

Synthetic Applications of Photoinduced Electron Transfer Decarboxylation Reactions

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new tools

Abstract: Photoinduced electron transfer (PET) decarboxylation of alkyl carboxylates *in water* leads to primary, secondary or tertiary carbon radicals which undergo C-C coupling reactions either in an intra- or intermolecular fashion. Intramolecular coupling gives rise to heterocyclic ring systems (lactams, lactones, cyclopeptides, cyclic ethers, crown ethers) with ring sizes from 5 to 28 and a broad variety of functionalities. Intermolecular coupling gives Grignard-type adducts (but with different chemo- and regioselectivities as for carbanion reactions). Yields of these reactions are mostly high, dilution conditions are not necessary, quantum yields are in the range of 0.5–0.6, and chemo- as well as regioselectivities are excellent. The electron-accepting chromophores which have been investigated are the imides of phthalic, maleic, quinolinic and trimellitic acid.

Selectivity can be further controlled by two simple tricks:

- Only triplet excited acceptors are active in these electron-transfer reactions, thus sensitization excludes other (homolytic) pathways;
- Donor groups (SR, NR₂, aryl, OR, C=C) other than the carboxylate can be activated by lowering the pH (and thus protonating the COO-donor).

In intramolecular reactions, substrate concentration up to 0.1 M were applied successfully and the reactions were completed in 10–12 h for multigram conversions.

Key words: photodecarboxylation, phthalimides, chirality memory, alkali metal carboxylates, α -keto carboxylates, macrocyclization

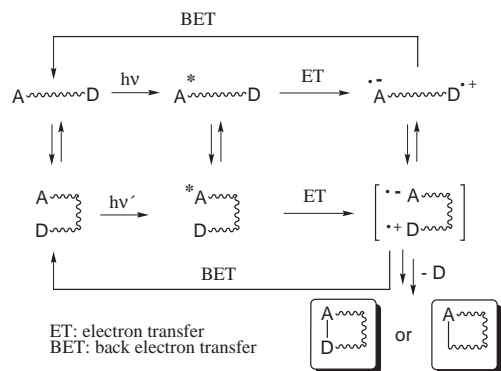
Introduction

The last decade has seen the evolution of an impressive and unpredictable rich chemistry involving radical reactions.¹ Not only the efficiency of radical reactions was improved and multicomponent catalytic cycles developed but also simultaneously selectivity became a predictable feature. Regioselectivity of radical additions can now be exactly controlled. The degree of stereoselectivity of radical coupling, cyclization and/or addition reactions is constantly improved. There are numerous methods for the generation of radicals e.g. by thermal, electrochemical or metal catalyzed processes. In this context, *photochemistry* is a universal tool in the sense that not only carbon radicals can be produced by several pathways but also heteroatom radicals with a multitude of reactivity features. Photons are optimal "reagents" which can be adapted to specific excitation sites by tuning the wavelength and by adding sensitizers or quenchers which help to activate selectively one chromophore in the presence of others. The excess energies in electronically excited states of organic molecules are high (ca. 70–120 kcal/mol) and not only change the

chemical behavior but also the redox properties, i.e. singlet or triplet excited states are at the same time much better reductants and oxidants compared to their ground state precursors.² This fact has long been known but only in the last two decades an explosive development of photoinduced electron transfer (PET) reactions has occurred.³ In many of these reactions the products were the same or at least similar to homolytic photochemical reactions. Thus, electron transfer steps often stayed undiscovered for a long time. Obviously, in order to reach ground state closed-shell products, the charges produced in electron transfer steps have to be annihilated, e.g. via charge recombination or via elimination of positively charged (protons, trialkylsilyl cations) and/or negatively charged (halides, thiolates, etc.) fragments. Summing up these steps, many photoinduced electron transfer processes can be "written" also in a homolytic fashion. The differences become immediately obvious when the influences of solvent polarity, donor and/or acceptor redox potential and geometrical factors are considered. Especially the possibility of long-range electron transfers has opened a new field for synthetic applications, e.g. the preparation of macrocyclic molecules.⁴

The chemistry which we are describing in this report is connected to previous experiments in the field of electron transfer reactions with triplet excited carbonyl components as electron acceptors and thioethers⁵, alkenes⁶, alcohols⁷ and arenes⁷ as the electron donating groups in inter- and intramolecular photoadditions or photo-cyclizations, respectively. The principle behind these reactions is shown in Scheme 1. An illustrative description of this scenario was given by P. J. Wagner describing the substrate as a *bug that opens its mouth when struck by light, can hold it open only for a short time, and during that time can swallow anything within striking range of its open mouth including its own tail*.⁸

Adopting this picture to electron transfer (ET) events, two possibilities exist for the charge separation step: long-range ET at the stage of the extended donor-acceptor couple or, after conformational equilibration, short-range ET at the stage of the closely approached donor-acceptor couple. A third possibility is the excitation of a ground-state donor-acceptor complex which is lowered in energy by specific interactions, i.e. charge-transfer, hydrogen bonding or metal complexation. The latter case might lead to highly selective secondary reactions with the reactive ends of the molecule in close proximity already in the Franck-Condon state.



