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Visible-Light-Driven Reductive (Cyclo)Dimerization of Chalcones over Heterogeneous Carbon Nitride Photocatalyst

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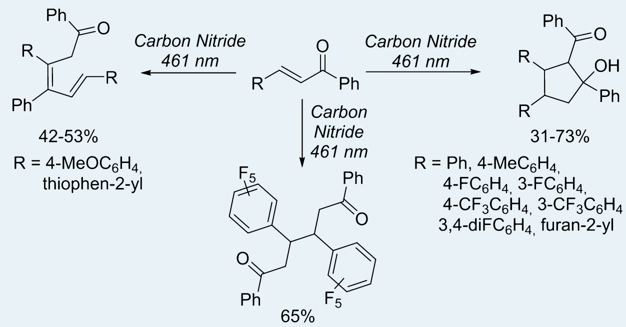
Supporting Information

ABSTRACT: Single-electron reduction of chalcones to the respective radical anions is a useful technique to activate these molecules toward subsequent transformations. Herein, a metal-free photocatalytic version of chalcones reduction in the presence of triethanolamine as a convenient electron donor and using heterogeneous carbon nitride visible-light photocatalyst is presented. The reaction proceeds via a long-lived radical species of the heterogeneous organic semiconductor. The scope of the reaction was studied, and regioselectivity of the chalcone radicals coupling was investigated. (1) Ten chalcones gave selectively polysubstituted cyclopentanoles with 31−73% isolated yield; (2) Two chalcones bearing electron-donor groups, 4-$MeOC_6H_4$ and 2-thienyl, gave selectively the β-ketodienes in 42% and 53% isolated yield, respectively; (3) Pentafluorophenyl substituted chalcone gave exclusively the product of the radicals coupling followed by hydrogen transfer from triethanolamine−hexane-1,6-dione in 65% isolated yield. Reductive cross cyclodimerization of a mixture of two different chalcones proceeded regioselectively with the formation of one product out of four possible. The mechanism was investigated by cyclic voltammetry and linear sweep voltammetry and suggests that the reaction proceeds through proton-coupled electron transfer.



KEYWORDS: *organic photoredox catalysis, carbon nitride, chalcone, cyclopetanole, proton coupled electron transfer*

The rising demands to the efficacy of chemical processes prompt chemists to develop more performing and durable catalysts in order to enable challenging organic transformations with high selectivity, less energy input, and avoiding use of auxiliary reagents. A heterogeneous carbon nitride photocatalyst was originally developed for water splitting.[1] However, in the past few years a new branch—carbon-nitride-based organic photoredox catalysis—that comprises a number of novel reactions has emerged.[2,3] This is to be added to a number of carbon nitride materials with a stoichiometry C_3N_x and mesoporous carbon nitrides with developed surface area reported by Vinu et al.[4,5] Carbon nitride materials are applied in different areas including, for example, hydrogen production,[6] CO_2 sorption and conversion, and organocatalysis.[7−9]

Cyclopentane moiety occurs often in many biologically active commercial compounds (Scheme 1a).[10−14] Scheme 1b briefly summarizes available methods of cyclopentane core construction. Most of these methods are based on cyclization of ω-functionalized alkynes,[15−17] α,ω-enynes,[18,19] or α,ω-dienes.[20,21] These methods are considered as primary for simple cyclopentanes. However, if heavily substituted cyclopentanes are of interest, synthesis of the respective precursors (e.g., substituted α,ω-enynes) might be a challenging multistep process.

Alternatively, reductive cyclodimerization of chalcones, readily available from the corresponding aldehydes and ketones, offers a route to polysubstituted cyclopentanes just in one step.[22−27] This reaction typically requires transition metal salts taken in equimolar ratio with respect to the substrate and allows for homocoupling of chalcones only. Earlier Xia and Zhao reported that homocoupling of chalcones can be also achieved by combining homogeneous $Ru(bpy)_3(PF_6)_2$ photocatalyst in the presence of $Sm(OTf)_2$.[27]

Given our own results in developing new organic photoredox reactions, for example, synthesis of 1,3,4-oxadiazoles,[28] photocatalytic Kindler reaction and Hantzsch pyridine synthesis,[29,30] oxidative C−H thiolation of toluenes,[31] as well as reciting a number of reports from Blechert and Wang, such as trifluoromethylation of heterocycles,[17] oxidative coupling of benzylamines,[32] and selective oxidation of alcohols and hydrocarbons,[33,34] all mediated by carbon nitrides, we assume this class of materials to be effective for the reductive dimerization of chalcones. Using heterogeneous photocatalyst, we can benefit from recyclability and high stability of this material. As a result, regioselectivity and therefore cross

