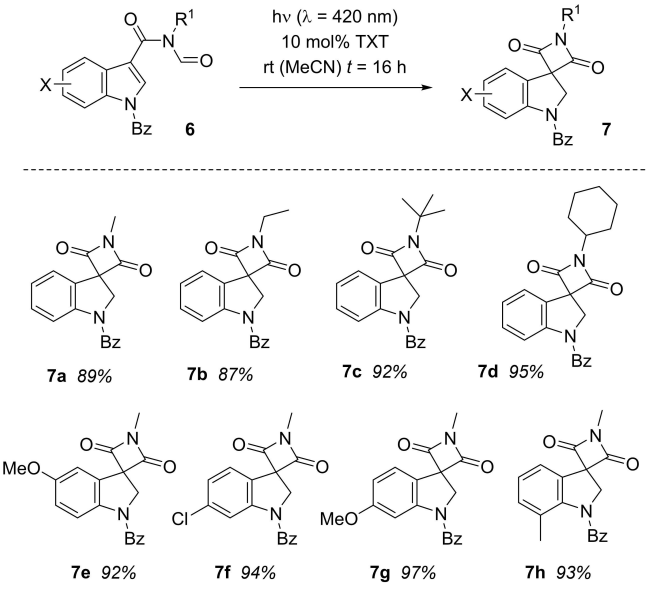
In particular, the electron-rich aryl rings *para*-methoxyphenyl (PMP) or dimethoxyphenyl increased the preference for a single diastereoisomer as seen for products **5g–5l**. Reactions were typically run on a scale of 0.15 mmol but yields remained unaffected if the reaction was performed on larger scale (product **5h**). The reaction showed the expected tolerance towards functional groups which are not oxidation sensitive such as silyl (**5e**), alkenyl (**5f**), alkoxy (**5g–5l**, **5p**, **5q**), chloro (**5l**, **5o**), trifluoromethyl (**5m**), and fluoro (**5n**).

The high regioselectivity achieved with substrates **4b** and **4c**, which reacted exclusively at the benzylic C–H bond, indicated already that the weakest C–H bond is most reactive. The bond dissociation energy (BDE) for the C–H bond in benzylic position is tabulated as 355–370 kJ mol^{-1}.[16] The OC–H bond in formyl compounds displays a similar BDE which in turn suggested that hydrogen abstraction from the respective formamides might also be possible. Compounds **6** were readily prepared from indol-3-carboxylic acid chlorides which served to acylate secondary *N*-substituted (R^1) formamides followed by *N*-benzoylation of the indole (see the Supporting Information for further details). The reaction of the *N*-formyl substrates was performed under conditions identical to the conditions previously applied to carboxamides **4**. Gratifyingly, a clean transformation to the desired 2,4-dioxospiro[azetidine-3,3′-indolines] **7** was observed. Eight representative products were prepared (Scheme 3) in consistently high yields.

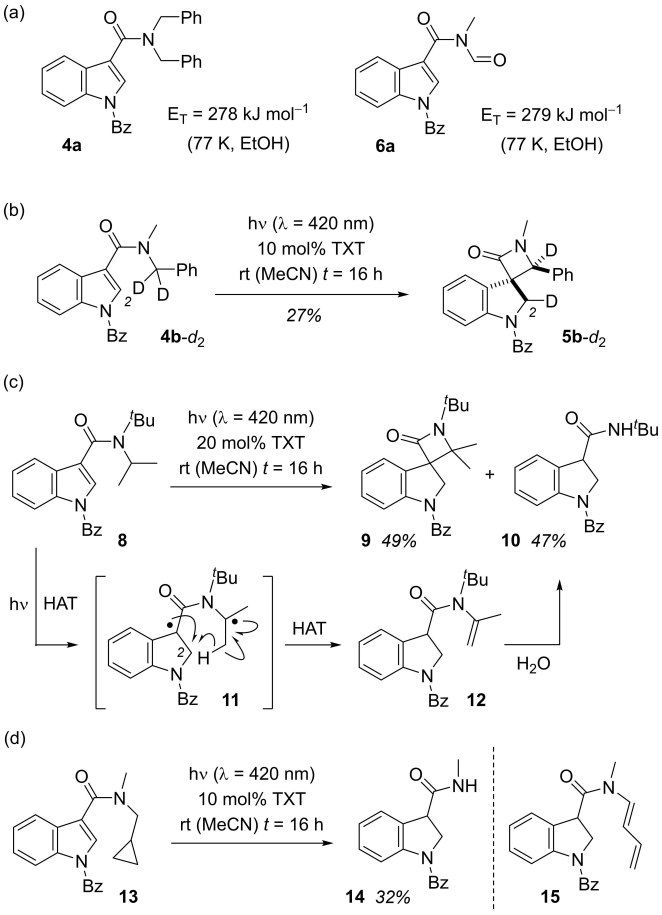
Mechanistic Studies and Consecutive Reactions

