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Visible Light Organophotoredox-catalyzed Synthesis of Horner Precursors

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Abstract

A metal-free photoredox-catalyzed *α*-heteroarylation of 2-bromophosphonoacetic esters allows the synthesis of precursors for the Horner- (HWE-)olefination from indoles in a single step. Numerous functional groups are tolerated in this photoinduced radical coupling under mild conditions and the subsequent reaction with aldehydes generates 2-(indol-2-yl)acrylates in high yield.

Introduction

Photoredox–catalyzed reactions have become important tools in nowaday's arsenal of preparative methods.[1] They permit e.g. the formation of C–P and C–C-bonds under exceptionally mild conditions and tolerate many functional groups in the respective substrates, which makes them powerful tools for the modification and construction of complex heterocyclic structures.[2] While the field of photoredox-catalysis is still dominated by metal-based systems such as luminescent complexes of Ru and Ir, cheap and readily available organic dyes have been recognized as attractive alternatives with a favourable ecological footprint.[3] An interesting example of such a transformation is the coupling of

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2-bromomalonates **1** with indoles and other electron-rich heterocycles, catalyzed by the excited Ru-complex $Ru(bpy)_3Cl_2$ (**2**) as reported by Stephenson and co-workers (Scheme 1a).[4] This reaction has inspired numerous synthetic transformations as well as mechanistic investigations since.[5] A related enantioselective addition of 2-bromomalonates to chiral enamines, generated in situ from a corresponding aldehyde, was reported by MacMillan and coworkers who employed the same photocatalyst.[6] This transformation was later modified by the groups of König and Zeitler by using eosin Y (**4**) as a metal–free photocatalyst (Scheme 1b).[7] Recently, Liu and coworkers developed a visible light catalyzed difluoromethylenephosphonation of arenes and heteroarenes using $Ir(ppy)_3$ (**5**) as a photocatalyst (Scheme 1c).[8] On the basis of these reports, we wondered whether 2-bromophosphonoacetate **7** could be used in a similar fashion. Their addition to the 2-position of differently substituted indoles (**6**) would result in the formation of synthetically useful precursors for the Horner-type olefination of aldehydes in a single step (Scheme 1d).[9]

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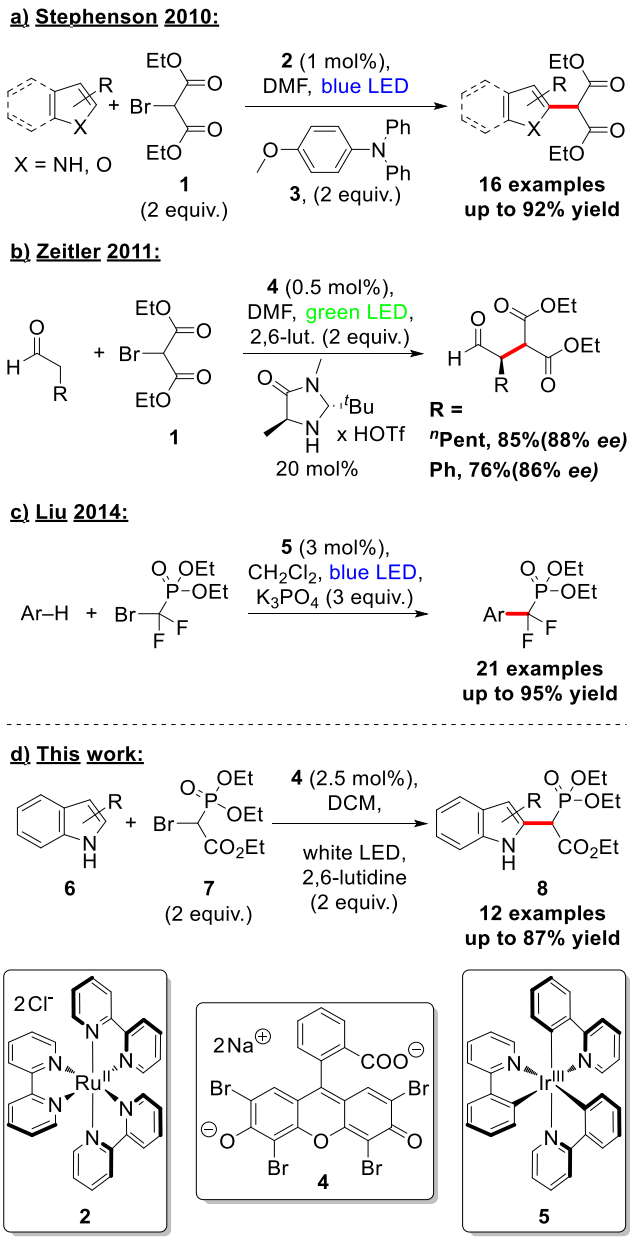

