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Clean Photochemical Synthesis Mediated by Radical–Radical Reactions: Radical Buffer or the Persistent Free Radical Effect?

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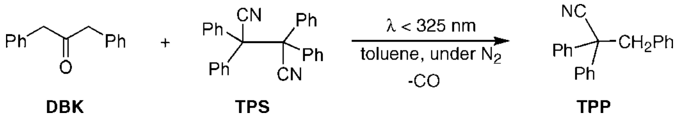
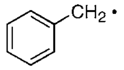
ABSTRACT



A new synthetic methodology is reported that takes advantage of the persistent free radical effect (PFRE), where clean products can be obtained in good yields from radical cross-combination reactions, despite their reputation for being of little synthetic value and for resulting in complex mixtures; these problems can be avoided when the PFRE is used as a synthetic tool.

Primary, secondary, and even tertiary benzylic radicals are considered to be *stabilized but transient* radicals: while these C−H bonds are much weaker than in a corresponding alkane, benzylic radicals usually undergo self-termination reactions at close to the diffusion-controlled limit.[1] A classic example is the benzyl radical **1**, which follows a second-order decay with a half-life of a few microseconds under conditions of laser excitation.[2] However, the diphenylacetonitrile radical **2** is at least 1000 times longer lived. Its remarkable persistence (and lack of reactivity toward O_2) is attributed to other factors, notably the presence of an α-cyano group.[3] Spin density calculations show that for **1**, the unpaired electron exhibits mild delocalization through the aromatic moiety. Interestingly, **2** shows ∼22% contribution of the unpaired electron on the nitrogen atom.

Dimers of persistent carbon-centered radicals have recently been prepared from their corresponding monomers; their UV−vis spectra revealed that, in toluene solution, they are in thermal equilibrium with the radical species.[4] The bond dissociation energy for the central C−C bond for the dimer of **2** was measured as 26.2 ± 0.5 kcal/mol. Thus, even at room temperature, a small fraction of the radical **2** will be present.



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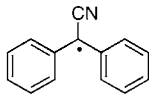
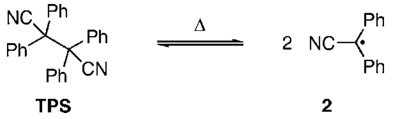


2

The dimer formed from **2** (1, 1, 2, 2-tetraphenyl succinonitrile, TPS) is stable at room temperature; we have used the term dynamic stability to describe its behavior before, since TPS is in fact in equilibrium with the corresponding radical, as shown in Scheme 1.

TPS owes its apparent stability to the fact that the radicals are unreactive toward O_2 and virtually unreactive toward

Scheme 1. Thermal Dissociation of TPS



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hydrogen abstraction from solvents such as toluene. Thus, the usual fate of the radicals is to recombine to reform TPS. If a new species, capable of reacting with the radicals, is introduced in the system, one can anticipate reactions with radical **2** leading to new products. We considered exploiting this characteristic buffer-like behavior via a kinetic phenomenon known as the Fischer−Ingold persistent free radical effect (PFRE).

The PFRE is normally examined in systems where two different radicals are generated simultaneously, frequently from a single precursor.[5] As shown in Scheme 2, the fact that the transient radicals ($T^\bullet$) undergo self-reaction, while the persistent radicals ($P^\bullet$) do not, leads to an accumulation of the latter. If the cross-reaction to form T−P is reasonably fast, it soon takes over as the dominant form of decay for $T^\bullet$. The system is "self-adjusting" in that the accumulation of $P^\bullet$ continues until the kinetic condition favoring cross-reaction is established. After this point, $T^\bullet$ and $P^\bullet$ are consumed in stoichiometric amounts.

Scheme 2. Operating Mechanism for the PFRE[a]

$$\text{Source} \longrightarrow T\bullet + P\bullet + \text{non-radical products}$$

$$T\bullet + T\bullet \xrightarrow{k_{TT}} \text{T-T}$$

$$T\bullet + P\bullet \xrightarrow{k_{TP}} \text{T-P}$$

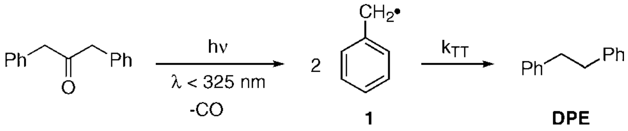
$$P\bullet + P\bullet \xrightarrow[\text{slow}]{k_{PP}} \text{P-P}$$

[a] P = persistent radical, T = Transient radical. Usually $k_{PP} = 0$.