Scheme 1

State- and Spin-Selectivity of Carbonyl Photochemistry

Selectivity has become the most important feature in synthetic organic chemistry since several decades. As far as ground state chemistry is concerned, chemo-, regio-, and stereoselectivity are the essential factors which determine the success and the usefulness of a reaction. Photochemistry makes an additional possibility available, i.e. spin-selectivity, which has been long known and studied for many photochemical model reactions. Notwithstanding, it should be emphasized that spin-selectivity allows the modification of a chemical reaction solely by taking advantage of the different lifetimes and reactivities of two (or more) electronically excited states of the same molecule (spin-isomers⁹).

Biographical Sketches



Axel G. Griesbeck, born in 1958, received his doctoral degree in 1984 (with Prof. Gollnick at the University of Munich). After postdoctoral studies in Würzburg (1985-1986 with Prof. Adam), the ETH Zürich (1986-1987 with Prof. Seebach), and the Weizmann-Institute, Israel (1987) he performed his Habilitation in Würzburg and was appointed Privatdozent

in 1991. His was visiting professor at the University of Madison in Wisconsin in fall 1993 and in Tsukuba, Japan in the summer of 1996 and 1999. In 1994 he moved to the University of Cologne as a Professor of Organic Chemistry. His current research interests are preparative and mechanistic organic photochemistry, the synthesis of unnatural ami-

no acids, amino acid derivatives, heterocyclic and macrocyclic ring systems, singlet oxygen chemistry, gas-phase thermolyses and the synthesis of polyquinanes. He has received the Grammaticakis-Neumann prize of the Swiss society for photochemistry and photophysics in 1997.



Michael Oelgemöller, born in 1969, studied chemistry at the University of Münster, received his diploma degree with Prof. Mattay in 1995 in the field of photochemical acylation of quinones and potential solarchemical applications. From 1996 to 1999 he con-

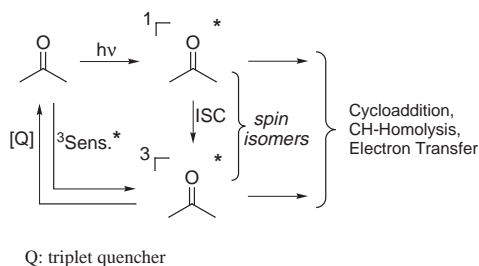
ducted his doctoral thesis in Cologne. In 1998 he spent three months in Korea in the group of Prof. S.C. Shim in Taejon as a KOSEF-fellow. Main topic of his doctoral thesis were photocyclizations induced by electron transfer either from sulfur-substituted amino acids or

from alkyl carboxylates and α -keto carboxylates.



Wolfgang Kramer, born in 1969, studied chemistry at the University of Cologne, received his diploma degree in 1996 and started with his doctoral work in the photochemistry research group in Cologne. Main topic of his thesis are intramolecular photodecarboxylative cy-

clizations induced by electron transfer from alkyl carboxylates and the synthesis of complex polycyclic target molecules from the pool of chiral amino acids.



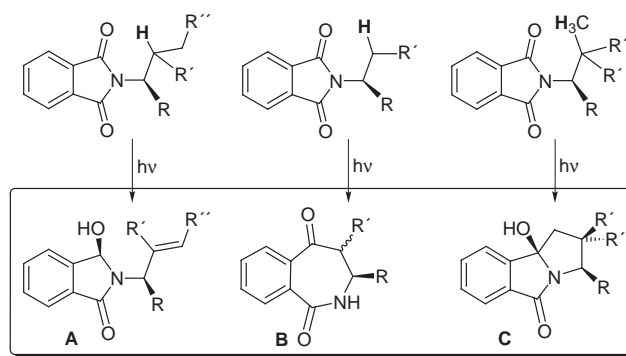
Scheme 2

Triplet states could be selectively generated by triplet-triplet energy-transfer (sensitization) and selectively deactivated by quenching. The latter process allows the study of the singlet state behavior in chemical transformations. Spin-multiplicity does not only influence the reactivity of the excited molecules (due to energy and lifetime effects), but also alters the regio- and stereoselectivity of the product-forming steps. In singlet photoreactions, stereoselectivity is often controlled by the optimal geometries for radical-radical combinations, whereas in triplet photoreactions the geometries most favorable for inter-system crossing (ISC) are considered to be of similar relevance. These geometries can be quite different from the former ones due to differences in spin-orbit coupling (SOC) values. We have reported these aspects for Paternò-Büchi reactions and developed a model for the prediction of the stereoselectivity in photocycloadditions of excited aliphatic and aromatic aldehyde triplets and singlets.¹⁰ Searching for other chromophores with pronounced differences between singlet and triplet reactivity we focused on the phthaloyl group, whose photochemistry has been investigated intensively by Kanaoka and co-workers in the last two decades and summarized in several reviews.¹¹