Scheme 1: a) Stephensons Ru-catalyzed photocatalytic radical functionalization of heterocycles; b) Zeitlers photo-organocatalyzed enantioselective α-functionalisation of aldehydes; c) Lius difluoromethylenephosphonation of (hetero)arenes d) regioselective radical functionalisation of indoles **6**, generating Horner-precursors **8**

Results and Discussion

Our initial studies aimed at identifying suitable reaction conditions for the phosphonoacetylation by investigating the model reaction depicted in Table 1. Triethyl 2-bromophosphonoacetate (**7**) was used as the radical precursor, which was obtained in 78% yield by NBS-bromination of commercially available triethyl phosphonoacetate. *N*-Boc-

tryptamine **6a** was chosen as the model hetarene for this coupling reaction since the blocked 3-position of the indole moiety would prevent potential regioselectivity issues during the screening process. The 1-position of the indole was left unprotected. Tryptamine **6a** also performed well as substrate in the reaction described by Stephenson and co-workers.[4] Upon employing the original reaction conditions which use $Ru(bpy)_3Cl_2$ as a photocatalyst and 4-methoxy-*N,N*-diphenylaniline (**3**) as a reductive quencher, the reaction proceeded smoothly providing the desired product in 74% yield after 20 h when a 462 nm blue LED was used as the light source (entry 1). Comparable results were obtained by utilizing a method described by the Weaver group, employing $Ir(ppy)_3$ and dicyclohexylisobutylamine as a reductive quencher (entry 2).[10] While these methods both showed good applicability to the desired coupling reaction, they required the stoichiometric addition of the employed amines, which are not commercially available or rather costly at best. Moreover, the use of expensive and potentially toxic late transition metal catalysts is not ideal with respect to sustainability and cost. Zeitler and coworkers have demonstrated that xanthene dyes such as rose bengal or eosin Y offer comparable redox potentials and reaction kinetics, so we wondered whether they might permit the reductive radical generation from 2-bromophosphonoacetate esters and the closure of a redox-neutral catalytic cycle without any additional quenchers added.[7] Both rose bengal and eosin Y were tested in combination with 2,6-lutitine as an inexpensive, non-redox-active base. Upon irradiating a solution containing 2.5 mol% of the respective xanthenes dye with a 520 nm green LED for 94 h, the desired product was obtained in 19% and 43% yield, respectively (entries 3 and 4). Interestingly, irradiation with blue light under otherwise identical conditions increased the yield to 32% for rose bengal (entry 5) and even to 82% for eosin Y (entry 6) in a shorter reaction time. This observation was somewhat unexpected when considering the absorption spectra of these dyes, both showing a maximum absorption for green light.[11] Screening of various solvents revealed DCM to be the most suitable for this reaction, providing the product in 83% yield after 20 h (entry 7). The yield dropped to 71% when the catalyst loading was lowered to 1 mol% (entry 8). Due to initial problems with the reproducibility as well as the long reaction times, the reaction setup

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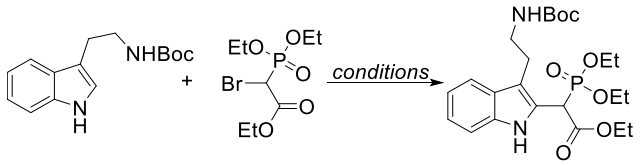
was modified and white LED stripes were used for irradiation instead of a single high power blue LED. This resulted in a more rapid conversion and good reproducibility of the individual runs.[12] In this way we were able to obtain compound **8a** in 78% isolated yield after 14 hours of irradiation. Unfortunately, two equivalents of the brominated phosphonoacetate **7** were required and the yield dropped significantly to <15%, when only 1.25 equiv. were added (entry 10). As expected, no reaction could be observed in the absence of light or the catalyst (entries 11 and 12).