Inspired by the PFRE, a novel synthetic method was devised: produce persistent radicals thermally from their corresponding dimers, while generating transient radicals in situ photochemically. The persistent radical−dimer equilibrium behaves as an effective "radical buffer", with the former trapping the transient radicals to form the cross-reaction product, while the dimer, through the equilibrium of Scheme 1, keeps the "supply" of radicals available. While the radicals used here are not strictly "persistent", since they react to form the dimer, their combination is effectively "incomplete" as a result of the radical ↔ dimer equilibrium. As a consequence, TPS will appear to have lost its stability, when in reality it is not directly involved in any new reactions.

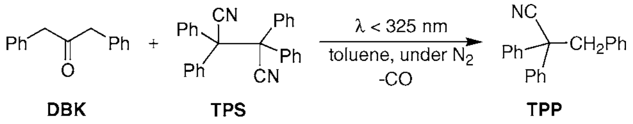
The photochemistry of dibenzyl ketone (DBK) is well-known:[6,7] steady-state photolysis in toluene using UVB lamps leads to 1, 2-diphenylethane (DPE) as the only significant product, formed by combination of two benzyl radicals according to Scheme 3.

Scheme 3. Photochemistry of DBK



Therefore, by combining the photoreaction of Scheme 3 and the thermal equilibrium of Scheme 1, we obtain a simple, yet effective, one-pot synthesis of 2,2,3-triphenylpropionitrile, TPP, as illustrated in Scheme 4. Although other examples of synthesis employing the PFRE are described in the literature,[8−16] we believe this method to be the first to involve C−C bond formation through independent control of persistent and transient radicals.

Scheme 4. Synthesis of 2,2,3-Triphenylproprionitrile.



Lamp irradiation of a toluene solution (27 °C) containing 3.0 mM TPS and 1.2 mM DBK led to TPP as the main product, along with a considerable amount of DPE (formation of the cross-product was optimal using an excess of TPS starting material). When the steady-state irradiation was carried out at ~50 °C, the amount of DPE was significantly reduced, consistent with the more efficient trapping of **1** by **2** as the steady-state concentration of the latter increases when the equilibrium of Scheme 1 is displaced at higher temperatures. After 40 min of UVB irradiation, 75% of the DBK was converted to TPP, with the remainder being DPE, formed initially in the reaction (Figure 1a).

Subsequently, a large-scale photolysis was carried out using 300 mg of DBK and 500 mg of TPS in 250 mL of

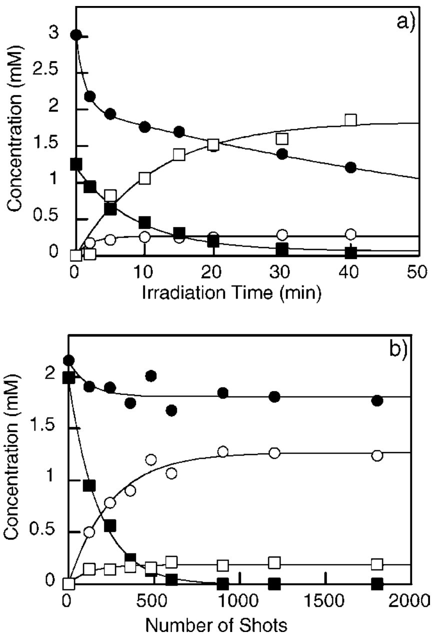


Figure 1. (a) Lamp photolysis of 3.0 mM TPS and 1.2 mM DBK; (b) pulsed laser photolysis of 2.0 mM TPS and 2.0 mM DBK. Both irradiations performed at room temperature in deareated toluene and followed by GC−MS: TPS (●), DBK (■), DPE (○), TPP (□).

deaerated toluene in a 300 mL quartz Erlenmeyer flask. Following 20 h of UVB irradiation, 0.36 g of TPP was isolated, corresponding to a conversion of 53%.