Activation of Amino Acids for Photochemical Transformations

Amino acids can be photochemically activated by means of chromophoric groups at the nitrogen and the carbon terminus, respectively. Whereas for C-activation only little is known, *N*-activation via acylation is a straightforward and well-studied method especially in functional group protection chemistry. An especially promising chromophore is the phthalimido group whose photophysics has been intensively studied in the last years.¹² The major advantages are: long-wavelength shifted absorption (300–320 nm), low reduction potential ($E_{\text{red}} = -1.4$ V vs. SCE in acetonitrile) and clear singlet/triplet differentiation (short-lived $^1n\pi^*$, long-lived $^3\pi\pi^*$) which is a prerequisite for spin-selective transformations. Phthalimide groups can be easily introduced using a variety of chemical methods without loss of enantiomeric purity of chiral starting materials. In the last years we discovered a series of photochemical transformations involving homolytic CH-activation at specific positions of amino acids and thus de-

veloped routes to β,γ -unsaturated α -amino acids (**A**), benzazepines (**B**) and benzopyrrolizidines (**C**).¹³

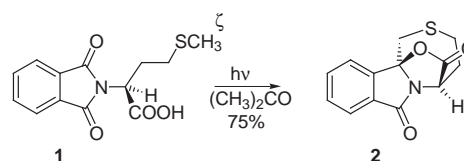


Scheme 3

These products were formed in enantiomerically pure form (EPC-synthesis) and, in many cases, with high diastereoselectivities and in good chemical yields. The quantum yields for these reactions, however, were only moderate (around 10%). Photophysical processes dominate the fate of electronically excited *N*-phthaloyl derivatives of alkyl-substituted amino acids. For these cases the lowest triplet state T_1 , which is efficiently produced either by direct excitation and ISC or by triplet sensitization is unreactive in homolytic CH-abstractions. This might be due to the low energy of the T_1 -state (ca. 3 eV) and its ($\pi\pi^*$) electronic configuration.

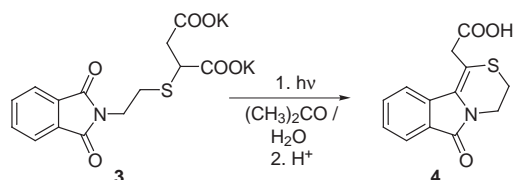
Photoinduced Electron Transfer Cyclizations of Phthalimides

The concept of electron transfer initiated macrocyclization has been developed by Kanaoka and coworkers¹⁴ for thioalkyl-substituted phthalimides and follows the reaction principle described in Scheme 1. We became interested in these processes when trying to develop a method for the synthesis of cyclopeptides from sulfur-containing oligopeptides. A prerequisite for such a method is that other potential electron-donating substituents were unreactive under photochemical conditions. An illustrative example is the photocyclization of *N*-phthaloyl methionine (**1**). When irradiated in pure acetone, this compound gave the tetracyclic lactone **2** in high yields.⁵ This reaction is unusual in the sense that photolysis of unprotected *N*-acyl amino acids normally leads to efficient α -decarboxylation.¹⁵ Thus, electron transfer reactions involving thioalkyl groups can compete with rapid proton transfer.



Scheme 4

Spatial separation of the carboxy group from the chromophore additionally lowered its reactivity in ET-reactions. An example is the photolysis of the thioalkyl substituted ε -phthalimido hexanoic acid (**3**): when irradiated in aqueous acetone, the product **4** derives solely from PET involving sulfur oxidation. Under neutral conditions the carboxy group is unreactive and can be tolerated in PET-cyclizations.¹⁶

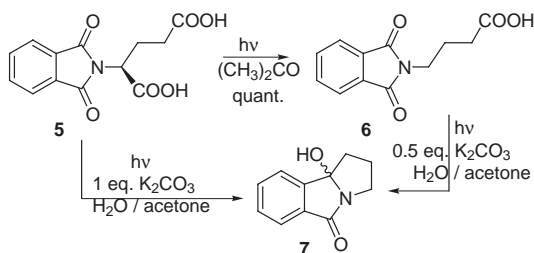


Scheme 5

If, however, the carboxy group is localized in α -position with respect to a PET-active heteroatom such as an alkylthio group (i.e. a structural unit CRR'-Het-CRR'-COOH), oxidation of the heteroatom is followed by rapid decarboxylation to give a heteroatom-stabilized carbon-centered radical. This behaviour is also visualized in the photo-cyclization of substrate **3**.

Decarboxylative Photocyclizations of Phthalimides

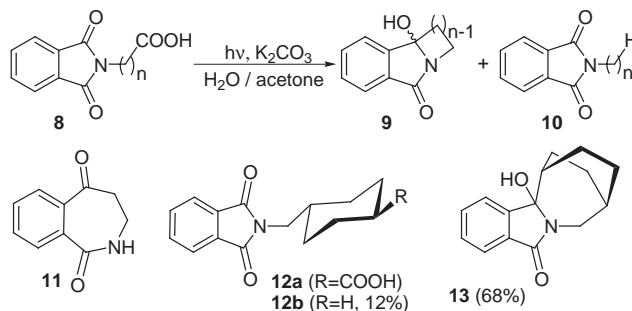
During the investigation of the synthetic use of photochemical α -decarboxylation of *N*-acyl α -amino acids we discovered an interesting regioselectivity phenomenon. The glutamic acid derivative **5** was transformed quantitatively into the *N*-protected GABA **6** under nearly all photochemical conditions investigated. This primary photoproduct was stable when directly excited or triplet-sensitized, however, in the presence of base it rapidly cyclized with extrusion of CO₂ to give the benzopyrrolizidine **7**.¹⁷ Water was necessary as cosolvent in order to suppress the formation of reduction products simply formed by CO₂/H-exchange (*vide infra*).



