

X-Ray Characterization of an Electron Donor–Acceptor Complex that Drives the Photochemical Alkylation of Indoles**

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Abstract: A metal-free, photochemical strategy for the direct alkylation of indoles was developed. The reaction, which occurs at ambient temperature, is driven by the photochemical activity of electron donor–acceptor (EDA) complexes, generated upon association of substituted 1H-indoles with electron-accepting benzyl and phenacyl bromides. Significant mechanistic insights are provided by the X-ray single-crystal analysis of an EDA complex relevant to the photoalkylation and the determination of the quantum yield (Φ) of the process.

The appearance of strong color on bringing together two colorless or nearly colorless organic compounds is not an uncommon observation for a chemist. This phenomenon inspired Robert Mulliken to formulate, in 1952, the charge-transfer theory.^[1,2] Accordingly, the association of an electron-rich substrate with an electron-accepting molecule can bring about the formation of a new molecular aggregate, called an electron donor–acceptor (EDA) complex.^[3] EDA complexes are characterized by the appearance of a weak absorption band, the charge-transfer band, associated with an electron transfer (ET) from donor to acceptor. In many cases, the energy of this transition lies within the visible frequency range. Over the last six decades, the photophysical properties of EDA complexes have been extensively studied,^[3,4] while their use in synthetic chemistry has found limited applications.^[5] As a common trait of these synthetic studies, the existence of EDA complexes as relevant reactive intermediates has generally been inferred from spectroscopic changes of the absorption spectra. In contrast, their isolation and structural characterization by X-ray single-crystal analysis,

which provides more compelling mechanistic information, was possible in only a few cases.^[6]

We report herein a metal-free, photochemical strategy which enables the direct alkylation of 2- and 3-substituted 1H-indoles with electron-accepting benzyl and phenacyl bromides. The reactions occur at ambient temperature and under illumination by a readily available compact fluorescence lamp (CFL). The most significant results of our studies are the isolation and full characterization by X-ray single-crystal spectroscopic analysis of a visible-light-absorbing EDA complex, and the finding that its photochemical activity drives the alkylation process.

Our initial investigations were motivated by the desire to photochemically generate open-shell reactive species under mild conditions.^[7] Recently, we discovered that transiently generated electron-rich chiral enamines **1** can actively participate in the photoexcitation of substrates by inducing the formation of EDA complexes with alkyl halides **2** of high electron affinity (Figure 1 a). Visible light irradiation of the colored EDA complex induced an electron transfer, allowing easy access to radical species. This reactivity enabled the development of a metal-free, stereoselective α -alkylation of carbonyl compounds.^[7a,b] To further expand the synthetic

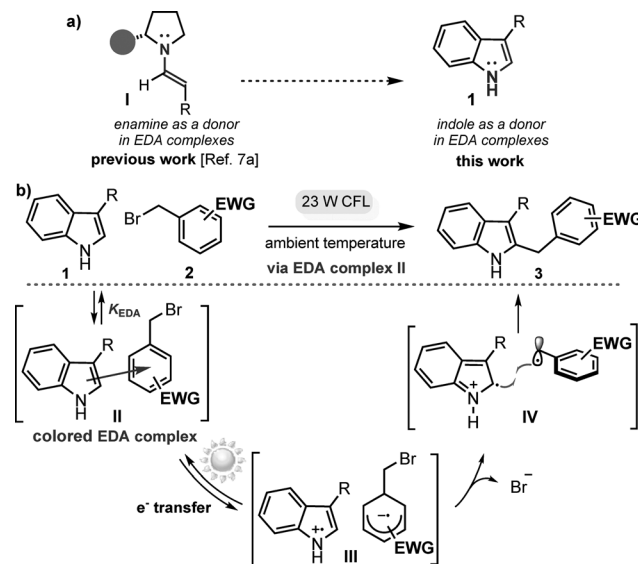


Figure 1. a) Expanding the EDA-complex activation strategy to other donors. b) The alkylation of indoles driven by the photochemical activity of EDA complex II and our mechanistic proposal. EWG: electron-withdrawing group; K_{EDA} : association constant for the formation of complex II.