Under 308 nm laser excitation, the reaction products were dominated by DPE (~65% conversion), with only small amounts of TPP formed (Figure 1b). This suggests conditions favorable to recombination, despite the presence of the equilibrium concentration of **2**.

Laser flash photolysis (LFP) experiments of 2.7 mM DBK and 3.2 mM TPS in benzene reveal the characteristic absorption of benzyl radicals at 317 nm following 308 nm laser excitation[2] (Figure 2a). At 25 °C, the decay of **1** follows clean second-order kinetics, indicating that recombination to give DPE is the only important reaction path, consistent with the product studies described above. At this temperature, the decay of **1** is virtually insensitive to the presence of TPS (Figure 2b). Only after ~90% of the radicals have decayed the second-order fit of the data [(signal)$^{-1}$ vs time] (see inset in Figure 2b) shows some deviations from linearity, suggesting minor involvement of another mode of decay, presumably the cross combination of Scheme 4 leading to TPP.

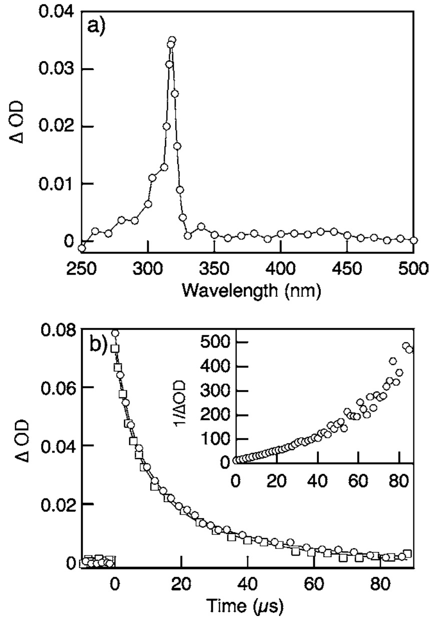


Figure 2. (a) Transient absorption spectrum of 2.7 mM DBK and 3.2 mM TPS in toluene, 0.64 μs after 308 nm laser excitation; (b) 2.7 mM DBK with (○) and without (□) the presence of 3.2 mM TPS, traces taken at 320 nm after 308 nm laser excitation at 25 °C, fitted with second-order expressions. Inset: DBK and TPS in toluene, (signal)$^{-1}$ vs time.

In contrast with the 25 °C results, at higher temperatures the difference between the decay traces in the presence and absence of TPS is clear, as shown in Figure 3. The inset graph shows that this is not an artifact of DBK itself; thus, the effect of TPS is to accelerate the decay rate for **2**.

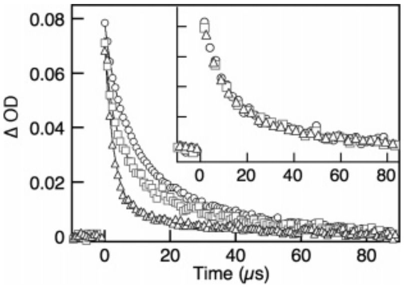


Figure 3. 2.7 mM DBK and 3.2 mM TPS in toluene after 308 nm laser excitation, monitored at 320 nm and fitted with second-order or first + second-order expressions at ~25 °C (○), ~55 °C (□), and ~85 °C (△). Inset: 2.7 mM DBK, fitted with second-order kinetics at ~25 °C (○), ~55 °C (□), and ~75 °C (△).

It is interesting to compare the results from laser and lamp irradiation. Pulsed laser irradiation tends to favor the formation of T−T (DPE in our example). This reflects the thermal and light intensity dependence of the supply of the two radicals. In general, we expect $k_{TT} \geq k_{TP}$. Therefore, cross-reaction can only dominate if the conditions of eq 1 are fulfilled.

$$k_{TP}[T^{\bullet}][P^{\bullet}] \gg k_{TT}[T^{\bullet}]^2;\ \text{i.e., \&}\ k_{TP}[P^{\bullet}] \gg k_{TT}[T^{\bullet}] \qquad (1)$$

Since radical concentrations generated by pulsed lasers can easily be 4 orders of magnitude higher than those achieved under lamp illumination, the latter provides an easier way to meet this criterion.

