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Intermolecular Photoredox Coupling: Alternative to Norrish Type II Reaction and Yang Cyclization in Ketones with γ-C–H Bonds

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A new reaction pathway for the photoconversion of butyrophenone in acetonitrile was investigated. In addition to the classic intramolecular photoreactivity of ketones with γ-C–H bonds (Norrish type II fragmentation and Yang cyclization), intermolecular generated species were isolated and characterized: 1,2-Dibenzoylethane, 2-phenacylacetonitrile (oxidized species) and pinacols (reduced species). They account for approx. 20% of the converted starting material, similar to the Yang product. The acetophenone enol intermediate, formed in situ via the Norrish type II reaction, has been identified as an H-atom donor for the main intermolecular reaction steps, and has been distinguished from other conceivable mechanistic possibilities. Experimental results with analogue compounds suggest that the intermolecular product formation pathway may be of general relevance.

Butyrophenone (**6**) holds a special place in the history of photochemistry as stated by Sundaresan, Jockusch and Turro.[1] The intramolecular deactivation pathways by photoreactions (Norrish type II fragmentation[2] to acetophenone enol and ethene,[1,3,4,5,6] and Yang cyclization[7] to 1-phenylcyclobutanol (**4**)[3,4,6,8,9]) are well established and can be found as common textbook knowledge. The formation of 1-tetralone (**3**)[4,8] has also been reported in the literature.

In contrast, to the best of our knowledge, 1,2-dibenzoylethane (**7**) has rarely been reported as a photoproduct in the literature, and is formed in only very small amounts.[3,10,11] To understand its photochemical formation from butyrophenone (**6**), further studies were carried out by irradiation in acetonitrile.[12]

The expected compounds acetophenone (**2**) and ethene (main products) as well as 1-phenylcyclobutanol (**4**) and 1-tetralone (**3**) were found, all formed by intramolecular reaction steps (HPLC and standard addition, MS-APCI, MS-ESI or GC). In addition, other photoproducts were obtained (oxidized and reduced species with respect to the H-atom balance), which must have been formed by intermolecular reaction steps.[13,14] Together they account for approx. 20% of the conversion, similar to 1-phenylcyclobutanol[3] (Figure 1). They are referred to in the following as "intermolecular photoproducts". No formation of oxetanes,[15] hydrols,[13,16] mixed recombination products[17] (from phenacyl and ketyl radicals), and hydrogen[18] has been observed. The time course of the stable components shows the parallel formation of 1,2-dibenzoylethane (**7**) and the sum of the pinacols (**5**, **8**–**12**) (Figure 2). The 1,2-dibenzoylethane signal (**7**) is already observed (HPLC) in the initial phase of the reaction after a very short irradiation time (2 min, the total turnover would require at least 60 min). Variation experiments of the reaction parameters (Figure 3) show reduced intermolecular product formation at 0.005 M and none at all at 0.0005 M butyrophenone concentration. The experiments also indicated complex mutual dependencies between turnover time, irradiation intensity, temperature, solvent and the presence of UVB radiation (through the use of quartz glass between the light source and reaction volume). In the case of the 0.05 M reactant concentration, intermolecular photoproduct formation was generally observed. Qualitative comparative experiments (using 0.05 M butyrophenone) showed an increased formation of the intermolecular photoproducts at rather long turnover time, low temperature, relatively high radiation intensity and the use of UVB light sources and quartz glass.

The irradiation of the analogues hexanophenone and octanophenone (both 0.05 M) provided also evidence of an increased formation of 1,2-dibenzoylethane (**7**) compared to the acetophenone system (**2**) (see below). First experiments to irradiate the aliphatic analogue 2-pentanone show a hexane-2,5-dione signal which is about a factor of 2 higher than the corresponding signal found after acetone irradiation[17] (each HPLC and standard addition).