Scheme 6

In the last year we have intensively reinvestigated this model reaction and found that α -decarboxylation is about 10 times faster than γ -decarboxylation. Whereas the first step (**5**→**6**) was not influenced in the presence of triplet quenchers, the rate of γ -decarboxylation (**6**→**7**) was

strongly reduced. In order to elaborate scope and limitations of this new cyclization reaction, we focused on the synthesis of medium- and large-ring compounds testing a variety of ring sizes (from 4 to 26) and spacer groups. Firstly, alkyl chains were used to separate the phthalimide and the carboxylate part. There was no trace of a cyclization product when *N*-phthaloyl glycine (**8a**) was irradiated under standard conditions, only *N*-methylphthalimide was formed. The homologous substrate, 3-phthalimidopropionic acid (**8b**) did already give 10% (relative yield from NMR-analysis of the crude product mixture) of the benzazepine-1,5-dione **11**, a secondary product of the primarily formed cyclobutane **9b** (Scheme 7).¹⁸



	a	b	c	d	e	f	g
n =	1	2	3	4	5	10	11
9 (%)	-	10 (11)	75	61	71	72	78
10 (%)	95	45	< 5	< 5	8	< 5	< 5

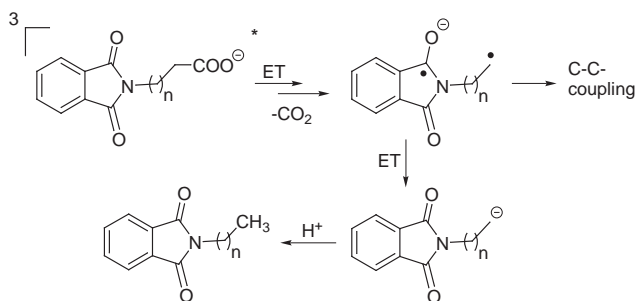
Scheme 7

Substrates with longer alkyl chains did result in the formation of the corresponding annulation products **9** in yields not lower than 61%. In all cases also small amounts (ca. 5-10%) of the CO₂/H-exchange products **10** were detected. Only the starting material from tranexamic acid with a *trans* 1,4-cyclohexane spacer (**12a**) did show a slightly higher degree of decarboxylation leading to the monosubstituted cyclohexane **12b**. But also in this case, the cyclization product **13** was formed in good yield. The latter example already indicated, that a decrease in conformational flexibility of the connecting hydrocarbon chain does not strongly influence the efficiency of the ring formation. Furthermore, the conversion of **12a** into **13** showed that also α -branched carboxylic acids can be used as substrates in the title reaction. It is remarkable that in no case dimeric products could be detected by NMR or MS-analysis, nor "Kolbe-dimers" neither cross-cyclization products. The former products were expected under Kolbe electrolysis conditions and thus, photochemical activation gives a completely different product pattern. The photocyclization of the cyclohexane-linked substrate **12a** was also successfully performed in acetonitrile using 4-carboxybenzophenone as triplet sensitizer, demonstrating

that the T_1 -state is responsible for the reactivity. The addition of organic cosolvents (and/or sensitizers) was not necessary for highly water-soluble substrates such as the glutamic acid derivative **5** or the GABA substrate **8c**. These reactions can be performed in pure water and the reaction progress is monitored by the pH which constantly rises during the reaction (approx. from 6 to 9) until complete conversion of the substrate. Before exploring the flexibility of the linker structure between electron donor and electron acceptor group we investigated the intermolecular version.

Decarboxylative Photoadditions to Phthalimides

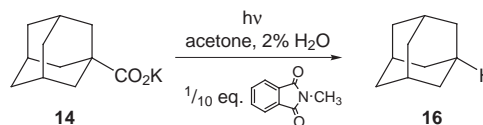
The intramolecular photodecarboxylation reactions described above resulted in medium- and large-sized ring systems in good to excellent yields. Two factors were responsible for lower yields, a trivial and an interesting one. The trivial reason is, that the products have to be extracted from the water phase which always leads to some loss in material, the more interesting reason is the formation of "simple" decarboxylation products. This lab jargon term describes products where seemingly the first step of the reaction (i.e. electron transfer and decarboxylation) proceeded but the radical-radical combination was overtaken by hydrogen abstraction. In some cases we actually could isolate acetone dimers indicating that hydrogen abstraction could also occur directly from the solvent, however, in many cases acetone was not the hydrogen source. For these cases we postulate a secondary electron transfer from the imide radical anion to the carbon radical leading to a carbanion which is immediately protonated by water.