Table 1. Screening and optimization of reaction conditions for the photocatalytic addition of bromophosphonoacetate **7**[a)]



6a **7** **8a**

Entry	cat. (mol%)	*h·υ*	additive (equiv.)	solvent	t (h)	Yield (%)[b)]
1	$Ru(bpy)_3Cl_2$ (1)	blue LED	(*p*-$CH_3OC_6H_4$)NPh_2 (2)	DMF	20	74%
2	$Ir(ppy)_3$ (1)	blue LED	K_2CO_3 (2), Cy_2N^tBu (0.5)	MeCN	20	78%
3	rose bengal (2.5)	green LED	2,6-lutidine (2)	MeCN	94	19%
4	eosin Y (Na_2) (2.5)	green LED	2,6-lutidine (2)	MeCN	94	43%
5	rose bengal (2.5)	blue LED	2,6-lutidine (2)	MeCN	72	32%
6	eosin Y (2.5)	blue LED	2,6-lutidine (2)	MeCN	48	82%
7	eosin Y (2.5)	blue LED	2,6-lutidine (2)	DCM	20	83%
8	eosin Y (1)	blue LED	2,6-lutidine (2)	DCM	20	71%
9	eosin Y (2.5)	white LED-stripes	2,6-lutidine (2)	DCM	14	78%[c)]
10[d)]	eosin Y (2.5)	white LED-stripes	2,6-lutidine (2)	DCM	22	<15%
11	eosin Y (2.5)	-	2,6-lutidine (2)	DCM	48	N.R.
12	-	white LED-stripes	2,6-lutidine (2)	DCM	48	N.R.

[a)]Reaction conditions: **6a** (1 equiv.), **7** (2 equiv.), solvent (60 µmol/mL), *cat.*, *additive*, 25 °C, *h·υ*; [b)]determined *via* ^{1}H-NMR spectroscopy using 1,4-bis(trimethylsilyl)benzene as an internal standard; [c)]isolated yield; [d)] 1.25 equiv. **7**; N.R.: no reaction

Under the optimized conditions, the scope of this reaction was investigated (Scheme 2). N-acylated or N-sulfonylated tryptamines reacted readily, providing the corresponding

products **8a–d** in high yields. The reaction also afforded *N*-benzylamine **8e**, as well as ester **8f** in only slightly reduced yield. The protected tryptophan derivative **8g** could be obtained in 68% yield, making this reaction potentially attractive for the late stage functionalization of peptides. In general, 3-unsubstituted indoles only provided the respective 2-substituted products, highlighting the complete regioselectivity of this reaction. Potentially sensitive alkyl as well as aryl bromides (**8h,i**) were well tolerated in this reaction, as were donor-substituted indoles (**8j**), although the yield was slightly reduced in the latter case. For the reaction involving indole-3-carbaldehyde, the corresponding phosphonoacetate **8k** could only be isolated in 15% yield, which can presumably be explained by radical side reactions like at the aldehyde function. While unsubstituted indole reacted readily providing the desired product **8l** in 76% yield, no conversion of the starting material could be observed for *N*-functionalized indoles like *N,N'*-Di-Boc-tryptamine **6a'**, *N*-benzylindole (**6l'**) or *N*-Cbz-indole (**6l''**). This is most likely due to steric hindrance imposed by the protecting group, preventing an addition of the bulky phosphonoacetate moiety. Interestingly however, in the case of *N*-methylindole, 27% of the expected 2-substituted indole **8m** alongside with 28% of the 3-substituted product **8m'** could be obtained. When 2-methylindole was employed in the reaction, no addition occurred and only the previously reported oxidative dimerization of the starting material to the oxidized dimer **9** took place when the reaction was not performed under an inert atmosphere.[13] Attempts to employ other heterocycles than indoles in this reaction were unsuccessful and no conversion could be observed for substrates like pyrrole, benzofuran, benzoxazole, benzimidazole or benzothiazole.