In developing the mechanism proposed in Scheme 1 for the formation of intermolecular photoproducts, the following experimental findings were also considered: 1. The irradiation of acetophenone (**2**) (0.05 M) resulted in about a factor of 10 less intermolecular product formation than that from butyrophenone (**6**) (HPLC, MS). 2. The irradiation of the analogue propiophenone (0.05 M), which is α-alkyl-substituted

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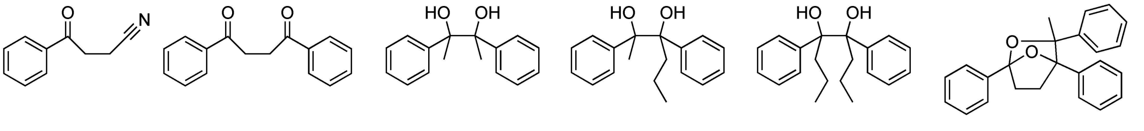
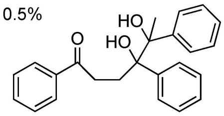
oxidized forms of the initial reactant | reduced forms of the initial reactant (both enantiomeric pairs in each case)



compound:	**2-phenacyl-acetonitrile**	**1,2-dibenzoylethane**	**acetophenone pinacol**	**acetophenone-butyrophenone pinacol**	**butyrophenone pinacol**	**3-methyl-1,3,4-triphenyl-2,7-dioxabicyclo[2.2.1]heptane**
			meso- and (*S**,*S**)-form	(*S**,*R**)- and (*S**,*S**)-form	*meso*- and (*S**,*S**)-form	(1*S**,3*R**,4*S**)- and (1*S**,3*S**,4*S**)-form
comp.-no.:	**1**	**7**	**5 and 8**	**9 and 10**	**11 and 12**	**13 and 14**
formed quantity:	4 mg	194 mg	62 mg	36 mg	40 mg	8 mg
selectivity in percent:	0.2%	11%	3.4%	1.8%	1.8%	0.5%

↑ probably formed in a thermal reaction from



acetophenone-1,2-dibenzoylethane pinacol

Figure 1. Intermolecular photoproducts of butyrophenone (**6**) (2.2 g, 2.25 mL, 0.05 M, complete conversion). No enantiomers were separated (due to instrument-based limitations). The small isolated quantities were determined gravimetrically, and were extrapolated to the total reaction volume. Reaction conditions: Irradiation (4 h) in acetonitrile (290 mL in a quartz flask) using 2 UVA-LED and 4 UVB light bulb sources (combined) under ventilator cooling (approx. 25 °C).