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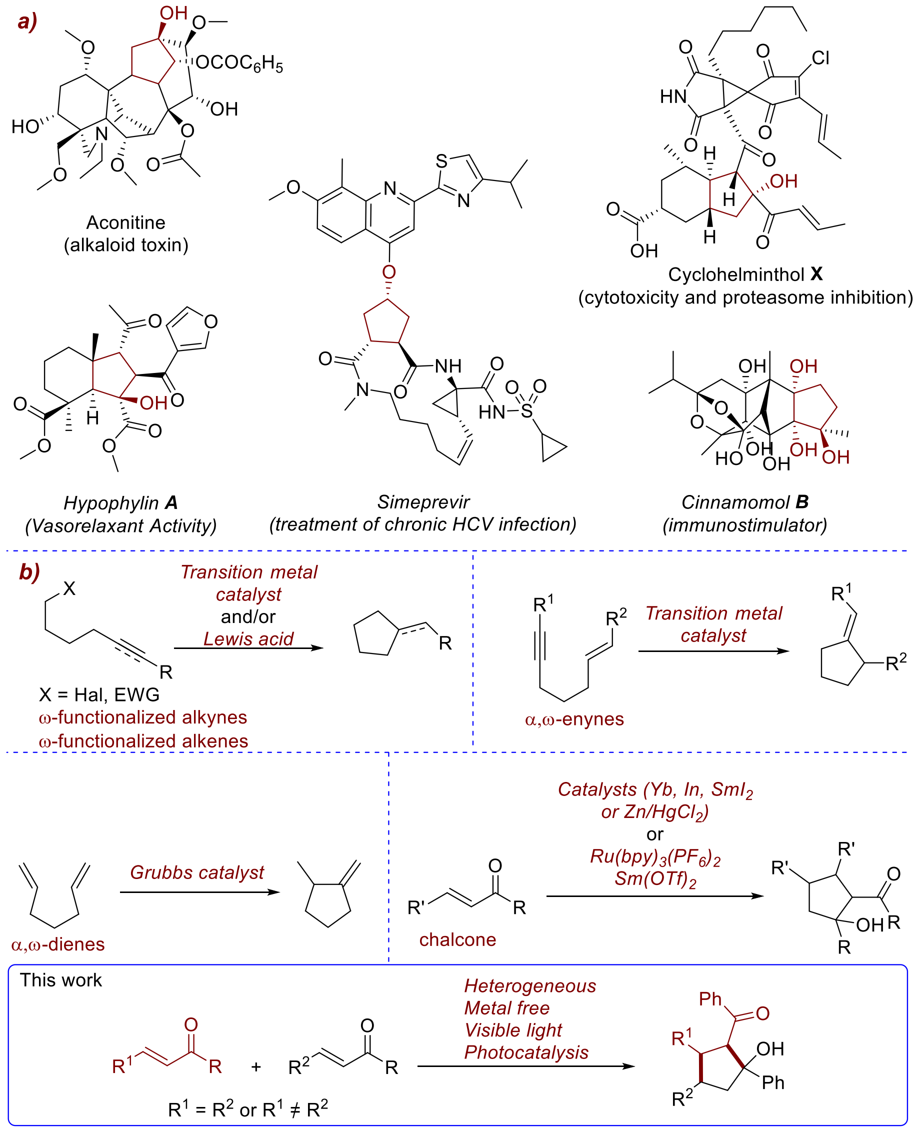
Scheme 1. Overview of Cyclopentanoles and Cyclopentanes



[a]Selected examples of biologically active cyclopentanole derivatives; [b]Known approaches to synthesis of cyclopentanes and the concept of this work.

cyclodimerization of chalcones, because of coordination of the substrate to the photocatalyst surface, can be achieved.

Among the variety of carbon nitride materials especially useful for organic photoredox applications are those bearing negatively charged nitrogen atoms, for example, poly(heptazine imides) (Figure 1) reported by Dontsova et. al,[35] or cyanamide-functionalized carbon nitrides reported by Lotsch et al.[36] The unique feature of these materials is to “trap” electrons and to give a long-lived radical anion,[31,37−39] which can be directly observed as green or deep-blue solids. They might also be beneficial for single-electron reduction of chalcones in order to generate the radical of chalcones and hence to trigger their coupling.