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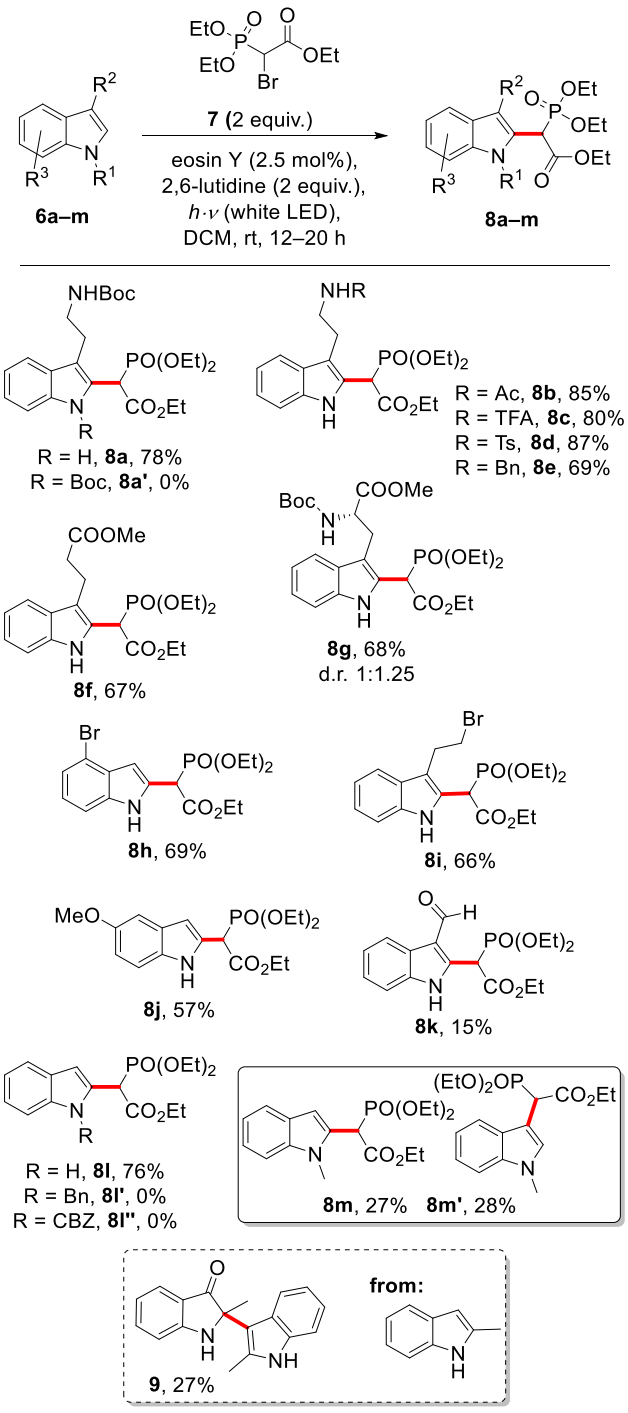

Scheme 2: Photocatalytic phosphonoacetylation of indoles.

A plausible reaction mechanism is displayed in Scheme 3. We propose that by photon absorption and intersystem crossing (ISC) of the photocatalyst eosin Y (EY), an excited triplet state EY* is formed, which can transfer an electron to bromophosphonoacetate **7** generating the eosine Y radical cation $EY^{\bullet+}$, bromide, and the radical **10**. The latter can then add to the indole aromatic system, providing the benzylic radical **11**, which can thereafter