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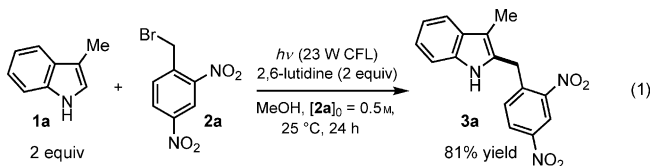
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potential of the EDA-complex activation strategy, we envisaged the use of donor substrates other than enamines **I**. Given the electronic similarities with **I**, 1*H*-indoles **1** were considered as suitable donors, which could effectively form an EDA complex **II** upon association with alkyl halides **2** (Figure 1 b). While precedents in the literature demonstrate the indole tendency toward EDA associations,^[8] the potential of productively using the photoactivity of indole-based EDA complexes in synthetic chemistry has remained almost unexplored.^[9]

We hypothesized that visible light irradiation of the transiently generated complex **II** might induce an electron transfer, affording the contact radical pair **III**. The presence of bromine as a suitable leaving group within the radical anion partner may trigger an irreversible and rapid fragmentation, affording the bromide anion along with the positively charged intermediate **IV**, which brings two radicals in very close proximity. This condition could facilitate a radical combination within the solvent cage to yield the target indole alkylation product **3**. The indole nucleus is a privileged scaffold^[10] found in numerous natural products and biologically active compounds, which makes the development of a photochemical indole alkylation strategy synthetically relevant.^[11]

The feasibility of our plan was tested by reacting 3-methyl indole (**1a**) with 2,4-dinitrobenzyl bromide (**2a**) in MeOH under irradiation by a 23 W CFL lamp [Eq. (1)]. The



reaction, conducted in the presence of 2,6-lutidine (2 equiv) to neutralize the acid generated during the process, afforded the C2-benzylated indole **3a** in 81% yield (optimization studies are detailed in Table S1 of the Supporting Information, SI). Control experiments, carried out by performing the reaction either in the dark or under an aerobic atmosphere,^[12] did not provide any reactivity, testifying to the photochemical and radical nature of the transformation.

From the outset of our investigations, we noticed that a marked red color appeared immediately upon mixing a methanol solution of **1a** with the bromide **2a**. The optical absorption spectrum of the solution showed a bathochromic displacement above 430 nm, where neither substrate absorbs (Figure 2 a). Adherence to the Mulliken correlation (see Figure S6 in the SI) further supported the formation of a colored EDA complex (**IIa** in Figure 1 b, where R = Me and EWG = 2,4-NO₂). Using Job's method^[13] of continuous variations, a molar donor/acceptor ratio of 1:1 in solution for **IIa** was readily established. Concomitantly, an association constant K_{EDA} of $(0.9 \pm 0.1) \text{ M}^{-1}$ in MeOH was determined by both spectrophotometric (using the Benesi–Hildebrand method)^[14] and NMR analysis (using the Foster method,^[15] see the SI for details). A most informative result came from

the isolation of stable dark-orange crystals, suitable for an X-ray diffraction analysis,^[16] grown by liquid diffusion of *n*-hexane into a dichloromethane solution of the EDA complex **IIa** at 0 °C and in the dark. X-ray structural determination^[17] confirmed the formation of **IIa** as a face-to-face π - π complex with a 1:1 donor-acceptor ratio (Figure 2 c). The cofacially oriented indole and 2,4-dinitrobenzyl moieties afford infinite alternate stacks along the crystallographic *b* axis. The average interplanar distance, measured between the centroid of the planar core of the 2,4-dinitrobenzyl or the indole and the plane containing its respective counterpart, is 3.33 Å (Figure 2 d). This interplanar spacing is significantly less than the van der Waals separation for aromatic molecules (3.40 Å),^[18] which is consistent with intermolecular binding forces being at work in the solid state. Interestingly, the charge-transfer band in the solid-state optical absorption spectrum of the EDA complex **IIa** is well resolved and confirms the significant bathochromic shift with respect to the individual substrates (Figure 2 b).