In this work, we present a new visible-light-driven metal-free methodology for the single-electron reduction of chalcones to the respective radicals using potassium poly(heptazine imide) (K-PHI) as a heterogeneous photocatalyst without using any coordinative additives. Cross reductive cyclodimerization is implemented by using advantage of the heterogeneous photocatalysis (Scheme 1b). Several hexa-3,5-dien-1-ones or hexane-1,6-diones are readily available via this method as well.

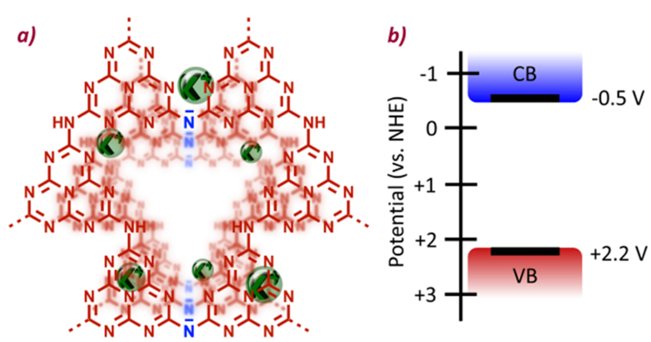


Figure 1. K-PHI chemical (a) and band (b) structure.

The photocatalyst, K-PHI, was synthesized according to the described procedure, and its characteristics are given in Figure S2.[30] Photocatalytic reductive transformation of chalcone **1a**,

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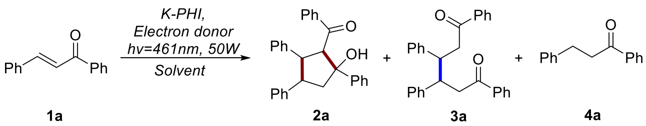
using triethanolamine (TEOA) as electron donor, was chosen as the initial reaction for study (Table 1). In the control

Table 1. Screening of the Reaction Conditions in Photocatalytic Formation of Cyclopentanole 2a[a]



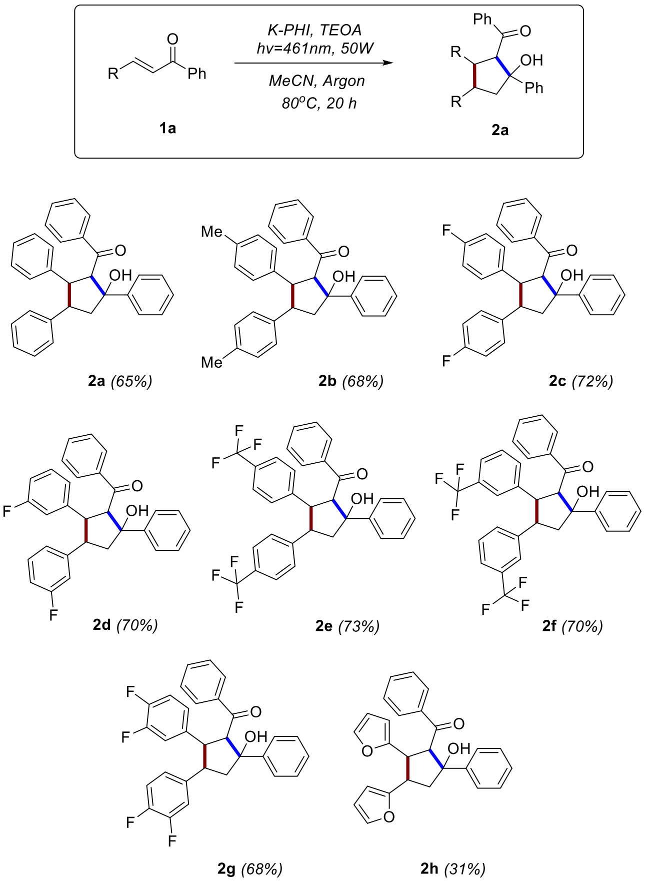
exp. no.	electron donor	conversion of **1a**, %[b]	selectivity of **2a**, %[b]
1[c]	TEOA (3 equiv)	0	-
2[d]	TEOA (3 equiv)	0	-
3	TEOA (3 equiv)	87	98
4	TEOA (6 equiv)	88	66
5	TEOA (10 equiv)	91	53
6[e]	TEOA (3 equiv)	92	56
7	TEA (3 equiv)	17	83
8	DiPEA (3 equiv)	91	43
9	Bn_2NH (3 equiv)	45	62
10	*i*-PrOH (3 equiv)	~1	0[f]
11[g]	TEOA (3 equiv)	88	91
12[h]	TEOA (3 equiv)	89	92
13[i]	TEOA (3 equiv)	85	94

