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A Clean and Selective Radical Homocoupling Employing Carboxylic Acids with Titania Photoredox Catalysis

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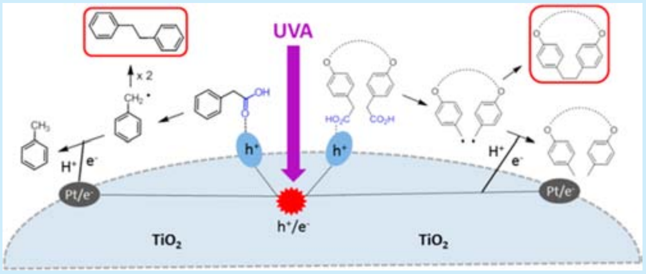
S *Supporting Information*

ABSTRACT: A titania photoredox catalysis protocol was developed for the homocoupling of *C*-centered radicals derived from carboxylic acids. Intermolecular reactions were generally efficient and selective, furnishing the desired dimers in good yields under mild neutral conditions. Selective cross-coupling with two acids proved unsuccessful. An intramolecular adaptation enabled macrocycles to be prepared, albeit in modest yields.



Homocoupling reactions are a valuable and effective tool for synthetic chemists. Indeed, dimeric moieties are present in a plethora of natural products and pharmaceutical formulations, underlining the importance of such protocols.[1] Transition metal mediated reductive homocouplings have been highly successful,[2] although the majority of these relate to the tethering of sp^2 hybridized carbon centers. Due to their highly reactive nature, radical dimerizations offer a promising means of carrying out $C(sp^3)-C(sp^3)$ assemblies.[3] Such reactions classically employed organohalides in combination with undesirable reagents such as tin hydride[4] or sodium metal.[5] The past decade has seen a movement toward greener, more sustainable synthetic protocols with particular emphasis on minimizing hazard and environmental impact while maximizing efficiency.[6] We recently developed an effective TiO_2-mediated photoredox protocol for the generation of alkyl radicals from carboxylic acids under anhydrous, anaerobic conditions.[7] CO_2 is the only significant byproduct, and the titania can be easily removed by filtration and subsequently recycled.[8] Herein, we report a fresh use of this approach to afford a range of sp^3-sp^3 linked homodimers in generally good to excellent yields.

The titania (Degussa's P25, now supplied by Evonik) was dispersed in distilled acetonitrile along with the desired carboxylic acid in an oven-dried Pyrex Schlenk tube. Photolysis was carried out using two hemispherical face-to-face arrays of UVA emitting tanning lamps, following purging of the reaction mixture with argon to exclude oxygen. The titania was removed by filtration through Celite thus enabling the product(s) to be easily purified as necessary. The P25 was readily recyclable, but due to its cheapness, this was seldom implemented.

Optimization of the reaction conditions was undertaken using phenoxyacetic acid **1a**. Overnight irradiation of **1a** furnished the desired 1,2-diphenoxyethane **2a** together with three minor components.[9] Using the unaltered P25 resulted in low overall yields with only modest selectivities being recorded. P25 doped with a 0.1% (w/w) loading of platinum proved a much more effective reagent, and using this, the optimum reaction conditions were found to be 8 equiv (with respect to **1**) of this material dispersed at 5 mg mL^{-1} in acetonitrile. Using these conditions 53% of **2a** was isolated following 21 h of photolysis. The related benzyloxyacetic acid **1b** returned **2b** in a more modest yield of 38% (Table 1; entries 1 and 2). Irradiation of phenylbutyric acid **1c** failed to return any dimer (entry 3). Surprisingly, photolysis of adamantane-1-carboxylic acid **1d** furnished 1-adamantyl methyl ketone **3** in a yield of 22% as the only product (entry 4). Presumably **3** was formed by reaction of the adamantyl radicals with the acetonitrile solvent. Benzyl radicals released from phenylacetic acid **1e** combined cleanly and selectively to furnish bibenzyl **2e** in an excellent yield (entry 5). As might be expected, allyl type radicals proved unselective, returning several isomers upon photolysis of β,γ-unsaturated acids **1f** and **1g** (entries 6 and 7). Ethynylacetic acid **1h** and cyanoacetic acid **1i** proved unreactive in our setup (entries 8 and 9).

