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Visible-Light-Mediated Charge Transfer Enables C–C Bond Formation with Traceless Acceptor Groups

Michael J. James, Felix Strieth-Kalthoff, Frederik Sandfort, Felix J. R. Klauck, Felicitas Wagener and Frank Glorius*

Dedicated to Richard J. K. Taylor on the occasion of his 70th birthday

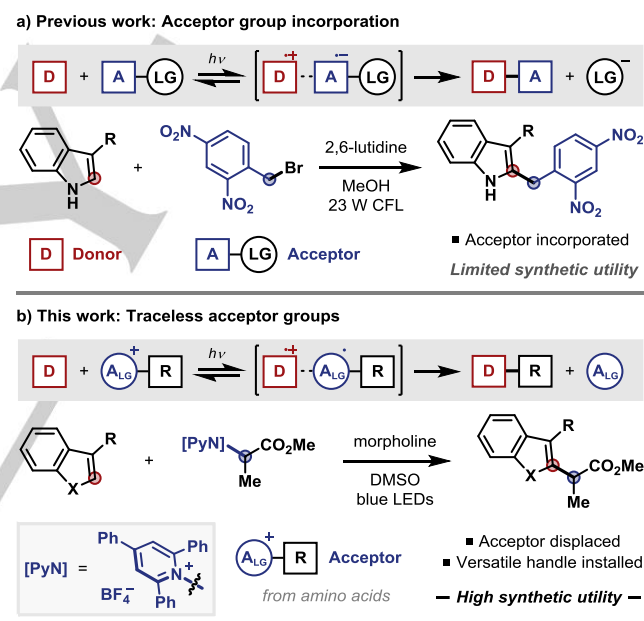
Abstract: The development and application of traceless acceptor groups in photochemical C–C bond formation is described. This strategy was enabled by the photoexcitation of electron donor-acceptor (EDA) complexes with visible light. The traceless acceptors, which were readily prepared from amino acid and peptide feedstocks, could be used to alkylate a wide range of heteroarene and enamine donors under metal- and peroxide-free conditions. The crucial role of the EDA complexes in the mechanism of these reactions was explored through combined experimental and computational studies.

The formation of C–C bonds continues to be one of the primary challenges in organic synthesis.^[1] To meet this challenge, a wide range of powerful radical-based methods have been developed.^[2] Of particular note, methods which can utilize abundant functional groups as alkyl radical precursors have received significant attention from the synthetic community.^[3] Most prominently, a number of decarboxylative strategies involving alkyl radicals have been developed to form C–C bonds.^[4] More recently, Watson and co-workers have elegantly demonstrated that redox-activated amines can be used in deaminative cross-coupling strategies.^[5] However, the majority of the aforementioned methods require the use of (expensive/high catalyst loading) transition metal catalysts or excess hazardous peroxides as oxidants. Thus, alternative methods which avoid these common tropes are of significant interest.

In recent years, a number of photochemical strategies have been developed to circumvent these limitations.^[6] In particular, pioneering studies by Melchiorre and co-workers have shown that photoexcited EDA complexes have significant potential to enable C–C bond formation under mild metal- and peroxide-free conditions.^[7,8] Strategies using these complexes in synthesis are typically operationally simple and can be readily performed with simple organic precursors. For example, electron-rich indole donors can be photochemically alkylated with highly electron-deficient dinitrobenzyl bromide acceptors (Scheme 1a). However, the scope of this strategy is generally restricted by the acceptors and their required high electron affinity. Moreover, the synthetic utility of these methods has remained limited by the fact that the electron-deficient arene moiety of the acceptor is typically incorporated into the final product. Thus, the design of broadly

compatible and *traceless* acceptors, which do not incorporate unwanted (electron-deficient) arene moieties into the final product, would significantly advance the scope and utility of this synthetic strategy.