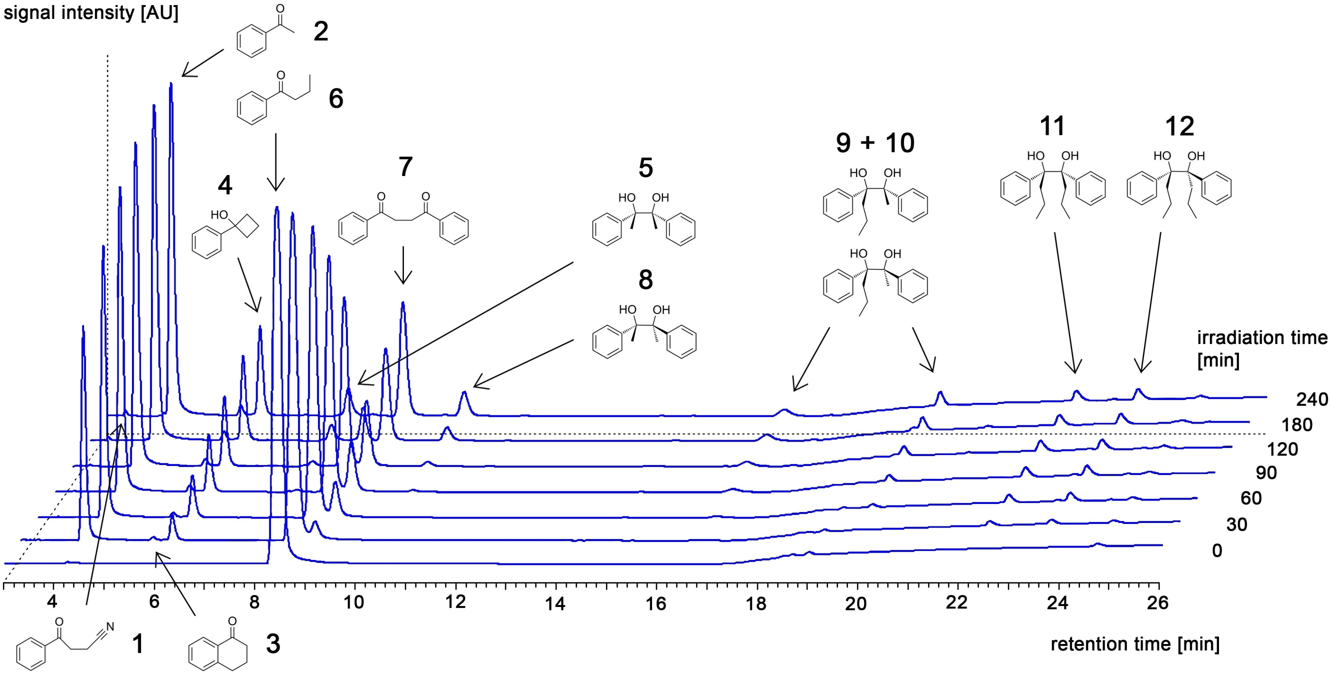


Figure 2. The time course of the stable components of the photochemical butyrophenone (**6**) turnover (2.2 g, 2.25 mL, 0.05 M, complete conversion), shown by layered chromatograms (HPLC, each sample taken after different irradiation times). The small amounts of presumed acetophenone-1,2-dibenzoylethane pinacol were not assigned (see Figure 1). Reaction conditions: Irradiation (4 h) in acetonitrile (290 mL in a quartz flask) using 2 UVA-LED and 4 UVB light bulb sources (combined) under ventilator cooling (approx. 25 °C).

but cannot undergo the Norrish type II reaction, gave comparable findings (HPLC, MS). 3. After synthesis and photochemical conversion of α-ethyl-substituted 1,2-dibenzoylethanes, no signal strengths matching those of the 1,2-

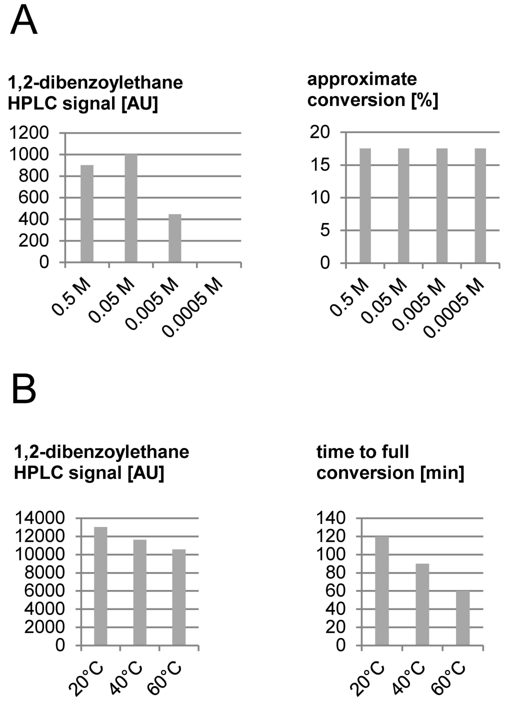


Figure 3. Selected results of reaction parameter variation experiments demonstrating the relevance of the intermolecular photoproduct formation under typical conditions using modern light sources (UVB, quartz glass, 3 mL reaction volume micro scale in thermostatic quartz jacket, 20 °C). A: Variation of the butyrophenone (**6**) concentration. For signal comparison, the different dilutions and the different conversions were taken into account by calculation, resulting in an approx. conversion of 15–20 % (assuming linearity of the concentration-signal ratios). B: Variation of the reaction temperature.