Scheme 8

Energetically, this secondary electron transfer is feasible and might play an essential role not only in the PET-decarboxylation leading to "simple" decarboxylation products. Numerous electron transfer cyclization reactions (e.g. the biomimetic tandem cyclizations of polyenes)¹⁹ can be written on paper as leading to carbon radicals which have to catch a hydrogen from somewhere to give the final products. In many cases the assumption of a secondary electron transfer can solve this query. The exchange of the carboxy group by hydrogen would be an useful alternative to the Barton-type activation²⁰ if this reaction also works in an intermolecular fashion. The classical substrate for radical type carboxy exchange is 2-

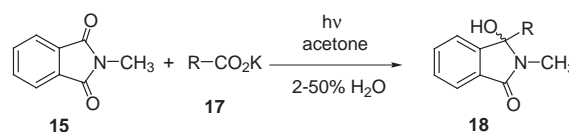
adamantane carboxylate **14** and actually this substrate was converted into adamantane (**16**) by using *N*-methyl phthalimide (**15**) as light-absorbing species. Complete conversion was achieved with 10 mol-% of the imide.



Scheme 9

In this reaction the phthalimide serves as a catalyst for an *electron transfer shuttle process*. The T_1 -state accepts an electron from the carboxylate and subsequently donates this electron to the adamantyl radical. The alternative reaction, hydrogen abstraction from acetone, is unlikely because reductive deactivation of the *N*-methyl phthalimide must be expected for this case.

Our hopes, that this reaction could be exemplary for other tertiary, secondary and primary alkyl carboxylates, however, were dashed.²¹ Nearly all carboxylates **17** investigated did add to *N*-methyl phthalimide (**15**) to give hydroxy phthalimidines **18**. The potassium carboxylates were used in excess (2-10 equivalents) in order to drive the reactions to completion.

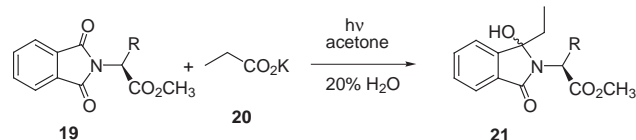


R	Me	Et	i-Pr	i-Pen	Bn	t-Bu	H	Ph
yield (%)	38	88	86	80	88	57	62	0

Scheme 10

Even potassium formate gave the reduction product in acceptable yield. In contrast to *intramolecular* reactions where decarboxylation was observed also from aromatic carboxylic acids, potassium benzoate was unreactive and *N*-methyl phthalimide was isolated back in 97% yield after prolonged irradiation. This reaction protocol is a powerful alternative to Grignard additions which are described in the literature for the synthesis of phthalimidines. The advantage of the photoinduced addition is that other carbonyl groups which are present in the substrates do not react with the alkyl radicals produced. This was demonstrated for a series of methyl esters of *N*-phthaloyl amino acids **19** which were irradiated in the presence of 5 eq. of potassium propionate (**20**). Five of these substrates are photolabile in the absence of external carboxylate reagents and are prone to hydrogen abstraction or intramolecular electron transfer reactions.²² Four substrates, the glycine (Gly)-, the phenylalanine (Phe)-, the phenylgly-

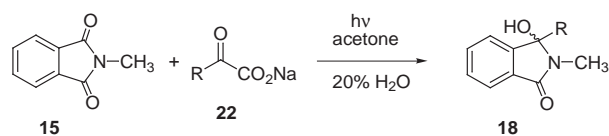
cine (Phg)- and the aspartic acid (Asp) derived compounds **19a**, **19f**, **19g** and **19h**, respectively, were photostable in the absence of alkylating reagents. In all cases, the *intermolecular* decarboxylative alkylation to give products **21a-i** dominated under the standard conditions (Scheme 11), and only minor amounts of intramolecular reaction products were detected.



Sub-str.	Gly	Ala	Val	Leu	Ile	Phe	Phg	Asp	Glu
yield (%)	88	89	51	55	63	72	85	64	62
d.e. (%)	-	52	53	57	69	64	65	57	64

Scheme 11

The formation of hydrogen abstraction products from the S_1 -state of the phthalimide is suppressed by performing the reaction in the presence of a triplet sensitizer (acetone, benzophenone) and irradiation at $\lambda > 320$ nm, i.e. outside the phthalimide absorption region. In this case, the reaction sequence is composed of energy transfer, electron transfer, CO_2 -extrusion and radical combination. The diastereo-selectivities of the ethyl radical addition with the amino acid esters are poor, which also speaks in favour of a free radical reaction. Beside simple carboxylates also α -keto carboxylates **22** were subjected to photodecarboxylation under standard conditions with *N*-methyl phthalimide and gave the products **18c**, **d**, **f**, and **g**, respectively. Obviously, photodecarboxylation is followed by photodecarbonylation for these substrates.

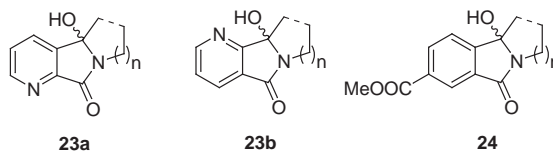


R	i-Pr	i-Bu	t-Bu	H
yield (%)	86	73	84	52

Scheme 12

Carboxylates and α -keto carboxylates tolerate many functional groups in the side-chain and are preferentially oxidized. It is instructive to compare the regioselectivity of PET addition reaction and Grignard reaction with unsymmetrical electron acceptor groups such as trimellitic acid imides or quinolinic acid imides. These substrates were

alkylated highly selectively with Grignard reagents whereas the PET addition of potassium alkanoates proceeded with low regioselectivity (ca. 60:40) to give the regioisomers **23a** and **23b**.