Herein, we describe the realization of this approach through the photoexcitation of EDA complexes between pyridinium salt acceptors and heteroarene or enamine donors with visible light (Scheme 1b). The traceless pyridinium salt acceptors were all readily prepared from abundant amino acid precursors following established condensation chemistry with a pyrylium salt.^[9]



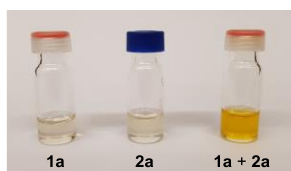
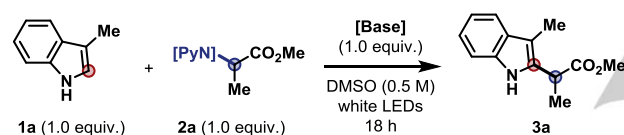
Scheme 1. Photochemical C–C bond formation with EDA complexes.

Our studies in this area initiated during our previous work using iridium photoredox catalysis to promote C–C bond formation with Katritzky pyridinium salts.^[10,11] In this work we observed that colourless pyridinium salts derived from amino acids formed strongly coloured solutions in the presence of indoles (Scheme 2). Furthermore, Aggarwal and co-workers,^[12a] and our own group,^[12c] recently demonstrated that Katritzky pyridinium salts can be used as productive acceptors in EDA complexes for C–B bond formation. Thus, based on this observation and our previous work, we questioned whether we might promote the photochemical alkylation of indole **1a** with pyridinium salt [PyN]-Ala-OMe **2a** without the use of a photocatalyst. First, the solution was irradiated with a light source covering a broad wavelength range (white LEDs), but no product formation was observed. However, upon addition of 2,6-lutidine small quantities of the

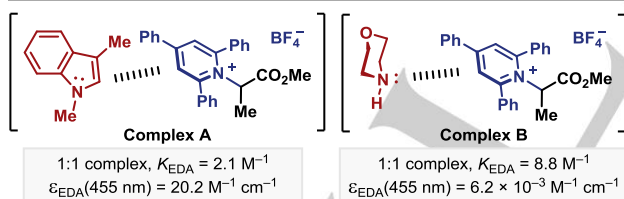
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desired product **3a** were detected. Following further base screening, a marked increase in reactivity was observed when redox-active bases were used, of which morpholine was the most effective. Further modification to the reaction conditions, such as increasing the amount of [PyN]-Ala-OMe and morpholine to 1.5 equivalents, decreasing the reaction concentration (0.4 M) and using 5 W blue LEDs ($\lambda_{\max} = 455 \text{ nm}$), enabled the product **3a** to be formed in 91% (NMR) yield (not shown). At this stage we sought to determine if an EDA complex was indeed formed in the reaction mixture using UV-Vis spectroscopy. Interestingly, from these studies we observed two 1:1 complexes of both indole **1b** and morpholine with [PyN]-Ala-OMe **2a** (**Complex A** and **Complex B**, respectively).^[13] Benesi-Hildebrand-type analysis revealed that both complexes had comparable binding constants (K_{EDA}) and thus likely exist as a dynamic equilibrium in solution. However, their molar extinction coefficients differed dramatically, which suggested that **Complex A** was the most photochemically active species. Furthermore, in the absence of light, only low levels of conversion to the product were observed. All reactivity was also completely suppressed in the presence of oxygen. These results together strongly suggested that this reaction proceeds through a radical process initiated by the photoexcitation of EDA **Complex A**.