A first step towards a mechanistic understanding of the reaction was taken by determining the triplet energies of the starting materials and by exploring whether energy transfer from the sensitizer is feasible. The triplet energy of TXT has been reported as $E_T = 268$ kJ mol^{-1} (77 K, EtOH).[17] We determined the triplet energies of representative compounds **4a** and **6a** by measuring their phosphorescence spectra at 77 K in EtOH. The energy of the (0,0) transition was calculated from the emission in the short-wavelength regime (point of inflection) and was in both cases slightly higher than that of TXT (Scheme 4a, see the Supporting Information for details). Still, given the long lifetime of the triplet state of TXT,[13] energy transfer should be thermally possible provided that the reactive triplet intermediate generated from **4** and **6** reacts rapidly.[18] The hypothesis that hydrogen abstraction occurs at position C2 of indole was corroborated by deuterium labelling experiments. Product **5b**-d_2 obtained from twofold deuterated substrate **4b**-d_2 exhibited one deuterium atom in position C2 (Scheme 4b).

The reaction was slower than the reaction of the non-deuterated substrate **4b** indicating that the primary kinetic isotope effect (KIE) is significant. Indeed, the KIE as determined by initial rate analysis[19] of the two reactions was found to be $k_H/k_D = 4.0 \pm 0.1$ (see the Supporting Information for further details). Further circumstantial evidence for a HAT was obtained by the reaction of *N*-isopropyl substituted amide **8**. The expected product of the cyclization **9** was accompanied by dealkylated carboxamide



Scheme 3. Synthesis of 2,4-dioxospiro[azetidine-3,3′-indolines] **7** from *N*-benzoyl protected indole-3-carboximides **6** by a visible light-mediated photochemical cyclization.



Scheme 4. Mechanistic work on the dearomative HAT/cyclization cascade of indole-3-carboxamides: a) Triplet energies (E_T) were determined for substrates **4a** and **6a** from their luminescence spectra at 77 K. The energies are in a range which enables energy transfer from thioxanthen-9-one (TXT). b) The reaction of deuterated substrate **4b**-d_2 proceeds more slowly than the reaction of **4b**. However, deuterium incorporation at position C2 of product **5b**-d_2 was complete (>99%) supporting a HAT to this position. c) Substrate **8** delivered in the HAT/cyclization cascade not only the expected product **9** but also amide **10**. The formation of the latter product is explained by a second HAT occurring within postulated intermediate 1,4-diradical **11**. d) The only product obtained from the reaction of substrate **13** was the reduced indole **14**. A potential precursor is ring-opened dienamide **15**.

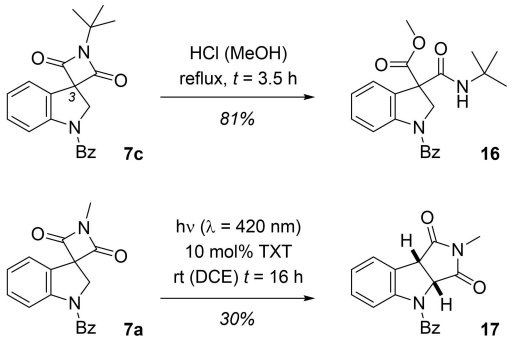
10 (Scheme 4c). Its formation can be explained by hydrolysis of enamide **12** which in turn is formed from 1,4-diradical **11**. The diradical is the putative precursor to product **9** which requires bond formation between the two radical centers. As an alternative reaction pathway, a hydrogen abstraction in related 1,4-diradicals with a dimethyl-substituted radical center is known[6b,14b] and accounts for the observed dealkylation. Unfortunately, it was not possible to substantiate the intermediacy of a radical center in α-position by a radical clock experiment. Compound **13** gave upon irradiation under the typical reaction conditions only the dealkylated product **14**. Although its formation could be explained in analogy to the reaction of compound **9**, the high BDE for a cyclopropane C–H bond (ca. 440 kJ mol^{-1})[16] makes this pathway unlikely. It is more likely that cyclopropane ring opening indeed occurs and is followed by allylic C–H abstraction to deliver hydrolytically labile compound **15**.