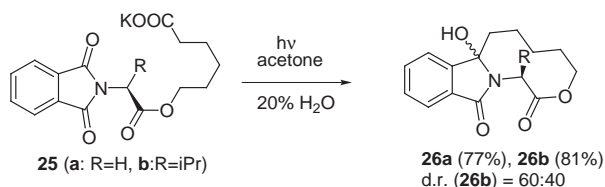


Scheme 13

On the contrary, the trimellitic acid imides were alkylated highly regioselectively at the *para* carbonyl group to give products **24**. These results are in perfect agreement with the assumption of an intermediary imide radical anion which reacts preferentially at the ketyl carbon with higher spin density. Grignard reactions with (ground state) quinolinic acid imides are controlled by reagent interactions with the pyridine nitrogen. The high regioselectivity obtained for trimellitic acid derivatives and the low selectivity with quinolinic acid derivatives was also observed for intramolecular reactions (indicated by the dashed line in Scheme 13).

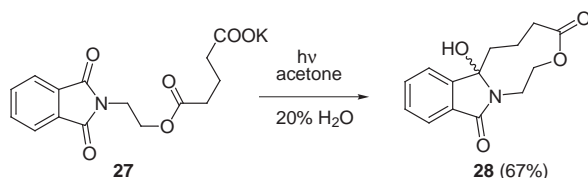
Variation of the Linker Structure

The C-C coupling reaction is highly efficient for substrates with hydro-carbon chains linking electron donor and acceptor group. Subsequently, we also investigated additional functional groups such as esters, ethers and amides. The pool of chiral natural compounds delivered the necessary building blocks for ester- and amide-spaced donor-acceptor couples. Thus, *N*-phthaloyl α -amino acids could be applied as primary components and coupled with ω -hydroxy carboxylic acids. The model compounds **25a,b** were cyclized in aqueous acetone in high yields to give ten-membered macrolides **26a,b**.²³ The diastereoselectivity of the radical combination step was only marginal for macrocyclization. It is important to mention that the absolute configuration of the amino acid derived stereogenic center was always preserved during photolysis. We have established this fact by degradation of several products back to the amino acid precursors and by chiral HPLC analyses.



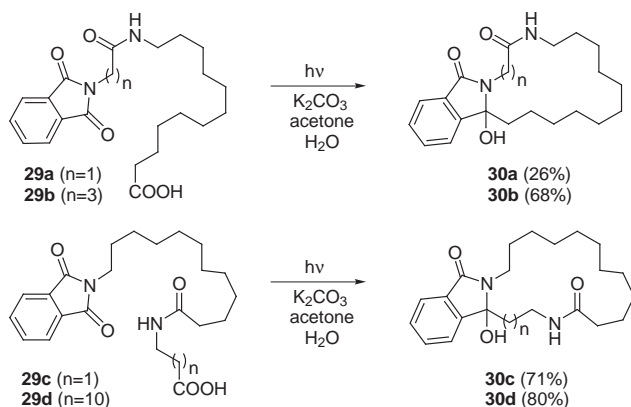
Scheme 14

The complementary strategy uses the coupling of *N*-phthaloyl β -aminoalcohols with 1,*n*-dicarboxylic acids. The glutaric acid derived substrate **27** could be successfully photocyclized, and the nine-membered azalactone **28** was formed in 67% yield.¹⁸ Smaller ring sizes, however, were not obtainable due to secondary photochemical transformations. A macrocyclic polyether which had already been prepared by Yoon and coworkers²⁴ using a terminal (trimethylsilyl)-methoxy as electron donating group (with subsequent elimination of the TMS cation) could also be obtained by our method in 65% yield.



Scheme 15

The most interesting family of target molecules in this context are macrocyclic oligopeptides. PET-decarboxylation of *N*-activated oligo-peptides would be a useful methodology which requires only modification of the *N*-terminus. Unfortunately, *N*-phthaloyl dipeptides such as Pht-Gly-Gly or Pht-Gly-Val did not cyclize at all but resulted in decomposition products after prolonged irradiation. Introducing long-chain ω -amino acids as the second building block improved the cyclization yield, e.g. the C₁-C₁₁-substrate **29a** gave 26% of the macrocyclic lactam **30a**. An amide group which is linked in close proximity to the phthalimide chromophore seems to reduce the cyclization propensity of the 1,*n*-triplet biradical formed after PET decarboxylation.



Scheme 16

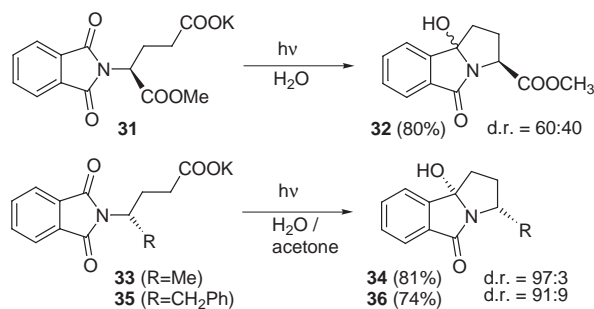
When using the more flexible substrate **29b**, the yield improved and further increase in the chain length of the *N*-terminal spacer led to an additional increase in cyclization efficiency as shown for the examples **29c** and **29d**. It is remarkable that the substrate with the most extended spacer gave the highest yield of cyclization product (**30d**, 80%).