dibenzoylethane (**7**) amount of the butyrophenone system (**6**) could be observed (HPLC, MS). 4. The synthesis of isotopically labeled acetophenones and their addition to the butyrophenone system (**6**) prior to irradiation revealed that de facto no isotopically labeled ketone building blocks are incorporated into 1,2-dibenzoylethane (**7**), but incorporation into formed pinacols (**5**, **8**–**12**) occurs approximately statistically (EI-, APCI-, and ESI-MS; after separation by TLC or HPLC). 5. For excluding any catalytic event (e.g. via enolization by alcohols[8,19,20]), small amounts of a second known component (1-phenylcyclobutanol (**4**), acetophenone pinacol (**5**, **8**), 1-tetralone (**3**), 1-naphthol) were added to acetophenone (**2**) prior to irradiation. No 1,2-dibenzoylethane (**7**) signal intensities (HPLC) comparable to those of the pure butyrophenone system (**6**) were found. Based on these experimental findings, the main pathways of formation of the intermolecular photoproducts shown in Scheme 1 are proposed. Other mechanisms initially conceivable with regard to Scheme 1A, which would proceed via (i) α-C–H-abstraction from ground-state ketones (**2**, **6**)[10,11] and subsequent release of ethene, (ii) α-C–H-abstraction after radical-radical coupling at the phenyl moiety[8,21] or (iii) [2+2]-cycloaddition of excited acetophenone enol,[22] are excluded on the basis of the literature[6,23] and experimental findings.

A: Acetophenone enol ketonizes uncatalyzed on the second-minute scale to acetophenone (**2**).[1,6,24] By H-atom transfer (HAT) from the intermediate acetophenone enol[3] to excited keto forms, phenacyl and ketyl radicals are formed.[20] These then react by phenacyl radical addition[25,26] to acetophenone enol, followed by H-atom loss via HAT or via ketyl radical transfer to ground state ketones (**2**, **6**),[27] and by radical recombination to give 1,2-dibenzoylethane (**7**)[26,28] and pinacols (**5**, **8**–**12**).[4,6,13,20,29]

B: By radical α-C–H abstraction namely HAT between excited keto forms and ground state acetonitrile, acetonitrile radicals[30] and ketyl radicals could be formed. The acetonitrile radicals could form 2-phenacylacetonitrile (**1**) (analogous to Scheme 1A) by addition to acetophenone enol (followed by H-atom loss) or by recombination with a phenacyl radical.

C: Recombination of a 1,2-dibenzoylethane ketyl radical with an acetophenone ketyl radical could form 1,2-dibenzoylethane-acetophenone pinacol (analogous to Scheme 1A). Presumably, 3-methyl-1,3,4-triphenyl-2,7-dioxabicyclo[2.2.1]heptane (**13**, **14**) has been formed from it during the work-up, by cyclization and release of water.

In conclusion, it can be assumed that the intermolecular photoredox coupling can occur as an alternative reaction pathway to the known Norrish type II process and can proceed with similar yields as the Yang cyclization. Therefore, it is proposed to add this option to the photoreaction modes and photoproducts of ketones with γ-C–H bonds typically shown in relevant textbooks[6,31] (Scheme 2).