[a]Reaction conditions: chalcone (50 μmol), electron donor, K-PHI (10 mg), acetonitrile (2 mL), 80 °C, 20 h, λ = 461 nm, under argon atmosphere. [b]Conversion of **1a** and selectivity for 2a were determined by GC-MS. [c]Without photocatalyst. [d]Without light irradiation. [e]25 °C, 60 h. [f]Trace amounts of **3a** were observed. [g]Second run. [h]Third run. [i]Fourth run.

reactions without the photocatalyst (entry 1) or without light irradiation (entry 2), no products were formed. Under light irradiation (λ = 461 nm, 51.7 ± 0.03 mW cm^{-2}, Blue LED) with K-PHI as the photocatalyst, three products formed: cyclopentanole **2a**, reduced dimer **3a**, and ketone **4a**, which is the product of the starting chalcone reduction. GC-MS also revealed that during the reaction, TEOA lost the H_2 molecule. The highest selectivity (98%) of the desirable cyclopentanole **2a**, with high conversion (87%) of the chalcone, was obtained after 20 h of the reaction at 80 °C using 3 equiv of TEOA in acetonitrile as a solvent (entry 3). Increasing the excess of TEOA (entries 4−5) led to slightly higher conversion (88−91%) of the chalcone, but at the same time provided significant amount of the dimer **3a**, thereby decreasing the selectivity of the cyclopentanole formation (53−66%). Lower selectivity toward **2a** (56%) was observed at room temperature (entry 6), which proves the prevalence of the thermodynamic control in the formation of the five-membered ring. Other amines as electron donors (entries 7−9) are less effective and gave lower conversions and/or lower selectivity. In case of *iso*-propanol, as the electron donor (entry 10), only traces of the dimer **3a** were formed in this reaction. The activity of the photocatalyst was almost the same even after four times of the catalyst recycling (entries 11−13), which proves good stability of K-PHI under the photocatalytic conditions.

Using the optimized reaction conditions, cyclopentanoles **2a−g** were synthesized and isolated in good yields (Scheme 2). Slightly higher yields were observed for cyclopentanoles **2c−g** substituted with fluorine atoms in the aromatic ring. The presence of fluorine reduces reduction potential of chalcones **1c−g** compared with the compounds **1a−b** and therefore facilitates reductive cyclodimerization. Chalcone **1h**, which contains electron-donor furyl moiety, gave the corresponding cyclopentanole **2h** along with a large amount of high-molecular-weight undefined compounds. From this mixture, the product **2h** was isolated with only 31% yield. Such result could be explained by the high impact of the electron-donor character of the substituent on the reaction path (see below explanation of the mechanism). In general the isolated yields are lower than the yields determined by GC-MS. It is related to the difficulty of the product separation in the presence of large amount of TEOA oxidation products using column chromatography.

Scheme 2. Scope of Cyclopentanoles 2a−h Synthesized via a Photocatalytic Reductive Cyclodimerization of Chalcones[a]



[a]Isolated yields are shown in parentheses.

We also attempted to couple chalcones bearing methyl substituent at the carbonyl group, such as (*E*)-4-phenylbut-3-en-2-one, 1-(cyclohex-1-en-1-yl)ethan-1-one and cyclohex-2-en-1-one as well as methyl cinnamate. However, none of these enones gave cyclopentanoles. The explanation originates from the significantly more negative reduction potentials of the aliphatic chalcones (E_{red} = −1.7 to −2.2 V vs SCE)[40] and methyl cinnamate (E_{red} = −1.9 V vs SCE),[41] due to worse resonance stabilization of the intermediary radicals, compared with aromatic ones (chalcone **1a**, E_{red} = −1.4 V vs SCE).[42] On the other hand, coordination of the substrate to the surface of the photocatalyst is essential for the electron transfer. This interaction is more efficient in case of planar aromatic chalcones rather than aliphatic ones. All in all, the method works well for (het)aryl-substituted chalcones and even better for arylsubstituted chalcones with electron-withdrawing groups due to efficient stabilization of the intermediates.