From these results it was clear that the process was most efficient when the acid derived radicals were stabilized by an adjacent functional group, with benzyl radicals being the most efficient and selective. Thus, it was decided to examine a range of acids based on the phenylacetic acid core structure. Incorporation of substituents on the phenyl ring proved a success, with dimers bearing both electron-releasing and -withdrawing groups being formed from the respective arylacetic acids (Table 2, entries 1 and 2). The extremely electron-poor perfluorophenylacetic acid **4c** was somewhat less reactive, requiring an extended reaction time of 40 h to return dimer **5c** in a yield of 53% (entry 3). Increasing the size of the aromatic units with naphthalenylacetic acids **4d** and **4e** furnished dimers **5d** and **5e** accompanied for the first time by significant quantities of the saturated alkanes (entries 4 and 5).

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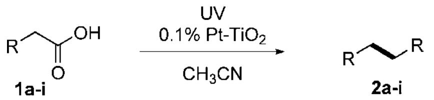
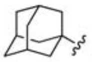
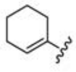
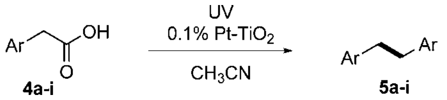
Table 1. Investigation of Homodimerization Scope



entry	R (acid)	time/ h	yield/ % (dimer)
1	PhO (**1a**)	18	53 (**2a**)
2	$PhCH_2O$ (**1b**)	18	38 (**2b**)
3	$PhCH_2CH_2$ (**1c**)	18	-
4	 (**1d**)	22	-[a]
5	Ph (**1e**)	16	87 (**2e**)
6	 (**1f**)	19	81 (**2f**)[b,c]
7	$PhCH_2CH{=}CH$ (**1g**)	19	49 (**2g**)[d]
8	C≡CH (**1h**)	18	-
9	C≡N (**1i**)	16	<5 (**2i**)[b]

[a]22% 1-adamantyl methyl ketone **3** isolated. [b]NMR yield(s). [c]Combined yield of three isomeric dimers. [d]Fraction containing five isomeric dimers isolated.

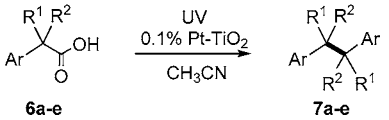
Table 2. Dimerization of Aryl- and Heteroarylacetic Acids



entry	Ar (acid)	time/h	yield/% (dimer)
1	4-$MeOC_6H_4$ (**4a**)	20	84 (**5a**)
2	4-$CF_3C_6H_4$ (**4b**)	19	74 (**5b**)
3	C_6F_5 (**4c**)	40	53 (**5c**)
4	1-naphth. (**4d**)	39	56 (**5d**)[a,b]
5	2-naphth. (**4e**)	52	56 (**5e**)[a,c]
6	2-thiophene (**4f**)	20	83 (**5f**)
7	3-thiophene (**4g**)	20	78 (**5g**)
8	3-benzothiophene (**4h**)	22	56 (**5h**)
9	3-indole (**4i**)	21	–

[a]NMR yield(s). [b]30% 1-methylnaphthalene also observed. [c]40% 2-methylnaphthalene also observed.

Table 3. Dimerization of *α*-Substituted Phenylacetic Acids



entry (acid)	Ar	R^1	R^2	time/h	yield/% (dimer)
1 (**6a**)	Ph	Ph	H	16	91 (**7a**)
2 (**6b**)	9-fluorene		H	40	7 (**7b**)[a,b]
3 (**6c**)	Ph	Ph	Ph	18	–[a,c]
4 (**6d**)	Ph	F	H	21	90 (**7d**)
5 (**6e**)	Ph	F	F	20	3 (**7e**)