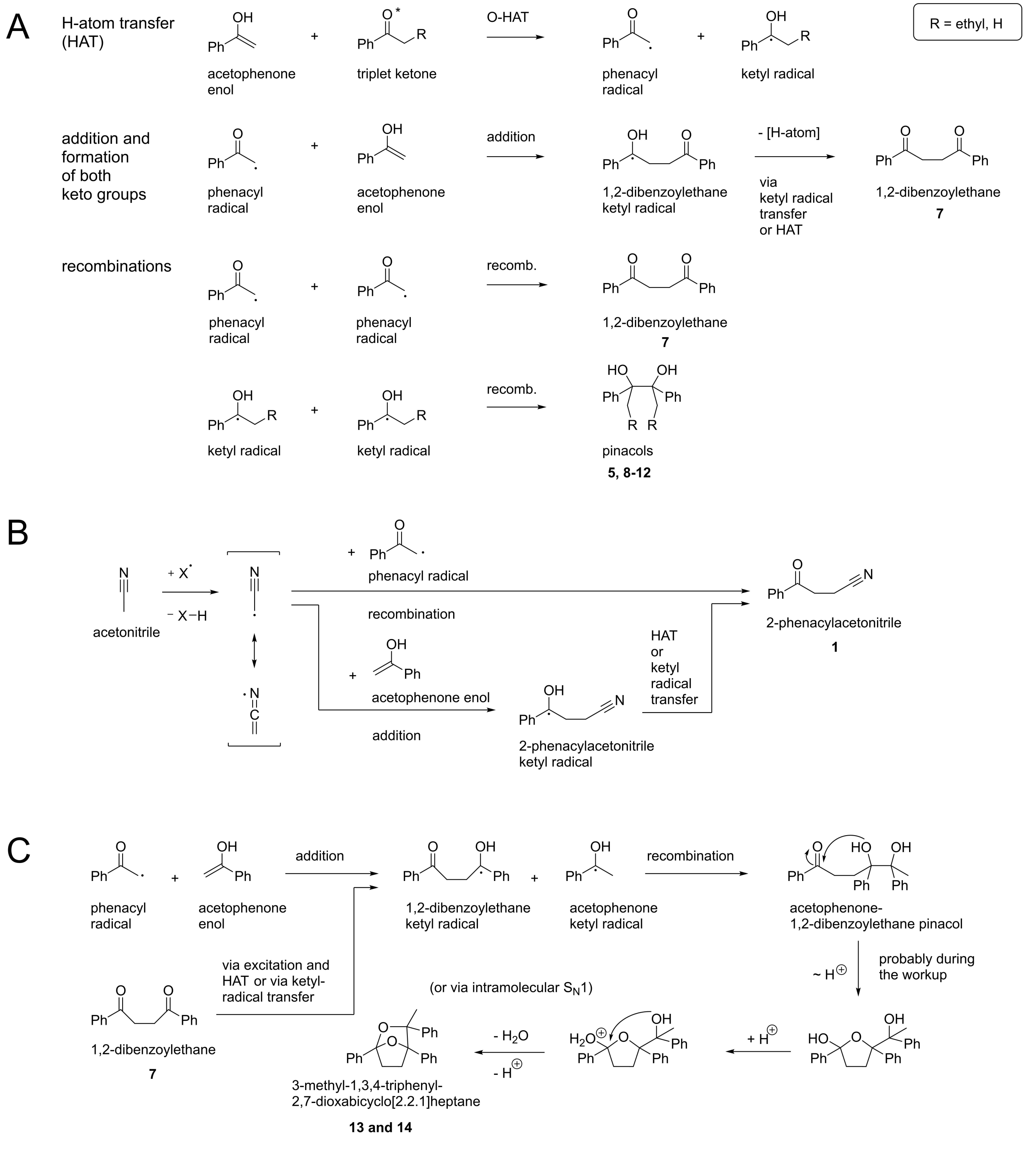
Experimental Section

(See Supporting Information for details):

The reaction volumes were irradiated using UVA-LED or UVA, UVB or UVC light bulb sources in borosilicate or quartz glass (cf. also[32]). Reaction volumes on a preparative scale (290 mL or similar) in acetonitrile (quality "for chromatography") were sealed (pressure compensation by gas syringes, also to capture the gas phase) and irradiated from the outside (after flushing with argon), under stirring and ventilator cooling. Reaction volumes on a micro scale (1 mL or 3 mL) were irradiated comparably and partly under isothermal conditions.