The 2,4-dioxospiro[azetidine-3,3′-indolines] are strained compounds which invite ring opening reactions of the azetidine ring. The quaternary carbon atom C3 becomes stereogenic in this process and the two substituents represent useful exit vectors for further functionalization.[20,21] As a simple transformation, the azetidindione **7c** was opened with methanol under acidic conditions and smoothly furnished ester **16** (Scheme 5).

If the photochemical reactions **6**→**7** were performed in 1,2-dichloroethane (DCE) but not in acetonitrile solution, by-products were observed. The side reaction was more closely studied on the specific substrate **6a** which delivered 25% of a product identified as imide **17**. The same product was also obtained in a slightly better yield when 2,4-dioxospiro[azetidine-3,3′-indoline] **7a** was irradiated under otherwise identical conditions. The five-membered imide[22] can be envisioned to be formed from **6a** by a HAT to the carbon atom C3 of indole[23] but it is not clear why the reaction does not occur in acetonitrile. It appears, as if the solvent favors a different regioselectivity of the HAT and that the 1,4-diradical formation from **7a** is reversible in DCE. In the absence of TXT there was no reaction at λ = 420 nm.

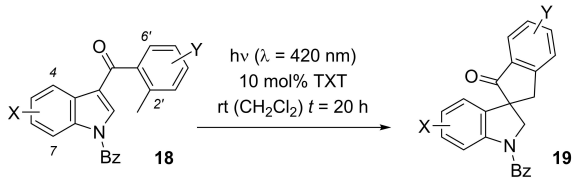
1-Oxo-1,3-dihydrospiro[indene-2,3′-indolines]

3-(2′-Methylbenzoyl)substituted indoles were considered as a second set of compounds that exhibits a hydrogen atom in a suitable position for HAT from indole. Like with the indole-3-carboximides, it turned out that *N*-benzoyl protection was required to enable a clean conversion in the presence of a suitable sensitizer. Preliminary optimization experiments revealed that TXT could be used again for this purpose but dichloromethane turned out to be a superior solvent when compared to acetonitrile. After a reaction time of 20 hours the reaction of the parent substrate **18a** was complete and delivered cleanly the spirocyclic product **19a** in high yield (Table 2, entry 1).



Scheme 5. Ring opening of 2,4-dioxospiro[azetidine-3,3′-indolines] **7c** by acid-catalyzed methanolysis and consecutive photochemical process occurring upon sensitized irradiation of **7a** at λ = 420 nm in 1,2-dichlorethane (DCE) as the solvent.

Table 2: Dearomative HAT/cyclization cascade of 3-(2′-methylbenzoyl)-substituted indoles **18** to spirocyclic products **19**.