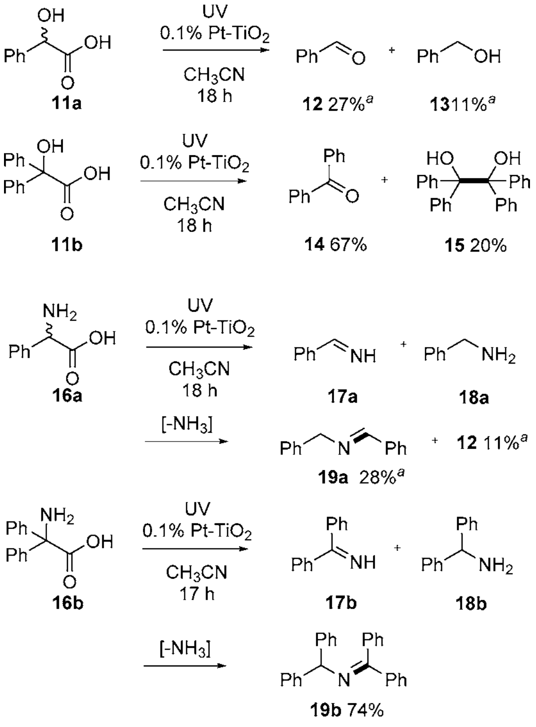
[a]NMR yield(s). [b]9*H*-Fluorene **8** (83%) also formed. [c]Triphenylmethane **9** (50%) and 9-phenyl-9*H*-fluorene **10** (26%) observed.

Heteroaromatics also proved effective; 2- and 3-thiopheneacetic acids **4f** and **4g** furnished the desired dimers in pleasing yields (entries 6 and 7) while the related benzo[*b*]thiophen-3-ylacetic acid **4h** reacted more modestly (entry 8). Photolysis of indole-3-acetic acid **4i** returned only unreacted starting material (entry 9).

The influence of additional substituents at the benzylic position was next examined. Diphenylacetic acid **6a** was converted to tetraphenylethane **7a** in a near-quantitative yield (Table 3, entry 1). In contrast, photolysis of the related 9*H*-fluorene-9-carboxylic acid **6b** produced the saturated alkane 9*H*-fluorene **8** as the major product (entry 2). Triphenylacetic acid **6c** gave rise to triphenylmethane **9** and 9-phenyl-9*H*-fluorene **10** (entry 3).[10] Gomberg's radical exists in an equilibrium with the quinoid dimer.[11] It is probable that this dimer was indeed formed during photolysis but that it converted back to its free radical form which was then transformed to **9** and **10** after encountering the electrons or holes of the photoexcited titania. Racemic *α*-fluorophenylacetic acid **6d** was converted to two stereoisomeric dimers **7d** in an excellent combined yield of 90% (entry 4).[12] Remarkably, incorporation of a second fluorine substituent at the same position in *α*,*α*-difluorophenylacetic acid **6e** essentially shut down the reaction. Following overnight irradiation, a mere 3% of the product dimer **7e** was isolated. It is well-known that the pyramidal character of C-centered radicals increases as more fluorine substituents are introduced.[13] Most probably this alters the geometry of the acid-derived radical, such that decarboxylation at the TiO_2 surface becomes energetically unfavorable.

When alcohol and amine groups were introduced the chemistry was diverted away from dimerization (Scheme 1). Racemic mandelic acid **11a** was converted to benzaldehyde **12** and benzyl alcohol **13**. Probably the *α*-hydroxybenzyl radical was reduced by the conduction band of the excited TiO_2 to

Scheme 1. Reactions of *α*-Hydroxy- and *α*-Amino-Substituted Phenylacetic Acids

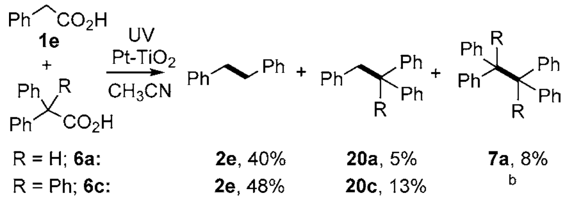


[a]NMR yield(s).

form an anion which was then protonated to furnish **13**. Oxidation to a cation and subsequent proton loss accounted for the formation of **12**. Benzilic acid **11b** returned benzophenone **14** in a good yield of 67%, presumably formed in a fashion analogous to **12**, accompanied by the homodimer **15** in a modest yield of 20%. The reaction of α-phenylglycine **16a** probably proceeded in a similar manner. In this instance it appeared that a condensation then took place between the products benzaldimine **17a** and benzylamine **18a** to form the secondary imine **19a** with loss of ammonia. Benzaldehyde **12** was probably also produced by hydrolysis of unreacted **17a** upon exposure to atmospheric moisture. The photolysis of α,α-diphenylglycine **16b** yielded only the secondary ketimine **19b** which was isolated in a pleasing yield of 74%. It is believed that this was formed in a similar condensation involving benzophenone imine **17b** and benzhydrylamine **18b**.