A series of experiments were performed to better elucidate the role of the EDA complex **IIa** in the model reaction.^[19] Experiments with successive intervals of irradiation and dark periods resulted in total interruption of the reaction progress in the absence of light, and recuperation of reactivity upon further illumination. In addition, a 300 W xenon lamp, equipped with a cut-off filter at 450 nm, was used to select a wavelength that could only be absorbed by **IIa** (both **1a** and **2a** require higher energy photons for excitation, Figure 2 a,b). The formation of the product **3a** with a comparable reactivity indicated the photoactivity of the EDA complex **IIa** as solely responsible for the indole alkylation. Finally, a quantum yield (Φ) of 0.2 was determined ($\lambda = 450 \text{ nm}$), which is consistent with the mechanism proposed in Figure 1 b, where a radical combination occurs within **IV** prior to diffusive separation of the radical pair out of the solvent cage.^[20]

We then evaluated the synthetic potential of the photochemical alkylation strategy, conducting the reactions at ambient temperature and using household CFL bulbs as the light source (Figure 3 a). As shown in Figure 3 b, 3-substituted 1*H*-indoles, including naturally occurring *N*-Cbz (carboxybenzyl) protected tryptophan and tryptamine, were selectively benzylated by **2a** at the C2 position to afford products **3a–e** in good yields. A *N*-methyl protected indole derivative was also a competent substrate (adduct **3a'**).

Moreover, we found that other bromide-containing acceptors productively combined with 1*H*-indoles to give photon-absorbing EDA associations. In addition to electron-deficient benzylic systems (product **3f**), a broad array of phenacyl bromides effectively participated in the C2-alkylation of **1a** (products **3g–k**). Importantly, 2-substituted 1*H*-indoles, bearing a variety of substituents at 2 and 5 positions, underwent an effective photochemical C3-alkylation with both electron-poor benzyl and phenacyl bromides (products **3l–p**, Figure 3 c). As a limitation of the method, the unsubstituted 1*H*-indole reacted sluggishly with **2a** to afford a mixture of C3- and C2-alkylation products in a 1.1:1 ratio and in a low overall yield of 14% after 36 h (results not shown).