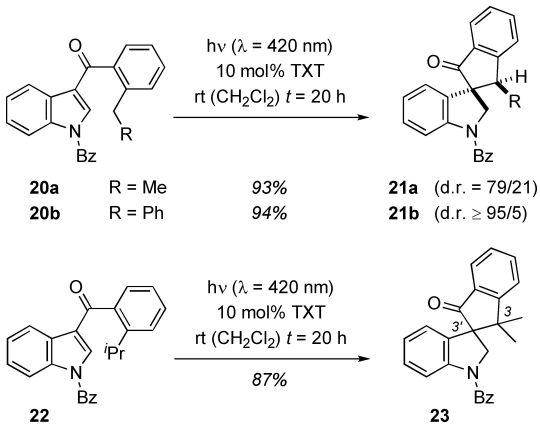
Entry[a]	Substrate	X	Y	Product	Yield[b] [%]
1	**18a**	H	H	**19a**	93
2	**18b**	5-F	H	**19b**	92
3	**18c**	5-Cl	H	**19c**	91
4	**18d**	5-Br	H	**19d**	90
5	**18e**	5-I	H	**19e**	94
6	**18f**	5-MeO	H	**19f**	92
7	**18g**	5-CN	H	**19g**	90
8	**18h**	4-CO_2Me	H	**19h**	89
9	**18i**	6-Cl	H	**19i**	93
10	**18j**	6-MeO	H	**19j**	95
11	**18k**	7-Me	H	**19k**	96
12	**18l**	H	4′,6′-Me_2	**19l**	97
13	**18m**	H	5′-F	**19m**	88
14[c]	**18n**	H	6′-MeO	**19n**	85

[a] Reactions were performed by irradiation at λ = 420 nm (emission maximum of the fluorescent lamps) in dichloromethane solution (c = 10 mM) at room temperature (t = reaction time). Thioxanthen-9-one (TXT) was used as sensitizer. [b] Yield of isolated product. [c] The reaction time was 24 hours.

The reaction product was reduced at the former C2 carbon atom of the indole and displayed a new bond to its former C3 carbon atom. The dearomative HAT/cyclization cascade proved to be robust towards substitution either at the indole core or at the phenyl part of the 3-(2′methylbenzoyl) group. Substrates **18** were readily available by Friedel–Crafts acylation of the respective indoles and subsequent protection at the indole nitrogen atom (see the Supporting Information for further details). Functional group tolerance was confirmed towards the most important halogen substituents (Table 2, entries 2–5) as well as towards a methoxy (entry 6), a cyano (entry 7), and an ester (entry 8) group within the indole ring. The position of the substituents (entries 8–11) was inconsequential for the outcome of the reaction and a substitution of the benzoyl group was also feasible (entries 12–14).

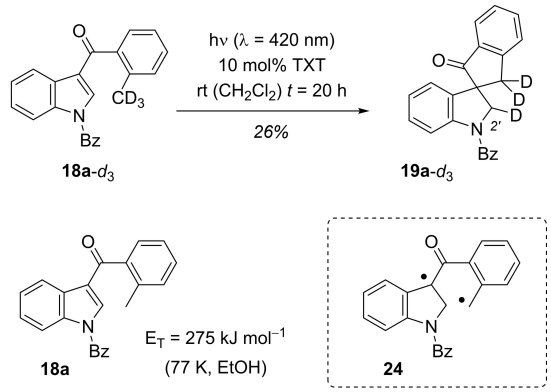
If the *ortho*-substituent within the benzoyl part of the substrate was changed from methyl to alkyl, the reaction worked equally well (Scheme 6, substrates **20a** and **20b**). In the case of products **21**, the relative configuration between the two sterogenic centers (simple diastereoselectivity)[12] was found to be preferably *trans* for the substituent R relative to the benzo ring of the indole. Thus, the outcome is comparable to the result obtained for products **5** (Scheme 2). In this case, the selectivity was more pronounced for R = Ph and product **21b** was isolated as a single diastereoisomer.

Remarkably, an isopropyl group in *ortho* position (substrate **22**) led to a single product **23**. Unlike for isopropyl-substituted substrate **8**, there was no second hydrogen abstraction leading to double bond formation but rather a bond between C3′ and C3 formed connecting two quaternary centers. The result is in line with the mechanistic

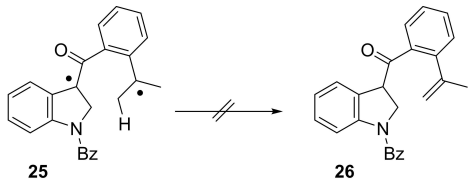


Scheme 6. Dearomative HAT/cyclization cascade of 3-(2′-alkylbenzoyl)-substituted indoles **20** and **22**. In the former case, products **21** were obtained as a mixture of diastereoisomers. In the latter case (product **23**), a bond was formed between two adjacent quaternary carbon atoms at positions C3′ and C3.