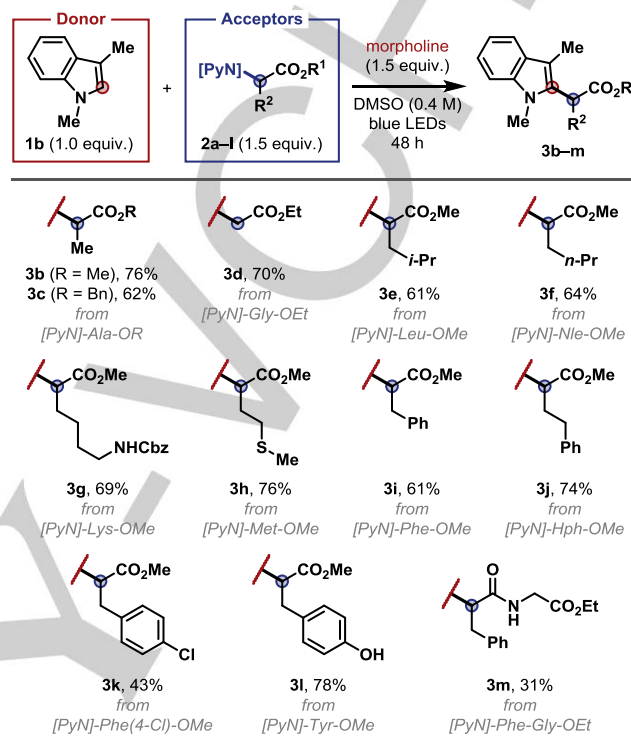
| [Base] | Yield |
|-------------------------|-------|
| none | 0% |
| 2,6-lutidine | 6% |
| imidazole | 12% |
| Et ₃ N | 57% |
| morpholine | 70% |
| morph. no light | 8% |
| morph. + O ₂ | 0% |



Scheme 2. Initial observation, optimization and EDA complex characterization. Yields were determined by ¹H NMR spectroscopy against an internal standard (1,3,5-trimethoxybenzene).

Next, having developed optimal reaction conditions and concluded our preliminary EDA complex analysis, we began to examine which other amino acid derived acceptors were compatible with indole **1b** (Scheme 3).^[14] First, simple aliphatic acceptor derivatives ([PyN]-Gly-OEt etc.) were converted into the desired products **3b–f** in consistently good yields. More functionalized acceptors derived from protected lysine and methionine precursors were similarly tolerated to afford products **3g,h** in good yields. Next, a variety of phenylalanine and tyrosine derivatives were used to prepare products **3i–l** in

modest to high yields. Finally, a dipeptide derived acceptor ([PyN]-Phe-Gly-OEt) was also successfully used to form product **3m** in modest yield. The yield of **3m** was unusually low due to the competing formation of an alkylated 2,4,6-triphenylpyridine byproduct.