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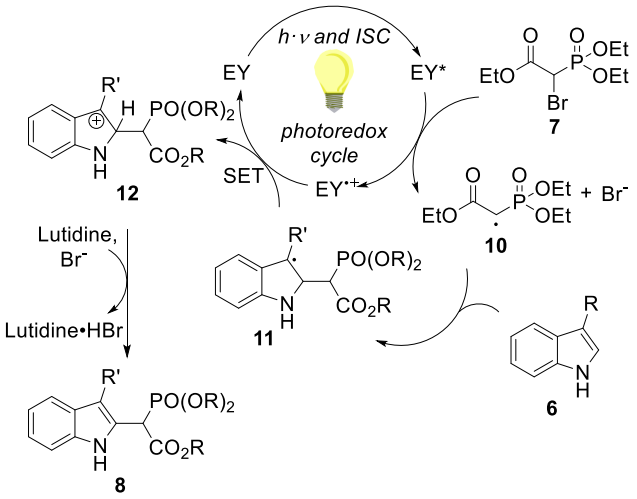
rearomatize to the obtained product **8** through single electron transfer (SET) to $EY^{\bullet+}$ and subsequent deprotonation. An alternative reductive catalytic cycle as discussed by König and Zeitler for the addition of bromomalonate to enamines seems less likely for the present reaction.[7] This mechanism, originally proposed by MacMillan and co-workers, relies on an initial oxidation of a catalytic amount of enamine, generating the catalytic species necessary to start the actual catalytic cycle.[6] Such a reaction course seems improbable for our case, since a corresponding initial oxidation of indole would require an oxidation potential exceeding that of the excited eosin Y.[14] The same applies for lutidine, which we believe to act as a mere acid scavenger for the HBr liberated during the course of the reaction and promoting the rearomatization step. When lutidine was replaced by the reductive quencher 4-methoxy-*N,N*-diphenylaniline (**3**), a similar yield and reaction progress was observed, supporting the hypothesis of an oxidative reaction cycle. It can however not be ruled out that a catalytic amount of bromophosphonoacetate **7** is deprotonated to the corresponding anion which could act as a reductive quencher to initiate a reductive catalytic cycle.



Scheme 3: Proposed Mechanism for the photocatalytic addition of bromphosphonoacteate **7** to indoles.

Next, the Horner-type olefination of the aryl-phosphonoacetates **8** was investigated. Again, the *N*-Boc-tryptamine derived compound **8a** was chosen as a model compound. Optimization

studies showed that the best results for this transformation could be obtained by the use of DBU in dichloromethane (Scheme 4a).[15] In this fashion, aldehydes like benzaldehyde or cinnamaldehyde could be transformed to the corresponding *E*-olefins **14a** and **14b** exclusively in 63% and 80% yield. The *E*-configuration was confirmed via ^{1}H-^{1}H-NOE-spectroscopy as well as (in the case of **14a**) by X-ray crystallography (scheme 4b). With aliphatic aldehydes like valeraldehyde and isobutyraldehyde, not only the *E*-olefins **14c** and **14d**, but also the respective *Z*-isomers **14c'** and **14d'** could be obtained, which was again determined by ^{1}H-^{1}H-NOE-spectroscopy. The isomeric products derived from valeraldehyde could be separated by flash column chromatography, yielding the *E*-isomer **14c** as major product in 79% yield. In the case of isobutyraldehyde, a 1.5:1 mixture of diastereomers was obtained in 40% yield which could only be separated by preparative HPLC. A possible explanation for the reduced yield and selectivity for the latter example could be the increased steric demand of the isopropyl group, which may impair the formation of the intermediate phosphoxetane. This effect is likely to be more prominent for the phosphoxetane diastereomer yielding the *E*-olefin in which the bulky indole moiety is *syn*- to the isopropyl group. Not surprisingly, ketones such as acetone or cyclohexanone are no suitable coupling partners since there is significant bulk and charge stabilization in the deprotonated phosphonates **8**. Using paraformaldehyde as the carbonyl compound led to a complex mixture of products (as judged by TLC), from which the desired olefin could not be isolated.