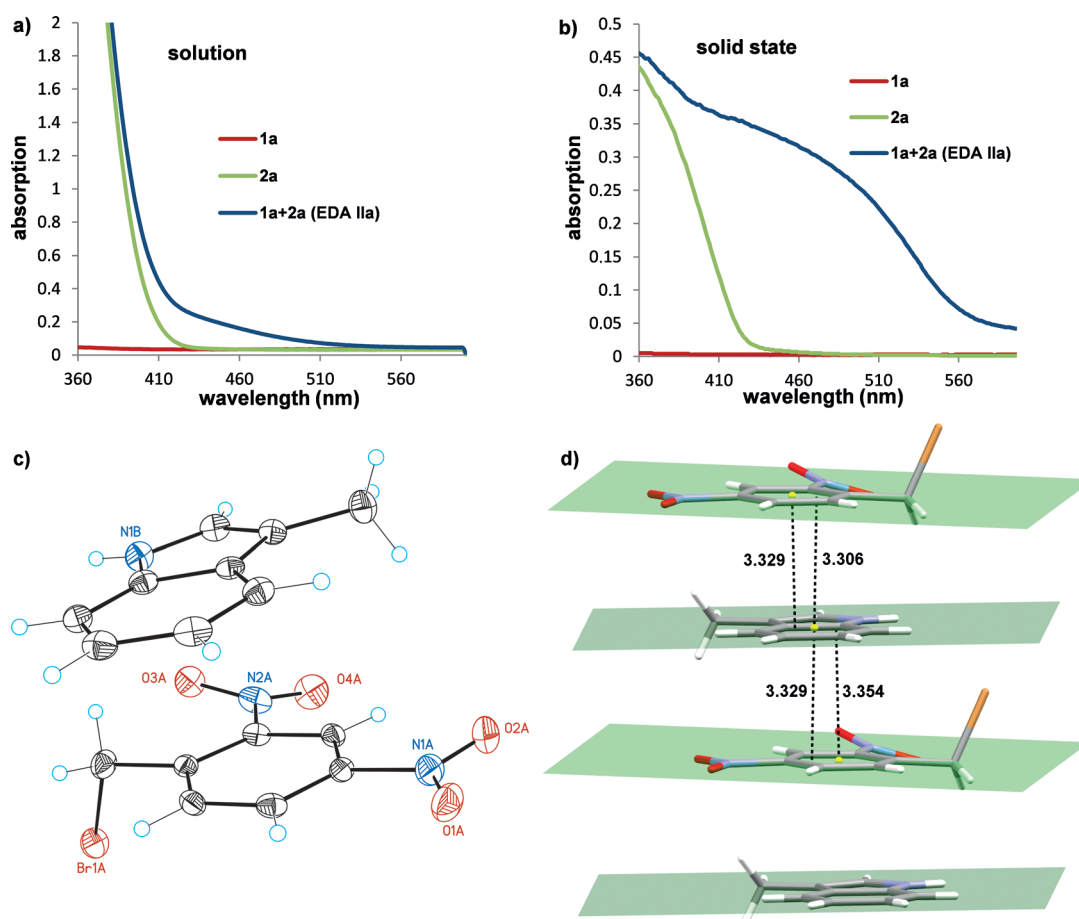


Figure 2. a) Optical absorption spectra recorded in MeOH in 1 cm path quartz cuvettes using a Shimadzu 2401PC UV/Vis spectrophotometer. [1a] = [2a] = 0.1 m. b) Optical absorption spectrum of the EDA complex IIa in the crystalline state. c) ORTEP plot (50% probability) of EDA complex IIa.^[17] d) Projection of the crystal structure along the *b* axis and distances used for calculating the average interplanar spacing (disorder has been omitted for clarity). C gray, H white, Br orange, N blue, O red.

We next examined the possibility of extending the photoalkylation to include 2,3-disubstituted 1*H*-indoles, an approach that would provide a direct access to valuable indolenine products by means of a dearomatization pathway.^[21] As detailed in Figure 3d, different substrates, including tetrahydrocarbazoles, reacted with 2a or phenacyl bromides to afford products 4a–f bearing a quaternary stereocenter. Gratifyingly, complete regioselectivity was achieved, with the C3-alkylated adducts being exclusively produced. Notably, while few metal-mediated protocols exist for the C3-benzylation of 2,3-disubstituted 1*H*-indoles,^[22] this chemistry offers the first methodology for the direct construction of indolenines adorned with a phenacyl moiety at C3 (4b,c and 4e). Of particular interest are the substrates with a pendant nucleophile, which cyclize onto the imine of 4 under the reaction conditions (Figure 3e). Specifically, *N*-tosyl (Ts) tryptamine and tryptophol participated in the reaction to afford the corresponding *cis*-fused pyrrolo- and furano-indolines 5 and 6,^[17] respectively, in high yields.

In summary, we have developed a straightforward method for the direct benzylation and phenacylation of substituted 1*H*-indoles, which requires mild conditions in order to proceed. Evidence has been provided that the chemistry is driven by the photochemical activity of EDA complexes, easily formed upon mixing readily available indoles and electron-accepting benzyl or phenacyl bromides. The isolation and X-ray characterization of an EDA complex relevant to the photochemical alkylation accounted for additional mechanistic insights. This study establishes the potential of indoles to actively participate in the photoexcitation of substrates while promoting synthetically useful transformations. Further efforts are being carried out to investigate the potential of EDA-complex activation in synthetic organic chemistry.