To extend the synthetic utility of this C−C bond forming process we investigated heterodimerizations between two different acids. The photocatalyzed reaction of phenylacetic acid **1e** with diphenylacetic acid **6a** produced the expected dimers **2e** and **7a** together with a minor amount of the cross-coupled product **20a** (Scheme 2). Reactions were carried out with different proportions of the acids and of TiO$_2$ but always gave the same three products.

Scheme 2. Homocoupling and Cross-coupling[a]



[a]NMR yields. [b] Head-to-tail trityl dimer not observed.

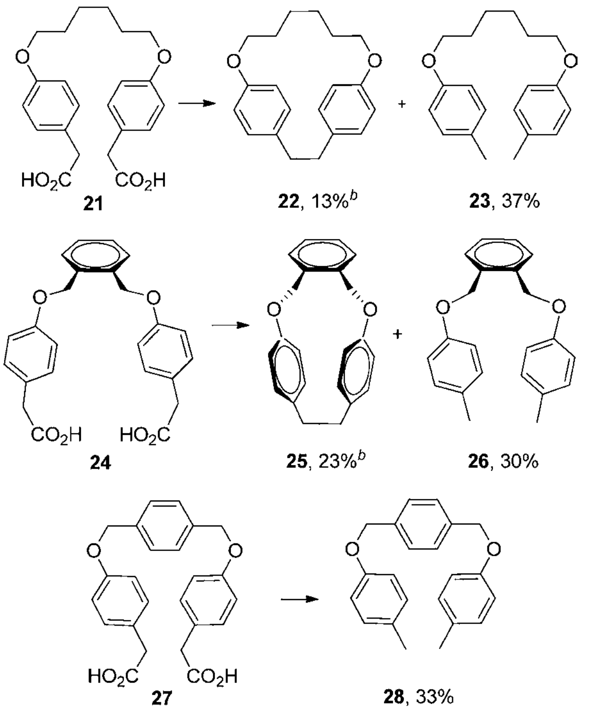
The persistent radical effect (PRE) leads to selective cross-coupling between a persistent and a transient radical when both are formed at equal rates.[14] It exploits the reluctance of persistent radicals to terminate via homodimerization reactions meaning that they can only be consumed by reaction with a transient species. Several elegant syntheses have made use of the PRE in recent years, the majority of these employing nitroxides.[15] We examined the reaction between **1e** and triphenylacetic acid **6c** in the hope that selective formation of the cross-coupled **20b** could be achieved. In fact, the homodimer **2e** was formed in excess of **20c** (Scheme 2). Photolyses with various reactant proportions gave similar results (see Supporting Information for details of this and other acids). Radical formation in our system arises from interaction with hole-trap sites on the titania. Therefore, it is probable that surface effects come into play making it unlikely that the different acids will react at the same rate, as required for the PRE. Furthermore, oxidations or reductions of the radicals by the titania are possible diverting them away from cross-coupling.

Many drug molecules and total synthesis targets contain macrocyclic ring systems, the macrolide family of antibiotics being just one notable example.[16] Macrocyclization reactions are mostly carried out under conditions of extreme dilution in order to minimize oligomerization and tend to suffer from low yields.[17] This, coupled with the tendency for macrocycle ring closures to be carried out late in a synthesis, has driven the search for new, more efficient macrocyclization methods. Based on the generally excellent yields and conversions obtained during the dimerization of arylacetic acids we extended our study to several intramolecular processes for the purpose of macrocycle syntheses.