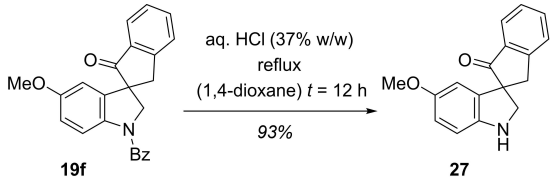
picture for this and the preceding reactions. In order to substantiate the suggested reaction pathway, it was shown for 3-(2′-methylbenzoyl)-substituted indoles that the hydrogen atom at position C2′ stems from the *ortho*-methyl group. Quantitative deuterium incorporation occurred exclusively at this position for product **19a**-d_3 obtained from deuterated substrate **18a**-d_3 (Scheme 7). In this case, the KIE was not quantified but the lower conversion as compared to the reaction **18a**→**19a** suggests also in this instance a slower reaction. The triplet energy determined for substrate **18a** paralleled the value recorded for indole-3-carboxamides **4a** and **6a** (Scheme 4).



Scheme 7. Mechanistic work on the dearomative HAT/cyclization cascade of 3-(2′-methylbenzoyl)-substituted indoles: (top) Cyclization of deuterated precursor **18a**-d_3 led to completed deuterium incorporation at position C2′. (bottom) The triplet energy (E_T) was determined for substrate **18a** from its luminescence spectrum at 77 K. The experiments support the intermediacy of 1,5-diradical **24**.



Scheme 8. A seven-membered transition state is avoided, which would be required for hydrogen abstraction within 1,5-diradical **25**. Product **26** is not formed from substrate **22** but only cyclization product **23** (Scheme 6).



Scheme 9. Removal of the benzoyl group in product **19f** by hydrolysis under acidic conditions (w/w = weight per weight).

Taken this and the previous results together, it appears reasonable to assume that the newly discovered reactions proceed by a related mechanism. Upon triplet-sensitized excitation of the indole core a subsequent intramolecular HAT from the substituent at position C3 to position C2 occurs. In the case of 3-(2′-methylbenzoyl)-substitution it is the *ortho*-alkyl group from which the hydrogen is abstracted and a 1,5-diradical forms (intermediate **24**). After ISC, ring closure to five-membered ketones is the sole reaction pathway. A second HAT as seen for radical intermediate **11** is avoided even if the radical center carries one or two substituents displaying the required hydrogen atoms.[24] This is particularly apparent for the putative intermediate **25** of the reaction **22**→**23** which would require a seven-membered transitions state to form product **26** (Scheme 8). Despite the fact that six hydrogen atoms (at two methyl groups) are available for HAT, cyclization is the only observed reaction pathway. Neither in these nor in the reactions of indole-3-carboxamides was any product observed which would indicate a cleavage reaction.[25]

Removal of the *N*-benzoyl group in products **19** could be readily achieved under acidic conditions. Exemplarily, product **19f** was hydrolyzed with HCl in 1,4-dioxane to produce indoline **27** in high yield (Scheme 9). Both the methoxy group and the spirocycle were stable under the reaction conditions.

Conclusion

In summary, a new photochemical reactivity pattern of the indole core has been discovered and employed for the construction of spirocyclic indolines. The triplet state of indoles not only serves as an intermediate for photocycloaddition reactions but can also act at position C2 as recipient of a hydrogen atom by an intramolecular HAT. This process has been found to occur smoothly if the substrates display suitable hydrogen atoms in the side chain attached to position C3 of the indole core. The intermediate 1,4- or 1,5-diradicals likely benefit from the fact that the radical center at C3 is benzylic providing an additional thermodynamic driving force for the HAT. After ISC, the diradicals undergo ring closure to form a bond between two sterically congested carbon atoms. The resulting products exhibit not only an intriguing spirocyclic skeleton but offer also several opportunities for further functionalization (exit vectors). Removal of the indole protecting group is facile under acidic conditions enabling a further manipulation at the nitrogen atom.

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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 supplementary material of this article.

Keywords: C–H Activation · Heterocycles · Hydrogen Transfer · Photochemistry · Sensitizers

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