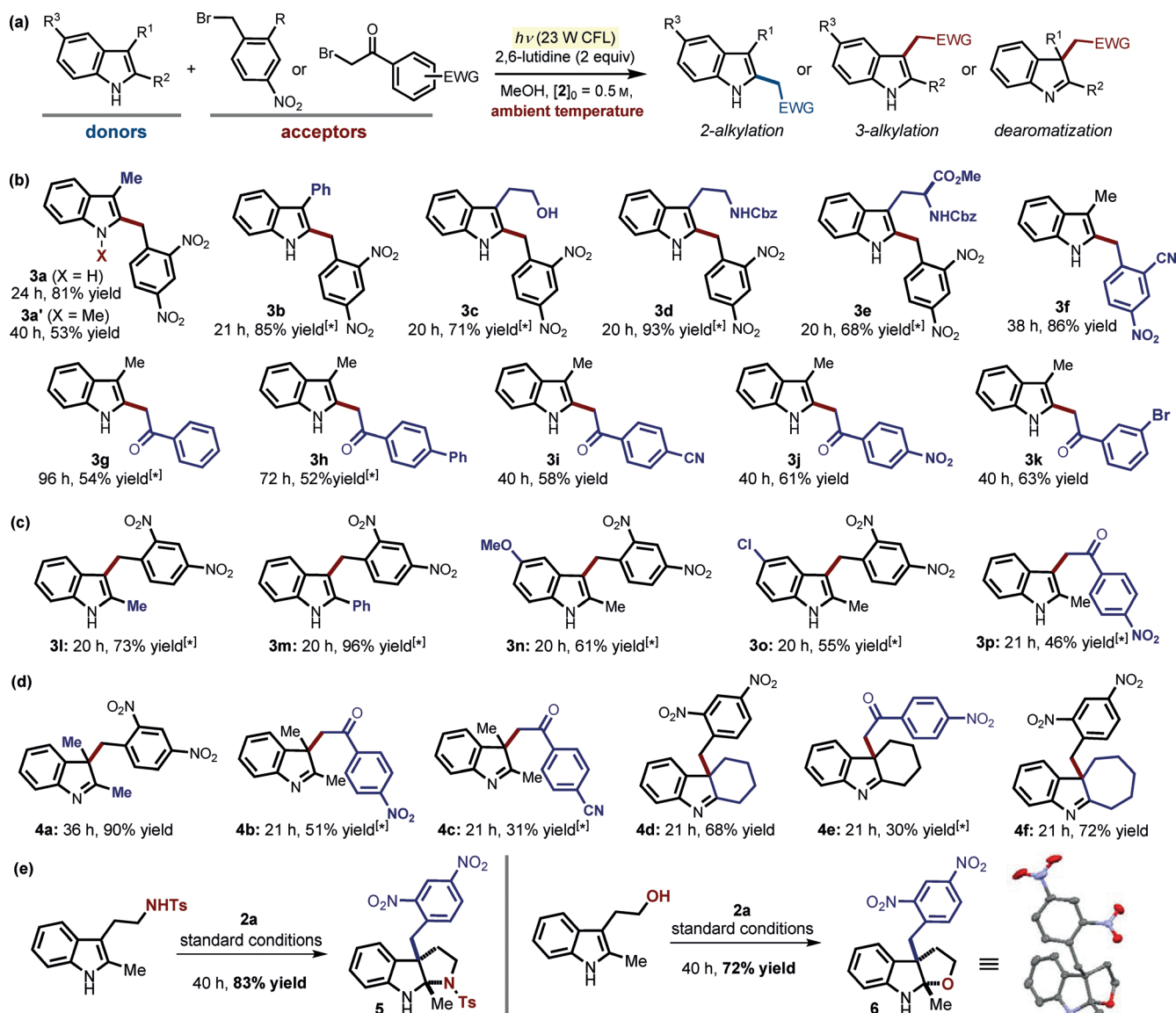


Figure 3. Evaluation of the scope of the photochemical indole alkylation strategy. a) General conditions: reactions performed on a 0.1 mmol scale using 2 equiv of 1H-indoles and a 23 W CFL bulb. Results represent the average of two runs per substrate. b) C2-selective alkylation: survey of the 3-substituted 1H-indoles and alkyl bromides that can participate in the reaction. c) C3-selective alkylation of 2-substituted 1H-indoles. d) Dearomatization of 2,3-disubstituted 1H-indoles to give indolenines 4. e) Dearomatization-annulation strategy. ^[*] Three commercially available 15 W black light CFL bulbs ($\lambda_{\max} = 360$ nm) were used to illuminate the reaction vessel because they provided a slightly better yield (about 10% higher) than 23 W CFL bulbs; for the emission spectra of the bulbs used in these experiments, see Figure S1 and S2 in the SI.

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[1] R. S. Mulliken, *J. Phys. Chem.* **1952**, 56, 801.

[2] For the seminal studies that inspired the charge-transfer theory, see: a) R. M. Keefer, L. J. Andrews, *J. Am. Chem. Soc.* **1950**, 72, 4677; b) R. S. Mulliken, *J. Am. Chem. Soc.* **1950**, 72, 600.