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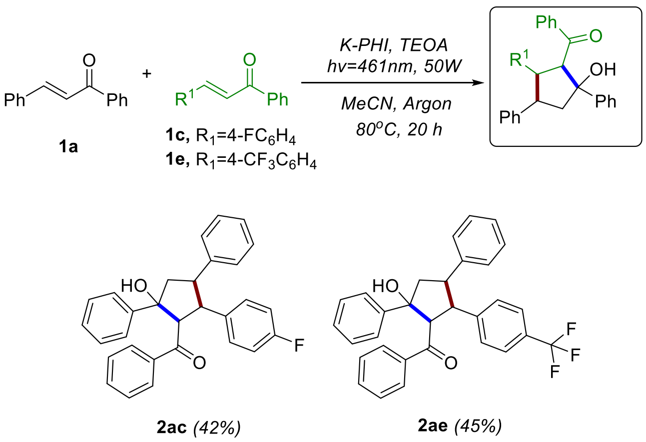
In order to check if cross cyclodimerization can be achieved using K-PHI, we mixed chalcones **1a** and **1c** in one pot in equimolar ratio (Scheme 3). In this case, we were also pleased

Scheme 3. Cross Reductive Coupling of Chalcones[a]

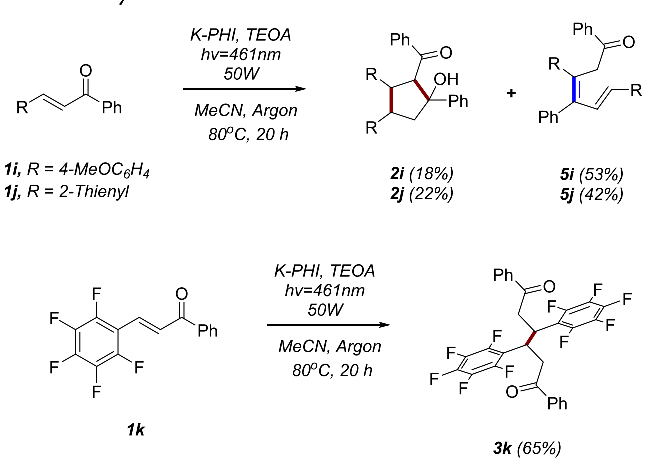


[a]Isolated yields are shown in parentheses.

to observe formation of unsymmetrically substituted cyclopentanole **2ac**. After purification, it was isolated with 42% yield. Similarly chalcones **1a** and **1e** gave the product **2ae** with 45% yield. These results were obtained under nonoptimized conditions. Notably, the yields of chalcones **2ac** and **2ae** are higher than their content in the theoretical mixture due to statistical distribution of the possible products (25%). In addition, in HR-MS of the reaction mixture we have not observed other cyclopentanoles derived from homocoupling of two chalcones (i.e., compounds **2a**, **2c**). All this implies the existence of regio-control in the photocatalytic reaction.

Behavior of the chalcones **1i–k** under the conditions of photocatalysis (Scheme 4) drastically differs from other described above. Chalcones **1i,j** gave a mixture of cyclopentanoles **2i,j** and dienone **5i,j** respectively, with the predominance of the dienone product (with ratio **5i**:**2i** of 3:1 and **5j**:**2j** of 2:1). Important to note, dienones **5** were not reported earlier. Synthesis of these compounds using a toolbox of traditional organic chemistry presumably would require

Scheme 4. Transformation of Chalcones 1i–k under Photocatalytic Conditions[a]



[a]Isolated yields are shown in parentheses.

several steps, while in the present method they are prepared in one step from the corresponding chalcones, though in moderate yield.

These results may be explained by the two competitive reaction pathways, involving two different reactive centers in the starting chalcone: double carbon−carbon bond and carbonyl group (see below explanation of the mechanism). Formation of the dimer **3k** as the single product for chalcone with pentafluorophenyl substituent evidently comes from higher thermodynamic stability of the linear structure. It keeps bulky pentafluorophenyl substituents far from each other due to a free rotation around a single carbon−carbon bond. Therefore, steric hindrance is minimal, compared with the restricted cyclic geometry.

The kinetic data of the chalcone **1a** conversion over time, as shown in Figure 2a, suggest that there is an induction period of

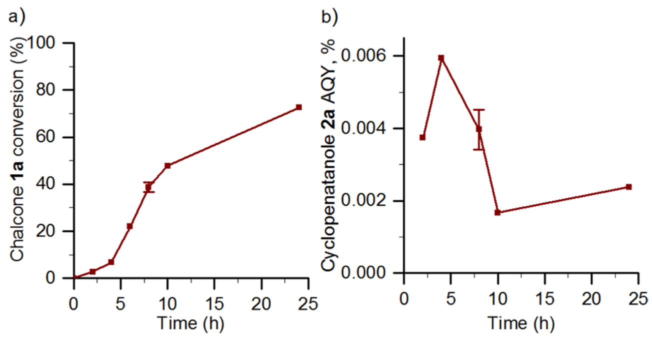


Figure 2. (a) Time-dependent conversion of the chalcone **1a**. (b) Time-dependent AQY of the chalcone **2a**.

ca. 4 h during in which the reaction proceeds slower. The induction period is explained by the accumulation of the long-lived K-PHI radical anion, that is, charging of K-PHI (see mechanism discussion below). The apparent quantum yield (AQY) of the cyclopentanole **2a** is 0.005%, while the relative error of AQY determination is 14%.