Recalling the mechanistic scenario shown in Scheme 1, three possibilities exist which might explain the efficiency of the photoinduced cyclization reaction: (a) an acceptor-donor couple already in the right geometry for electron transfer and C-C bond formation, (b) a long-lived conformationally relaxed triplet excited phthalimide state which approaches close-contact geometry, or (c) rapid through-bond electron transfer to give a radical ion pair which conformationally rearranges to the right geometry for bond formation. The latter alternative seems to be important only for substrates with rigid spacers such as the *trans* 1,4-cyclohexane system **12a**. The structure of the base used for deprotonation of the carboxylic acid influences the cyclization/hydrogen transfer ratio, e.g. **8c** gives more than 70% of *N*-propyl phthalimide when irradiated in the presence of lithium carbonate. This result accounts for route (a), because in route (b) the cation should not influence the rate of the formation of the close-contact geometry.

A Synthetic Route to Pyrrolizidines and Indolizidines

Annulated five- and six-membered rings were formed with the highest efficiency in decarboxylative photocyclizations. Thus, in principle a variety of pyrrolizidines and indolizidines should be accessible. In order to investigate this route we first studied the diastereoselectivity of the radical combination step in the presence of an additional stereogenic center. Essential prerequisite for this reaction is the use of alkali metal carboxylates which were prepared in situ or prior to the reaction. The in situ method uses heterogenic conditions and is superior for base-labile substrates. Many starting materials could be deprotonated prior to photolysis and irradiated in homogeneous solvent mixtures of organic solvents and water. Benzopyrrolizidines of the type mentioned here have also been synthesized using the azomethine ylide route using *N*-trialkylsilylmethylimides or phthaloyl glycine as 1,3-dipole precursors. This highly useful route developed by the groups of Mariano and Yoon²⁵ has the disadvantage that the stereogenic α -center is epimerized during the course of the reaction and only racemic products are available.

The in situ method with **31** gave approximately 20% of a simple decarboxylation product (i.e. the methyl ester of *N*-phthaloyl α -amino butyric acid) beside a 3:2 mixture of *cis*- and *trans*-**32**. When directly using the potassium salt of **31** in a 1:1 mixture of water and acetone as solvent less than 5% of the decarboxylation product was observed after quantitative conversion. Treatment of the product mixture with catalytic trifluoroacetic acid or formic acid led to nearly quantitative epimerization to give the *cis*-diastereoisomer. Epimerization at the stereogenic center of hydroxy lactams resulting in an 1:1 equilibrium has already been reported by us for the product of *N*-phthaloylvaline ester photolysis.²² In the glutamic acid case reported herein, however, the epimerization equilibrium is >9:1 in favor of *cis*-**32**.

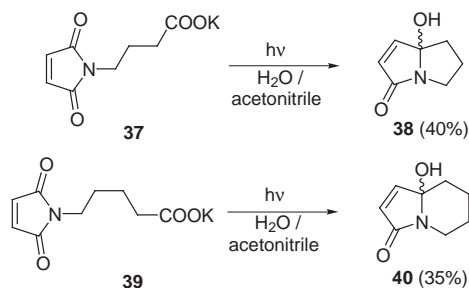


Scheme 17

Further transformations of this enantiomerically pure acyliminium precursor were investigated.²³ In order to study the stereoselectivity of the C-C coupling step in the presence of other directing groups we synthesized the methyl- and the benzyl-substituted starting materials **33** and **35** from *N*-Boc-phenylalanine and *N*-Boc-alanine. Photocyclization of the benzyl derivative **35** resulted in a 91:9 diastereomeric mixture of benzopyrrolizidinones **36** in 74% yield.

The relative configuration of the major diastereomer was proven by X-ray structure analysis. In the case of the α -methyl-GABA derivative **33** the stereoselectivity was even higher: a 97:3 mixture of *cis*- and *trans*-**34** was formed in 81% yield. The preferred formation of the *cis*-products might be due to a stereoelectronic effect which favors the pseudo-axial position of the hydroxyl group in the pyrrolizidine ring and leads to the thermodynamically favored *cis*-products. Although thermodynamic control was not observed for the glutamic acid derivative **31**, it might for a yet unknown reason operate for the starting materials **33** and **35**. We were very much surprised (and pleased) to find that also male-imides could be used in decarboxylative photocyclizations. Yoon, Mariano and co-workers have already described the photochemistry of 2-maleimido acetic acid.²⁶ This substrate reacted preferentially to give the [2+2] cycloaddition products, a typical photochemical behaviour for maleimides.

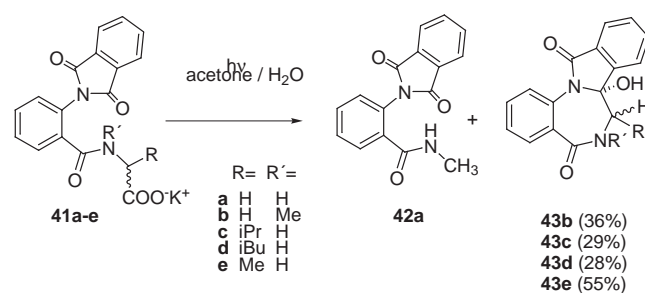
When using the potassium carboxylate of 4-maleimido butyric acid (**37**) or the homologous 5-maleimido pentanoic acid (**39**) the corresponding cyclization products were formed in moderate yields.²⁷ Thus this reaction could serve as a new way to substituted pyrrolizidines and indolizidines and experiments in this context are underway.