[3] Reviews: a) R. Foster, *J. Phys. Chem.* **1980**, 84, 2135; b) S. V. Rosokha, J. K. Kochi, *Acc. Chem. Res.* **2008**, 41, 641.

[4] Selected examples: a) E. F. Hilinski, J. M. Masnovi, C. Amatore, J. K. Kochi, *J. Am. Chem. Soc.* **1983**, 105, 6167; b) S. M. Hubig, T. M. Bockman, J. K. Kochi, *J. Am. Chem. Soc.* **1996**, 118, 3842.

[5] Reviews: a) R. Rathore, J. K. Kochi, *Adv. Phys. Org. Chem.* **2000**, 35, 193; b) T. Mori, Y. Inoue, *Chem. Soc. Rev.* **2013**, 42, 8122; For selected examples: c) J. M. Masnovi, J. K. Kochi, *J. Org. Chem.* **1985**, 50, 5245; d) T. Miyashi, M. Kamata, T. Mukai, *J. Am. Chem. Soc.* **1987**, 109, 2780; e) S. Sankararaman, W. A. Haney, J. K. Kochi, *J. Am. Chem. Soc.* **1987**, 109, 5235; f) S. Sankararaman, W. A. Haney, J. K. Kochi, *J. Am. Chem. Soc.* **1987**, 109, 7824; g) T. Gotoh, A. B. Padias, J. H. K. Hall, *J. Am. Chem. Soc.* **1991**, 113, 1308.

[6] a) G. Berionni, P.-A. Bertelle, J. Marrot, R. Goumont, *J. Am. Chem. Soc.* **2009**, 131, 18224; b) A. V. Vasilyev, S. V. Lindeman, J. K. Kochi, *New J. Chem.* **2002**, 26, 582; c) J. H. Kim, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **2001**, 123, 4951;