In order to get insight into the redox properties of the species employed in the photocatalytic reaction, we performed a series of electrochemical measurements in acetonitrile using $(n\text{-Bu})_4N^+ClO_4^-$ (0.1M) as a supporting electrolyte. Figure 3a shows the CV curves of different components of the reaction mixture. MeCN is stable on the reduction side at least up to −2.2 V vs Ag/AgNO$_3$ (0.01M) and on the oxidation side at least up to +1.8 V. As expected for amines, TEOA has the onset of oxidation +0.34 V, while it is stable against reduction up to −1.9 V. Oxidation of **1a** starts at +1.6 V, while reduction at −1.7 V. When excess of TEOA was added to **1a**, the resultant mixture still had the onset of oxidation at +0.34 V, suggesting that in the presence of **1a** in the photocatalytic experiment, TEOA is still more likely to act as electron donor. However, the reduction potential of **1a** was shifted to −1.4 V. It might be explained by proton-coupled electron transfer (PCET), assuming that intermediary $[TEOA]^{\bullet+}$ is acidic enough to serve as a proton donor. In agreement, the CV curve obtained for **1a** in the presence of HCl (4 mM), which is an even better proton donor compared with $[TEOA]^{\bullet+}$. In this case, the onset of the reduction current was observed at −0.5 V.

Figure 3b represents CV of chalcones **1a,c,e**. Thus, *p*-F substituted chalcone **1c** has the reduction potential of −1.7 V. *p*-CF$_3$ substituted chalcone **1e** has more positive potential of

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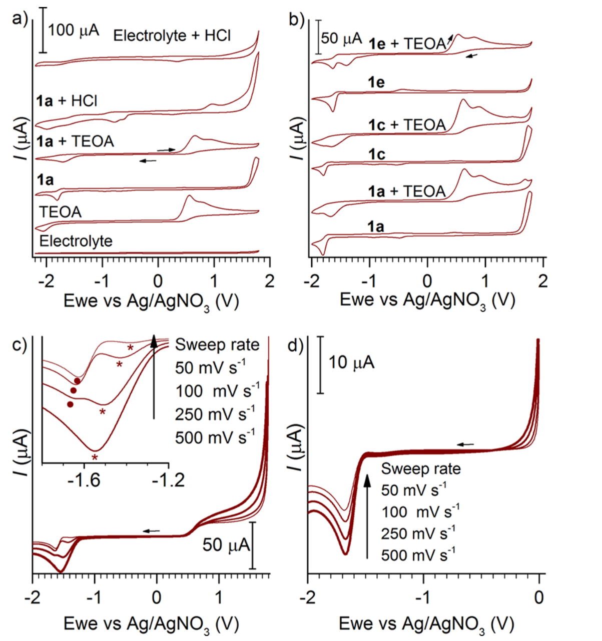

Figure 3. Electrochemical study. Three-electrode cell was used: glassy carbon (WE), $Ag/AgNO_3$ in acetonitrile (RE), Pt wire (CE). (a) Cyclic voltammetry (CV) curves were acquired at a scan rate 250 mV s^{-1}. Direction of scanning is shown with arrows and is the same for all CVs. Second cycle is shown. (b) CVs of a mixture of the chalcones (2.2 mM) and TEOA (7.6 mM) measured at 250 mV s^{-1}. (c) Linear sweep voltammetry (LSV) of **1e** (2.2 mM) measured at different sweep rates. Inset shows the magnified region of the LSV. (d) LSV of **1e** (2.2 mM) and TEOA (7.6 mM) measured at different sweep rates.

−1.5 V. These findings agree with the Hammett constants of the above-mentioned groups − $\sigma_p(F) = 0.06$ and $\sigma_p(CF_3) = 0.54$.[43] In the presence of TEOA (7.6 mM) the onset of the reduction current, for all chalcones, presumably due to PCET, was observed at lower overpotential, in the range from −1.1 V to −0.9 V.