Not surprisingly, in view of the strain involved, Pt−TiO$_2$ photocatalyzed reactions of *ortho*- and *para*-phenylenediacetic acids gave no [2.2]-*ortho*-cyclophane or [2.2]-*para*-cyclophane. Both returned the corresponding bibenzyl derivatives with evidence for oligomerization being detected by GC-MS.

Three precursor diacids (**21**, **24**, and **27**, Scheme 3), each containing two phenylacetic acid units linked in different ways, were prepared by treatment of 4-hydroxyphenylacetate with K$_2$CO$_3$ in the presence of an appropriate dibromide and subsequent basic hydrolysis. Photolysis of **21**, with its acid units flexibly linked by a methylene chain, afforded the doubly reduced, 1,6-bis(*p*-tolyloxy)hexane **23** as the major product. Pleasingly, however, the macrocycle 5,12-dioxa-1,4(1,4)-dibenzenacyclododecaphane **22** was obtained in a modest yield (13%) via intramolecular dimerization of the intermediate benzyl type radicals. A rigid, planar, phenyl ring was included in the linker between the two phenylacetic acid moieties, in the *ortho*- and *para*-xylene based diacids **24** and **27**. The objective was to decrease the rotational freedom of the chain thus encouraging macrocyclization. Photolysis of the *ortho*-analogue **24** was more successful with the cyclophane **25** being formed in 23% yield along with 30% of the 1,2-bis((*p*-tolyloxy)methyl)-benzene **26**. Diacid **27** returned only the dialkane product **28** in a modest yield of 33% following photolysis. Evidently the two reaction centers are held too far apart by the rigid *p*-xylene linker.

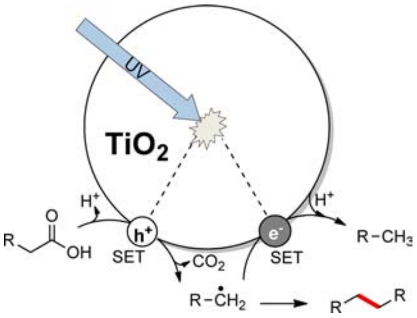
Scheme 3. Intramolecular Dimerizations to Cyclophanes[a]



[a]With Pt-P25, UV in CH$_3$CN for 18−20 h. [b] NMR yield(s).

A plausible mechanism (Scheme 4) involves photoexcitation of the TiO$_2$ by *ultra*-band-gap energy photons leading to the generation of an electron−hole pair that migrates to surface

Scheme 4. Postulated Mechanism



trapping sites.[18] Single electron transfer (SET) to the carboxylate of an acid at a hole-trap site furnishes a surface bound carboxylate radical cation. Decarboxylation by β-scission gives rise to a *C*-centered radical, in competition with back electron transfer. EPR studies of similar species have shown that a significant portion freely tumble in solution without being bound to the titania surface.[7] Termination occurs by homodimerization of two of these species in solution. Conversion of these radicals to saturated alkane products is thought to be the result of reduction/protonation at the TiO_2 surface that has some precedent.[19] The protons probably originate from hydroxyls at the titania surface. A simplified representation of these events is presented in Scheme 4.

In conclusion, we have developed a generally efficient protocol for the homodimerization of carboxylic acid derived radicals avoiding the use of harsh conditions and toxic reagents. This process is most effective with stabilized radicals, especially those based on the phenylacetic acid core. Efficient cross-couplings to yield heterodimers could not be achieved by exploiting a PRE. Macrocyclizations to form cyclophanes were achieved by photolyses of precursors containing two phenylacetic acid moieties. Yields were modest, but this is a well-documented feature of macrocyclizations. A straightforward reaction mechanism has been proposed which is promoted by TiO_2 as a reaction partner and catalyst and that is supported by previous work in our lab and by literature precedent.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental procedures and NMR spectra for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(9) Phenoxyacetone, 3-phenoxypropanenitrile, and phenol were also formed. See Supporting Information for full details.

(10) Compound **10** might have formed either by hole-oxidation of the trityl radical to a cation which then underwent electrophilic aromatic substitution with a neighbouring phenyl ring or via homolytic aromatic substitution followed by oxidative rearomatization.

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