Product isolation and characterization: After removal of the solvent, acetophenone (**2**) was allowed to evaporate and 1,2-dibenzoylethane (**7**) was partially separated by crystallization. The residue was fractionated by preparative RP-chromatography. Ethyl-substituted 1,2-dibenzoylethanes and isotopically labeled acetophenones were thermally synthesized and isolated using preparative RP-chromatography or flash-chromatography. The obtained products were characterized by a selection of the following methods resp. compared with literature data: NMR (^{1}H, ^{13}C, DEPT, COSY, HSQC, HMBC, NOESY), MS (APCI, ESI, EI) and IR (ATR). 1,2-dibenzoylethane (**7**) was additionally identified by a crystal structure. 3-methyl-1,3,4-triphenyl-2,7-dioxabicyclo[2.2.1]heptane (**13**, **14**) has been identified by spectra comparison (^{1}H- and COSY-NMR, MS-APCI) with a product prepared in larger quantities (via another reaction).

Component mixtures were investigated using analytical HPLC, mostly by using a MeOH-H_2O-gradient method.



Scheme 1. Proposed formation mechanisms of the obtained intermolecular photoproducts (explanations in the text).

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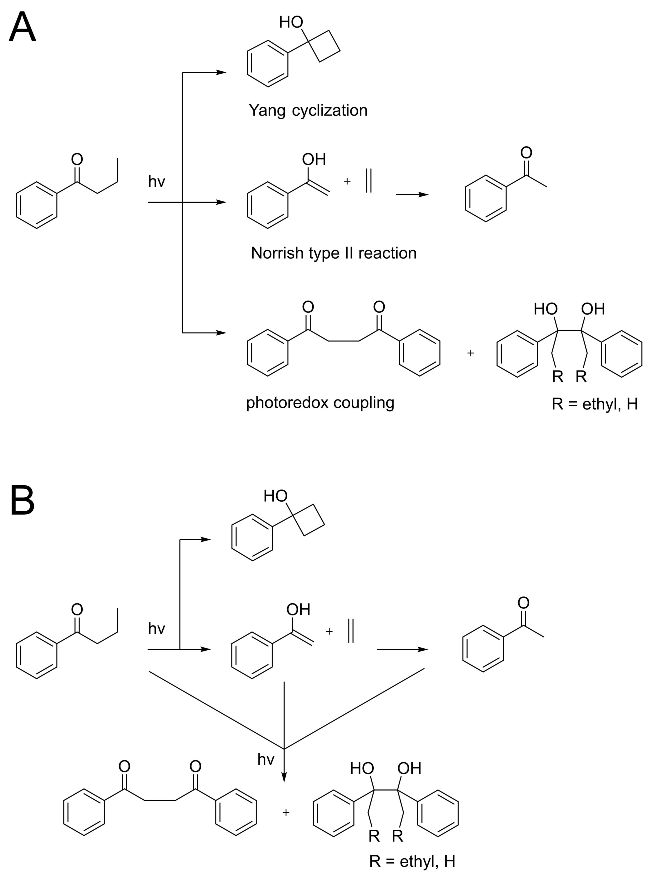
Conflict of Interest

The authors declare no conflict of interest.



Scheme 2. Photochemistry of butyrophenone (**6**), completed by the intermolecular products. A: The reaction products are shown regardless of the formation pathways. B: Condensed version of their formation pathways according to A in Scheme 1. (1-Tetralone (**3**), 2-phenacylacetonitrile (**1**) and possible 1,2-dibenzoylethane pinacols are not shown as they are only produced to a much lesser extent.)

Keywords: H-Atom transfer · Enols · Ketones · Photochemistry · Reaction mechanism

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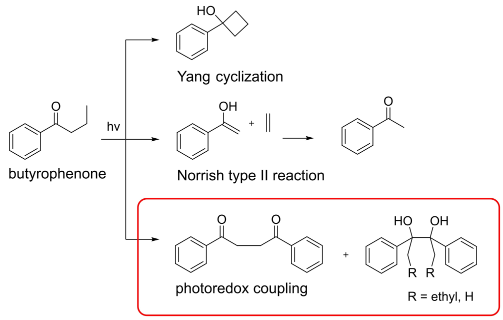

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1 – 6

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