Figure 3c shows LSV curves recorded for chalcone **1e** at different sweep rates. At high sweep rate, ≥ 500 mV s^{-1}, only the reduction peak at −1.55 V (marked with "star") is observed. When the sweep rate was decreased to 250 mV s^{-1}, an additional peak (marked with "filled circles") at −1.65 V appeared. By decreasing the sweep rate, the intensity of the former peak decreased while the later became more pronounced. The peak at the potential −1.65 V became dominant at the sweep rate of 50 mV s^{-1}. The onset of the reduction current in this case is −1.53 V, which is close to the one observed in the absence of TEOA (Figure 3b). Finally, when only the reduction region from 0 V to −2.2 V was scanned, regardless of the sweep rate, **1e** had onset of reduction at −1.5 V (Figure 3d).

These results imply that PCET assisted by proton transfer from $[TEOA]^{\bullet+}$ may be observed in the electrochemical cell at high sweep rate. On the other hand, in the photoreactor, the photocatalyst provides both reduction and oxidation sites at the same time. Therefore, PCET may be envisioned as a major process in the photocatalytic reductive cyclodimerization of the chalcones.

Taking into account the results of CV and LSV, the formation of the reductive dimerization products−cyclopentanoles **2**, dienones **5** and reduced dimers **3** could be explained by the following mechanism (Scheme 5). Excited under the visible light K-PHI* photocatalyst promptly removes an electron from TEOA (electron donor) and converts into long-lived radical-anion K-PHI$^{\bullet-}$ that is observed as deep-green solid (inset on the Scheme 5), reported earlier.[31,37,38] The chalcone **1** is reduced to the radical **7** via PCET. In this process, K-PHI$^{\bullet-}$ donates an electron, while $[TEOA]^{\bullet+}$ serves as a proton donor.

On the basis of the experimental data (Table 1, Scheme 2,4), the tentative intermediate **7** can undergo four reaction paths. First, it can be reduced via PCET by the intermediate **6** to the ketone **4** (Path A).

On an important note, we could not identify the exact structure of the final product of TEOA oxidation. However, from the GC-MS of the reaction mixture we deduced that TEOA lost H_2 molecule. On the Scheme 5 the product of TEOA oxidation is denoted as [TEOA-H_2]. A discussion about plausible structure of [TEOA-H_2] is given in the Supporting Information.

Second, intermediate **7** reacts with a molecule of starting chalcone **1**. Addition to the C-3 carbon atom of the chalcone **1** followed by SET from **6** leads to the intermediate **9**. This intermediate can be converted into the reduced dimer **3** (Path B). Pentafluorophenyl substituents in **1k** apparently stabilize the intermediate **9** and make cyclization to the respective cyclopentanole unfavorable. A small amount of the reduced dimer **3a** was also observed when chalcone **1a** was taken as a substrate. In agreement with this reaction path, a large excess of TEOA (Table 1, entry 4,5) facilitates formation of the reduced dimer **3** and as a result decreases the yield of the cyclopentanole **2a**.

Third, intramolecular aldol condensation of **9** gives cyclopentanole **2** (Path C). Path C is preferential for most of the chalcones.

Finally, addition of the radical **7** to the C-1 carbon atom of the chalcone **1** followed by SET leads to the intermediate **10**, that is converted to the compound **11** upon proton transfer from **8** (Path D). In case of the chalcones **1i,j**, electron-donor substituents in the aromatic ring increase the electron density on the double bond. An electron-rich substituent alters the reactivity of the radical-anion **7** and directs the attack at the carbonyl group (electrophilic center). Thermally induced elimination of H_2O molecule produces dienone **5**. Path D is preferential for the chalcones **2i,j**, bearing electron-rich groups.

The mechanism of cyclopentanol formation (Path C) is additionally supported by the results of the cyclopentanoles **2ac** and **2ae** synthesis from a mixture of chalcone **1a** and chalcone **1c** or **1e**. Because of the presence of electron-withdrawing *p*-F or *p*-CF_3 substituents, reduction of chalcones **1c** and **1e** is more favorable compared with the chalcone **1a**. The radicals, **7c** and **7e**, are then added to the double bond of the chalcone **1a**, but not vice versa. Therefore, the electronic structure of the chalcones in this reaction dictates the regioselectivity of the products formation.

Having the scheme of the mechanism, relatively low AQY may be rationalized by the multistep nature of cyclopentanole synthesis. Thus, formation of the key radical intermediate **7** requires stoichiometric amount of photons that first must be absorbed by the photocatalyst. Second, recombination of the photogenerated holes and electrons would apparently decrease the AQY of the whole process. Furthermore, at least three competing processes, for the intermediate **7a**, exist along with the primary reaction of the cyclopentanole **2a** formation.