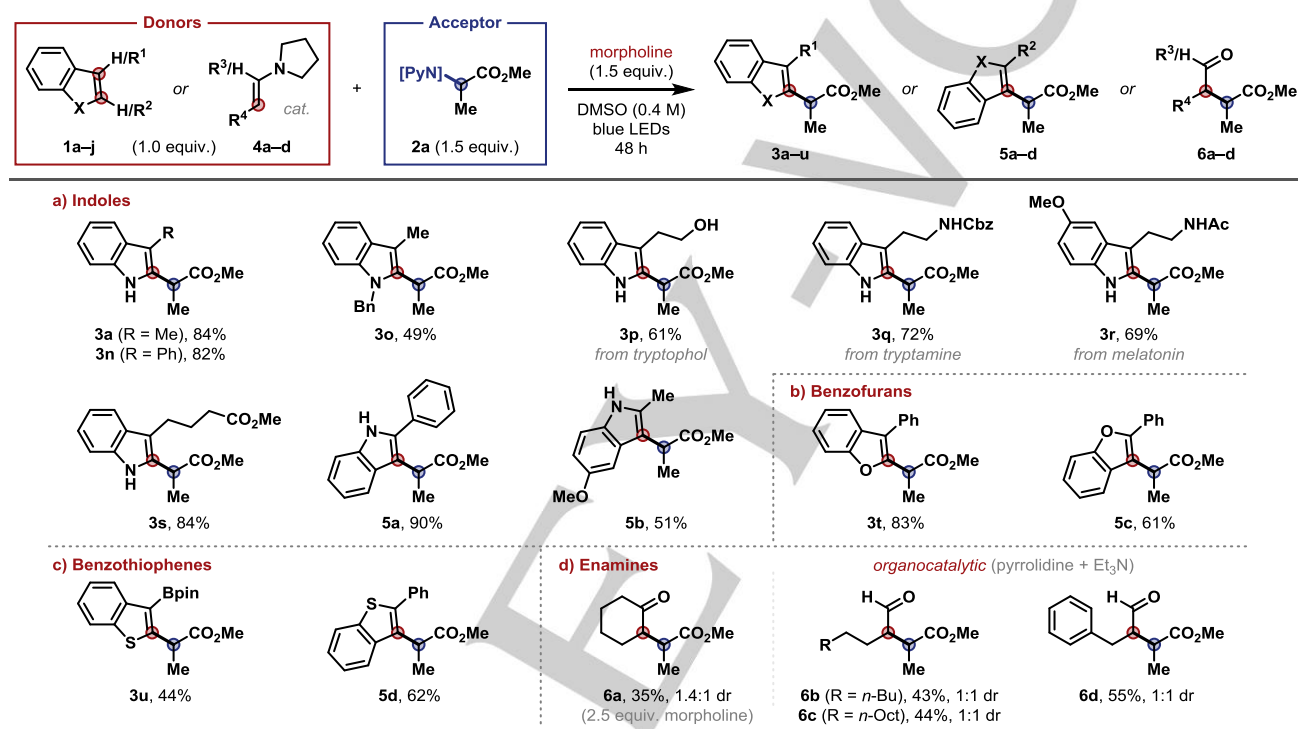


Scheme 3. Scope of amino acid-derived acceptors with indole **1b**. Isolated yields reported.

The scope of the donors with respect to [PyN]-Ala-OMe as the standard acceptor was then explored (Scheme 4a). First, simple 3-methyl/phenyl substituted indole donors were both alkylated to form the corresponding products **3a,n** in excellent yields. However, product **3a** was formed in diminished yield when the reaction was performed on a 1.0 mmol scale, suggesting that this reaction protocol is highly sensitive to the light intensity.^[15] An *N*-benzyl protected indole donor could also be used to form the desired product **3o** in acceptable yield. Encouraged by these results, we examined common indole natural product frameworks and found that we could readily alkylate tryptophol, Cbz-protected tryptamine and melatonin to form products **3p–r** in consistently good yields. A long-chain ester derivative **3s** was likewise prepared in excellent yield. Indole donors bearing substituents on the 2-position could also be tolerated, as shown with the formation of indole products **5a,b**. Next, satisfied we had demonstrated good compatibility with indole donors, we sought to determine if other heteroarenes could also be employed. Thus, inspired by the success of 2-/3-phenyl substituted indoles we examined the reactivity of their benzofuran analogues, which were both alkylated to afford benzofurans **3t**, **5c** in good to excellent yields (Scheme 4b). In an analogous fashion, 2-/3-substituted benzothiophene

derivatives were also alkylated to afford products **3u**, **5d** (Scheme 4c). Although modest yielding, the formation of borylated benzothiophene **3u**, was particularly pleasing as it illustrates the functional group tolerance and potential synthetic utility of this method. It should also be noted that, to the best of our knowledge, these are the first examples in which benzofuran and benzothiophene derivatives have been used as donors in productive EDA complexes. Finally, we tested the reactivity of enamines as donors with [PyN]-Ala-OMe (Scheme 4d). Without additional optimisation we found that cyclohexanone could be alkylated in modest yield, simply by using our standard reaction conditions with 2.5 equivalents of morpholine. Here, the in situ

formed enamine was alkylated to form product **6a** as a mixture of diastereoisomers in modest yield. Next, to establish the feasibility of an organocatalytic approach, we showed that by replacing morpholine with Et₃N, pyrrolidine (20 mol%) could be used to promote the organocatalytic alkylation of aliphatic aldehydes to form products **6a–d** as 1:1 mixtures of diastereoisomers in modest yields. It should be noted that the yields of these unoptimised reactions was likely reduced by the rapid and facile oxidation of the aldehyde products to the corresponding carboxylic acids.^[15] However, these reactions provide a clear proof of principle that an enantioselective variant might later be realized.