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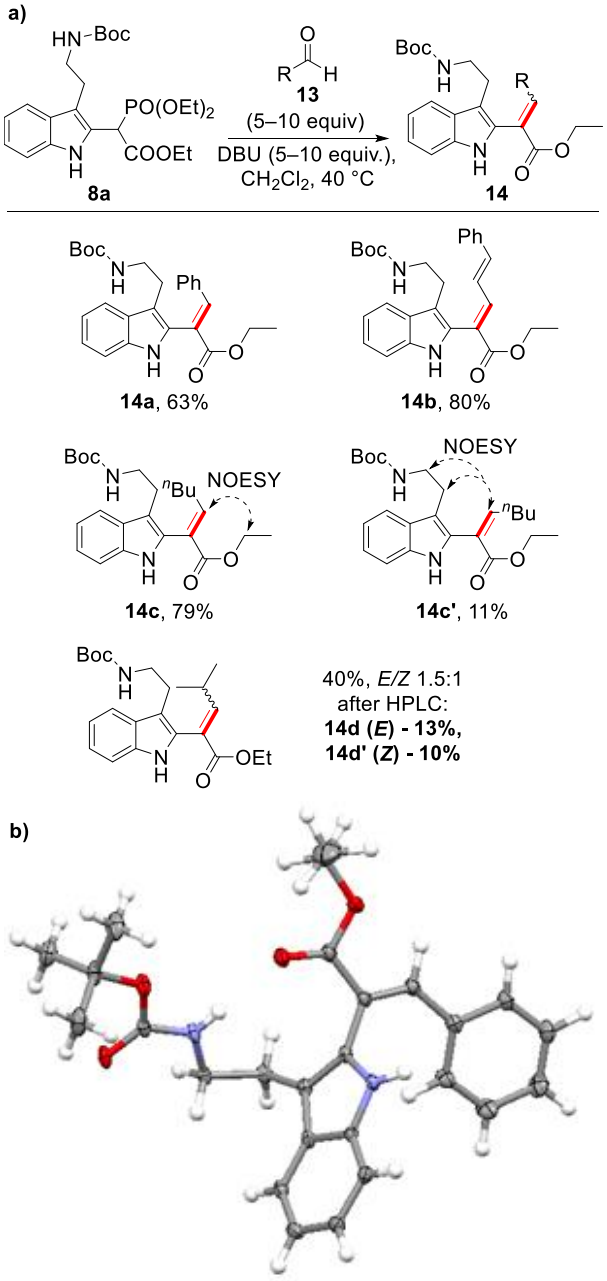

Scheme 4: a) Horner-type olefination of indolyl-phosphonoacetates **8**; b) X-Ray crystal structure of compound **14a**, solid state at 193K (thermal ellipsoids, 30% probability).

As discussed above, all of the Horner-type olefinations performed showed the expected *E*-selectivity, albeit to a varying extent. It appeared tempting to develop a modification of this protocol predominantly furnishing the isomeric *Z*-olefins which would provide control over the double bond geometry. Indolyl-diphenoxyphosphonoacetate **16** was thus chosen as an intermediate which could be reacted in an Ando variant of the Horner reaction (Scheme 5).[16]

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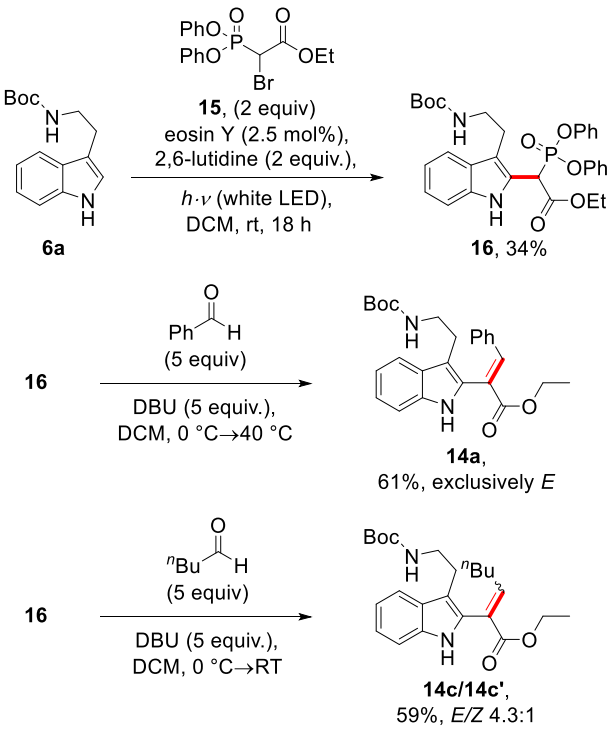
The preparation of the required diphenoxy bromophosphonoacetate **15** turned out to be not as straightforward as in the case of alkyl derivative **7.** A chemoselectivity in favour of the monobrominated product was rather challenging to achieve, as was its purification, which was extensively investigated by Brückner and co-workers.[17] NBS-bromination of ethyl diphenylphosphonoacetate, as described for the triethyl derivative, provided only 47% of bromophosphonoacetate **15**. Execution of the photocatalytic coupling to *N*-Boc-tryptamine **6a** under the previously established standard conditions provided the corresponding aryl phosphonoacetate **16** in 34% yield. When this compound was subjected to the Horner olefination with benzaldehyde, the *E*-olefin **14a** was exclusively obtained in 61% yield, similarly to our earlier findings in the alkyl series. We speculated that the *Z*-isomer potentially formed during the reaction might be photochemically isomerized to the *E*-olefin which is not an uncommon process for cinnamoyl-derivatives.[18] We therefore decided to repeat the reaction using valeraldehyde, providing the aliphatic α,β-unsaturated esters **14c/14c'**, which are less prone to isomerisation due to the hypsochromic shift of the absorption maximum of the product olefin. Here, an *E/Z*-ratio of 4.3:1 and 59% isolated yield of the diastereomeric mixture were observed. This is only a slight improvement towards the formation of the *Z*-isomer when compared to the 7.2:1 ratio obtained for the triethyl derivative while the yield was considerably lower.