Scheme 18

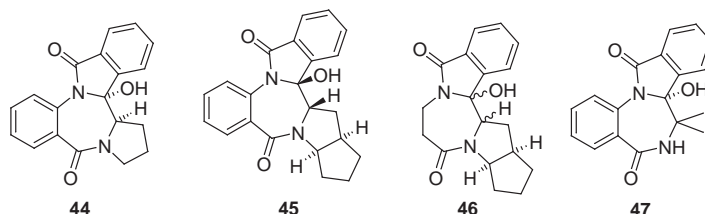
Chirality Transfer and Memory of Chirality

In the vast majority of the intramolecular examples described above, the carboxy group was linked to a methylene group and decarboxylation thus generated a primary carbon radical. Secondary radicals originate from the decarboxylation of α -amino acids as building blocks. In these cases, however, the asymmetric center is planarized during the reaction and the formation of racemic products must be anticipated from long-lived biradical intermediates. This effect was indeed found in the photochemistry of *N*-phthaloyl α -amino acids when the decarboxylation was coupled with deuteration at the C $_{\alpha}$ -carbon.¹⁵ This reaction most probably proceeds via a carbanion reaction similar to the *N*-phthaloyl glycine and *N*-trimethylsilylmethyl phthalimide photolyses investigated by Mariano and Yoon recently.²⁵ Numerous applications are obvious for the decarboxylative photocyclization if the protonation step could be efficiently suppressed. One interesting family of potential target molecules are the annulated benzodiazepines, a well-known and intensively investigated group of pharmaceutically important compounds. We investigated this application using anthranilic acid as the central skeleton which was chemically modified at the N- and C-termini. The glycine derivative **41a** was reactive, however, decarboxylation resulted in the formation of the *N*-methyl amide **42a** without any trace of cyclization. This behavior parallels the photochemistry of *N*-phthaloyl dipeptides¹⁸ and probably in both cases an intermolecular hydrogen bond (between the amide NH and the imide carbonyl) keeps the two radical centers apart. Consequently, additional alkylation of the amide group was expected to improve the cyclization efficiency. The sarcosine derivative **41b** did cyclize and gave the benzodiazepine **43b** in good yields.



Scheme 19

The photocyclization could also be achieved with alkyl-substituted amino acids as building blocks in the amide precursors: the valine, the leucine as well as the alanine derivatives **41c,d** and **41e**, respectively, gave in acceptable yields the corresponding benzodiazepines **43c-e**. The substrates were used as racemic mixtures and consequently racemic mixtures of the corresponding products were formed. In order to study the degree of racemization dur-



Scheme 20

ing the course of the reaction we studied the corresponding enantiomerically pure proline derivative. The decarboxylative photocyclization proceeded efficiently and product **44** was isolated in 36% yield after column chromatography and crystallization. The benzodiazepine **44** was formed with an e.e. of 86%.

Thus, during the essential step of the reaction, i.e. the formation of the new carbon-carbon bond, a high degree of chirality memory²⁸ was observed. From the bicyclic proline derivative benzyl (all-*R*)-2-azabicyclo[3.3.0]octan-3-oate the pentacyclic pyrrolbenzodiazepine **45** was formed in 12% yield in diastereomerically and enantiomerically pure form.²⁹ X-ray structure analysis revealed that the C-C-coupling step had occurred with complete inversion at the stereogenic α -center. In the case of **45** the formation of only one diastereomer might be due to asymmetric induction from the bicyclo[3.3.0]octane-skeleton whereas for the proline derivative **44** memory of chirality was observed for the first time in decarboxylative radical cyclization reactions. The reason for the high degree of memory of chirality might be the high barrier for rotation about the central arene-nitrogen and arene-carbon bonds in the axially chiral triplet biradical intermediate which allows efficient spin inversion and radical combination in the lifetime of this open-shell species. The selectivity strongly decreased (in accord with the mechanistic picture) for **46** from the conformationally more flexible β -alanine precursor. Also tertiary radicals can be generated via this procedure and cyclized efficiently (e.g. to give **47**).

Summary

The photoinduced electron transfer (PET) decarboxylation described in this report has developed to an interesting method for the synthesis of medium- and large-sized heterocycles, benzopyrrolizidines, pyrrolizidines, indolizidines and many more product families. The intra- as well as the intermolecular version are likewise efficient concerning chemical and quantum yields. The photolyses can be performed in the absence and also in the presence of triplet sensitizers using the long-wavelength region ($\lambda > 320$ nm). Water is the optimal solvent with organic cosolvents only necessary as solubility promoter. Beside phthalimides which we have used for the majority of our

investigations also other imides are reactive in PET-decarboxylations: maleimides, quinolinimides and trimellitimides. In some cases, catalytic amounts of the electron-acceptor was sufficient to generate alkyl radicals in water, a reaction could possibly be extended to a powerful radical source.

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