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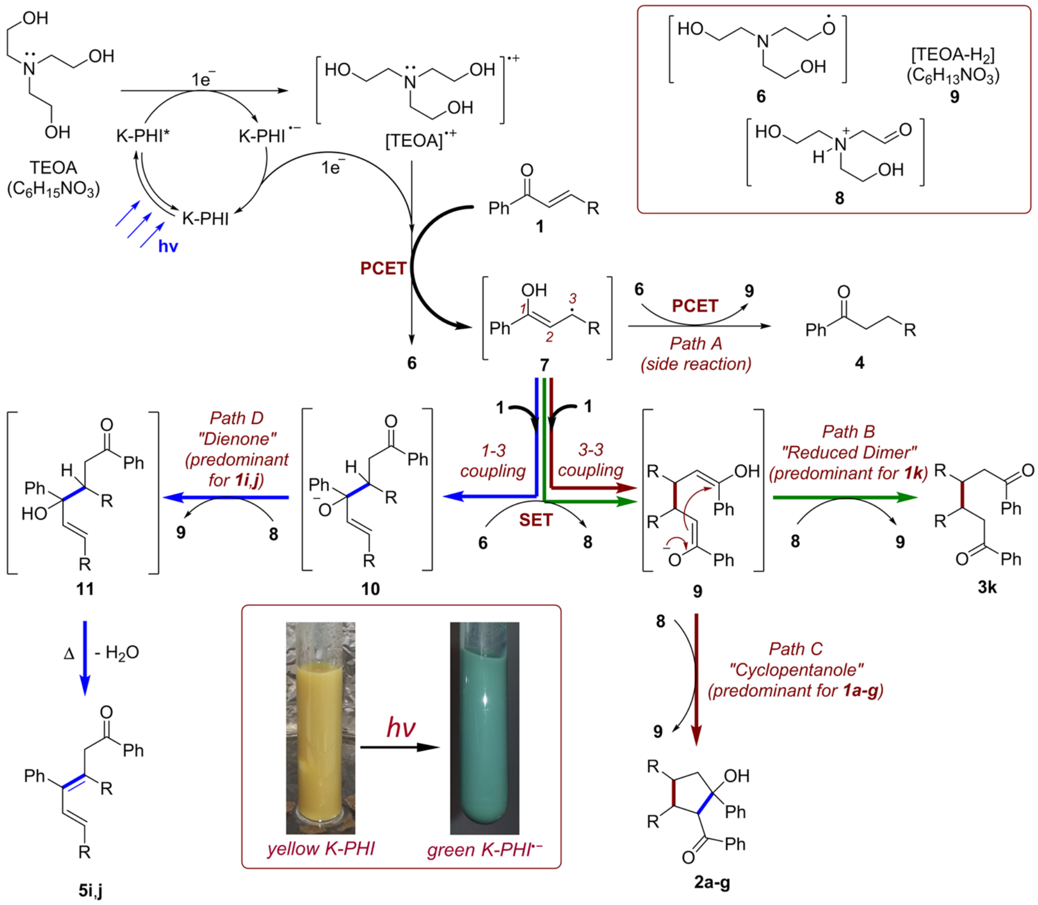
Scheme 5. Proposed Mechanism of the Photocatalytic Transformation of Chalcones[a]



[a]Appearance of the reaction mixture before irradiation (yellow suspension) and after irradiation (green suspension) is shown in inset at the bottom of the scheme. Possible structures of the intermediates and the product of TEOA oxidation are shown in top right rectangle.

Finally, dead ends, that is, quenching of the radical intermediates (e.g., 7) cannot be excluded.

In summary, the photocatalytic methodology of reductive dimerization of chalcones under visible light irradiation using a noble-metal-free, heterogeneous photocatalyst, potassium poly(heptazine imide), was developed. Cyclopentanoles were obtained in good yields as major products for the majority of substrates. Chalcones bearing electron-donor aromatic and heteroaromatic groups converted preferably to dienones—alternative products of the reductive dimerization. Presence of the bulky pentafluorophenyl substituent in the starting chalcone leads to the formation of the symmetric linear dimer as the single product, which is less sterically restrained, compared with the ring structure. The discovered photocatalytic transformation reveals a new simple approach for the dimerization of the double bond and is promising as a convenient tool for a modern preparative organic synthesis. The studied here reaction confirms the existence of regioselectivity in heterogeneous photocatalysis versus homogeneous version.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b04182.

Experimental procedures, characterization data for photocatalyst and all synthesized chalcones and cyclopentanoles (PDF)

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Notes

The authors declare no competing financial interest.

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