Scheme 5: Photoaddition and Horner-type olefination starting from phosphonoacetate **15**.

Since both the photocatalytic phosphonoacetylation as well as the subsequent Horner-type olefination ran smoothly in dichloromethane, we tried to develop a one-pot protocol for this transformation. Addition of DBU and benzaldehyde to a solution of **8a** directly after complete conversion in the preceding photoreaction however did not result in the formation of the desired olefin. Only a complex mixture could be detected via LC-MS after several days of reaction instead.

Conclusion

In summary, a photoredox-catalyzed synthesis of precursors of the Horner-type olefination from triethyl 2-bromophosphonoacetate and indoles has been developed. Eosin Y serves as an inexpensive catalyst and no external quenchers are required. Standard white light LEDs serve as an inexpensive energy source for this redox-neutral C–C-coupling reaction. Olefination reaction with aromatic as well as aliphatic aldehydes gave rise to 2-(indol-2-yl)acrylates in high yield and selectivity. This versatile and facile two-step synthesis hence could find application in natural product total synthesis as well as for the late stage

functionalization of indole structures such as tryptophane-moieties in peptides. The synthetic potential of a combination of a Horner olefination followed by photoredox chemistry was recently demonstrated by Reiser and co-workers for the synthesis of indolines and indenones.[19] An amalgamation of this methodology with the present sequence may permit even more elaborate photocatalytic sequences. While the origin of the higher reaction efficiency under irradiation with light of a wavelength shorter than the absorption maximum of the organic dye remains to be investigated, this effect has also been seen by us in other processes such as oxidative cyanations of amines. The excitation of a reduced or oxidized form of the dye could possibly account for this observation, as it was reported by König and co-workers for rhodamine 6G, which possesses a similar absorption spectrum as eosin Y.[20]

Experimental Section

General procedure A for the photoredox-catalytic phosphonoacetylation: A 10 mL Schlenk-tube was charged with the respective indole **6** (0.25 mmol, 1 equiv.), which was dissolved in dry and degassed CH_2Cl_2 (4.5 mL) under an atmosphere of nitrogen or argon. Ethyl bromo(diethoxyphosphoryl)acetate **7** (150 mg, 0.50 mmol, 2 equiv.), 2,6-lutidine (60 µL, 0.50 mmol, 2 equiv.) and Na_2-eosin Y (4.3 mg, 6.22 µmol, 2.5 mol%) were added and the solution was stirred under irradiation with white LED-stripes, until full consumption of the starting material **6** could be observed via TLC or LC-MS (12–24 h). The solution was filtered over a short plug of silica gel, the products were eluted with EtOAc and purified by column chromatography. If not stated otherwise, automated flash column chromatography (C18, 0%→100% MeCN in H_2O) was employed.

General procedure B for the Horner-type olefination: Phosphonoacetate **8a** (0.23 mmol, 1.00 equiv.) was dissolved in dry CH_2Cl_2 (2.5 mL) and cooled to 0 °C. The respective aldehyde (1.15 mmol, 5 equiv) and DBU (1.15 mmol, 5 equiv.) were added and the solution was stirred at 40 °C until full consumption of the starting material was indicated by TLC (If full conversion was not achieved, another portion of base and aldehyde were added as indicated for the respective compounds). The solution was

filtered over a short plug of silica, the product was eluted with EtOAc and purified by column chromatography.

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Keywords

Photochemistry; Olefination; Heterocycles; C-C coupling; Radical reactions

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