Scheme 4. Scope of compatible donors with acceptor [PyN]-Ala-OMe **2a**. Isolated yields reported.

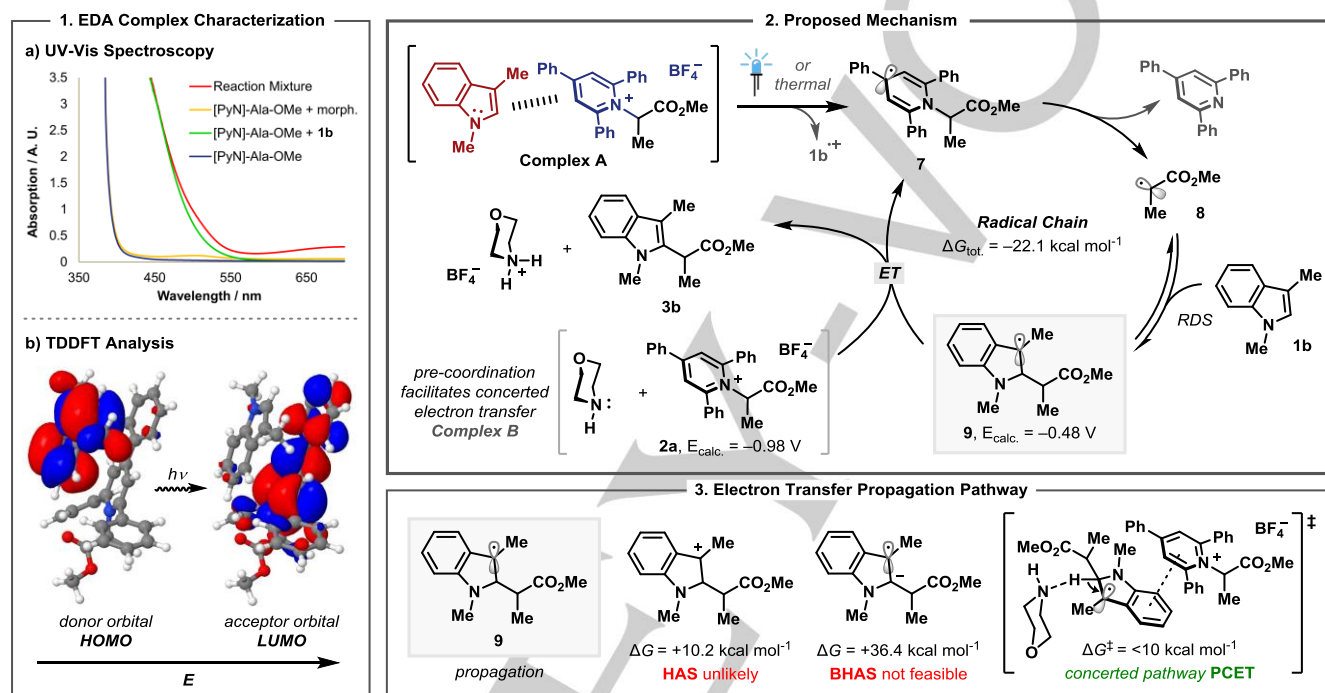
To gain further insight into the mechanism of these reactions, we elected to use indole **1b** as a model substrate for both experimental and computational analysis. First, based on the UV-Vis spectra of the reaction mixture and its components, we found no evidence for the potential formation of a ternary EDA complex between [PyN]-Ala-OMe, **1b** and morpholine (Scheme 5.1a). Thus, considering the greater molar extinction coefficient and the established reactivity of **Complex A** with other non-donor bases (see Scheme 2), we reaffirmed our initial hypothesis that **Complex A** was most likely the photochemically active complex that initiates a radical chain process. The validity of this hypothesis was further reinforced by computational studies using time-dependent density functional theory (TDDFT), which clearly demonstrated that upon visible light excitation of **Complex A**, a charge-transfer-type excited state is populated through an excitation from an indole-centered π orbital to a