- d) J. H. Kim, S. M. Hubig, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **2001**, *123*, 87.
- [7] a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750; b) E. Arceo, A. Bahamonde, G. Bergonzini, P. Melchiorre, *Chem. Sci.* **2014**, *5*, 2438; c) M. Nappi, G. Bergonzini, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 4921; *Angew. Chem.* **2014**, *126*, 5021; d) E. Arceo, E. Montroni, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 12064; *Angew. Chem.* **2014**, *126*, 12260.
- [8] a) A. Szent-Györgyi, I. Senberg, *Proc. Natl. Acad. Sci. USA* **1960**, *57*, 1334; b) A. Szent-Györgyi, I. Senberg, J. McLaughlin, *Proc. Natl. Acad. Sci. USA* **1961**, *58*, 1089; c) B. Smaller, I. Isenberg, S. L. Baird, *Nature* **1961**, *191*, 168; d) R. Foster, C. A. Fyfe, *J. Chem. Soc. B* **1966**, 926; e) M. T. Sung, J. A. Parker, *Proc. Natl. Acad. Sci. USA* **1972**, *69*, 1196.
- [9] To the best of our knowledge, only two examples have been reported where an indole-based EDA complex is responsible for a photochemical process, see: a) M. González-Béjar, S.-E. Stiriba, M. A. Miranda, J. Pérez-Prieto, *Org. Lett.* **2007**, *9*, 453; b) H. Koshima, K. Ding, Y. Chisaka, T. Matsuura, Y. Ohashi, M. Mukasa, *J. Org. Chem.* **1996**, *61*, 2352; For thermally-driven reactions where the intermediacy of indole-based EDA complexes has been proposed, see: c) J. Bergman, R. Carlsson, S. Misztal, *Acta Chem. Scand.* **1976**, *30*, 853; d) P. Sepulcri, R. Goumont, J.-C. Hallé, E. Buncl, F. Terrier, *Chem. Commun.* **1997**, 789.
- [10] R. J. Sundberg in *The Chemistry of Indoles*, Academic Press, New York, **1970**.
- [11] For recent examples of metal-catalyzed direct alkylations of indoles, see: a) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990; b) M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592; For a recent photochemical approach, see: c) S. Lerch, L.-N. Unkel, M. Brasholz, *Angew. Chem. Int. Ed.* **2014**, *53*, 6558; *Angew. Chem.* **2014**, *126*, 6676.
- [12] Molecular oxygen can quench the excited EDA triplet state, thereby interrupting the ET process leading to the radical ion pair **III** (Figure 1b). The radical mechanism was further corroborated by the experiments conducted in the presence of 2,6-di-*tert*-butyl-4-methylphenol (0.5 equiv), since product **3a** was not detected after prolonged exposure to light.
- [13] P. Job, *Justus Liebigs Ann. Chem.* **1928**, *9*, 113.
- [14] H. Benesi, J. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703.
- [15] R. Foster, C. A. Fyfe, *Trans. Faraday Soc.* **1965**, *61*, 1626.
- [16] For the X-ray characterization of synthetically unproductive, inert indole-based EDA complexes, see: a) A. W. Hanson, *Acta Crystallogr.* **1964**, *17*, 559; b) C. López, R. M. Claramunt, E. Pinilla, M. R. Torres, I. Alkorta, J. Elguero, *Magn. Reson. Chem.* **2009**, *47*, 917.
- [17] CCDC 1025725 (**IIa**) and 1025726 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] a) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, **1942**, p. 192; b) A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441; c) S. Alvarez, *Dalton Trans.* **2013**, *42*, 8617.
- [19] While crystals of **IIa** could be safely stored for four months in the dark at 0°C, irradiation from a 23 W CFL induced a fast yet unproductive degradation, as the alkylation product **3a** was not detected. The lack of reactivity in the crystalline state could be a consequence of either the absence of base (the model reaction in MeOH does not proceed at all without 2,6-lutidine) or an unproductive orientation of the substrates **1a** and **2a** in the solid state, as dictated by stabilizing packing interactions according to Mulliken's "Overlap and Orientation Principle", see: R. S. Mulliken, W. B. Pearson in *Molecular Complexes*, Wiley, New York, **1969**.
- [20] Although our studies do not definitively rule out a radical chain mechanism, they suggest that any chain propagation process must be short-lived to account for a quantum yield as low as 0.2.
- [21] For a review on dearomatization strategies, see: S. P. Roche, J. A. Porco, *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; *Angew. Chem.* **2011**, *123*, 4154.
- [22] a) Y. Zhu, V. H. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 111; b) A. Lin, J. Yang, M. Hashim, *Org. Lett.* **2013**, *15*, 1950.