On the other hand, meeting the criterion of eq 1 under conditions of laser excitation should be easier at higher temperatures, since the concentration of $P^{\bullet}$ will follow a van't Hoff dependence with temperature, controlled by the bond dissociation energy for the dimer. The traces of Figure 3 confirm these ideas; consistent with this, the yield of cross-combination products under conditions of laser excitation improves at high temperature. In light of these findings, the PFRE mechanism in Scheme 4 can be modified as shown in Scheme 5, in which the persistent radical is introduced from the corresponding dimer.

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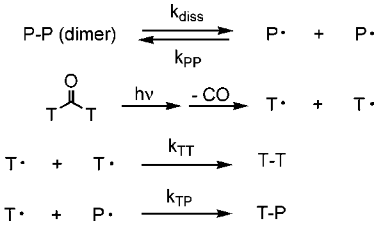
Scheme 5. Mechanism of Formation of Cross-Product, T−P



In typical examples of the PFRE, k_{PP} is near zero and the radical $P^•$ is truly "persistent"; however, this is not a requirement, as long as $k_{PP} \ll k_{TT}$. The example in this paper is somewhat different from the case in Scheme 2 in that the two radicals are not formed from a single precursor and are not produced in a stoichiometric ratio. We previously described the mechanism of Scheme 2 as "self-adjusting"; in fact, the mechanism of Scheme 5 also has this characteristic, except that the origin of the concentration adjustment is different. In Scheme 5, the concentration of persistent radical is supplied by the dissociation equilibrium for the dimer P−P. Thus, if $P^•$ is consumed by reaction with $T^•$, the equilibrium will maintain the persistent radical concentration, effectively acting as a radical buffer. In contrast with Scheme 2, the mechanism of Scheme 5 does not allow the concentration of $P^•$ to grow to any arbitrary value, but rather it is capped by the equilibrium constant. In effect, P−P is a "dormant" source of radical $P^•$; however, it is possible to adjust the concentration by changing the temperature. Interestingly, the combination of a thermal and a photochemical source for the two radicals allows virtually independent control of the supply of the two radicals, since photochemical reactions tend to show low temperature dependence, but their rate can be adjusted by changing the light intensity.

We anticipate that similar syntheses could be performed using only thermal sources for both $T^•$ and $P^•$, although it is clear that in this case one would lose the independent control of the two sources that is achieved by using a combination of thermal and photochemical sources.

To help us rationalize the results obtained, we expanded our earlier calculation of spin distribution in radicals **1** and **2**. The spin density distribution on radical **2** shows that about 50% of the unpaired electron is located on the benzylic carbon atom, and a 23% contribution of this density is developed on the nitrogen atom of the cyano group. This resonance delocalization increases the C−C(N) double bond character, reducing the bond length from 1.458 Å for the precursor of **2** to 1.418 Å for radical **2**. The combination of this delocalization with other favorable stereoelectronic effects leads to a *stabilized and persistent* benzylic radical.

Charge distributions computed using the ChelpG method assigns to the carbon radical center in **2** a value that is noticeably more positive (−0.225) in comparison to the value assigned to **1** (−0.451). Thus, with respect to each other, the diphenylacetonitrile radical displays greater electrophilic character and is activated toward nucleophilic attack from the benzylic radical **1**. Therefore, the resulting product distribution can be interpreted in terms of charge control: the significant difference between the charges favors cross-reaction between the two radicals.

Free-radical reactions, and in particular those involving radical coupling, have gained a reputation for yielding complex mixtures of products. However, we can circumvent this issue if we require the radical intermediates to be *disciplined*; that is, rigorous control of the kinetic parameters defining the radical−radical or radical-molecule reactions.[17] We show that reactions involving radicals with different persistent character can actually result in high yield clean synthetic procedures whenever a convenient source of the more persistent radical can be identified, as with radical **2** and a variety of similarly labile radical dimers.[4] In our examples, a dimer effectively behaves as a radical buffer, maintaining an adequate concentration of radicals. Other sources may be identified that allow similar concepts to be applied to synthesis design. For example, we anticipate that this concept could be further applied to the synthesis of unsymmetric peroxides, provided the transient radical reacts with oxygen and the resulting peroxyl can couple with the persistent radical − a concept similarly explored by Minisci.[18] This synthetic approach follows the same reactivity patterns normally identified with the persistent free radical effect.

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Supporting Information Available: Materials, instruments, and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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