pyridinium-centered π^* orbital (Scheme 5.1b).^[16] Thus we propose that following the photoexcitation of **Complex A**, a small quantity of the excited complex dissociates and escapes the solvent cage to initiate an exergonic radical chain process (Scheme 5.2).^[17] The dissociated pyridinyl radical **7** can then irreversibly fragment to afford electrophilic radical **8**, which based on DFT analysis is the turnover-determining intermediate of the radical chain.^[15] This electrophilic radical then reversibly adds to indole **1b** to form benzylic radical **9**. Here, the base is proposed to facilitate the propagation of the radical chain by enabling the thermodynamically unfavourable electron transfer between **9** ($E_{\text{calc.}} = -0.48$ V) and **2a** ($E_{\text{calc.}} = -0.98$ V) through a concerted proton-coupled electron transfer (PCET) type pathway (Scheme 5.3).^[18] Other alternative stepwise pathways proceeding through homolytic aromatic substitution (HAS) or base-promoted homolytic aromatic substitution (BHAS)

processes were determined to be thermodynamically unfeasible.^[19] It is possible that this three-component concerted electron transfer event could be assisted by the pre-coordination of morpholine to the acceptor (through **Complex B**), which would formally render this process a two-component collision. Furthermore, this rationale could account for why a significant increase in reactivity was observed when bases which can also function as donors were used.

In summary, we have described the development of a traceless acceptor group strategy to photochemically alkylate a wide

variety of donors with acceptors derived from abundant amino acid and peptide feedstocks. We hope this work will facilitate the development of other traceless acceptor systems with improved atom economy and even broader donor compatibility. The potential application of these acceptors in asymmetric protocols is also an area of significant interest. Overall, this strategy is expected to be of broad interest to the field of photochemical C–C bond formation and will enable a number of products to be selectively accessed using abundant precursors and operationally simple conditions.



Scheme 5. Proposed mechanism and supporting studies. HAS: homolytic aromatic substitution. BHAS: base-promoted homolytic aromatic substitution. PCET: proton-coupled electron transfer.

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Keywords: Visible light • C–C bond formation • EDA complexes • Amino Acids • Traceless acceptors

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- [14] During these studies the reaction time varied significantly (between 18–48 h) with each acceptor and so the reaction time was increased to 48 h as standard for all reactions.
- [15] For further information see the Supporting Information.
- [16] Further TDDFT studies suggest that Complex B could also initiate the radical chain (see the Supporting Information for details).
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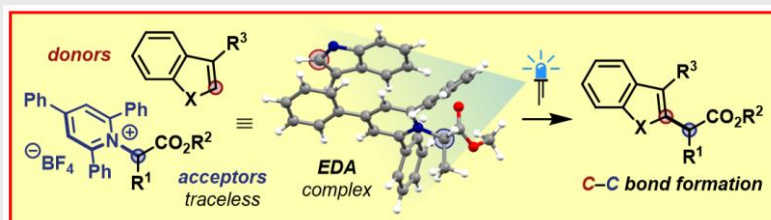
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**Visible-Light-Mediated Charge
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The development and application of traceless acceptor groups in photochemical C–C bond formation is described. This strategy was enabled by the photoexcitation of electron donor-acceptor (EDA) complexes with visible light. The traceless acceptors, which were readily prepared from amino acid and peptide feedstocks, could be used to alkylate a wide range of heteroarene and enamine donors under metal- and peroxide-free conditions. The crucial role of the EDA complexes in the mechanism of these reactions was explored through combined experimental and computational studies.