Acc. Chem. Res. **2007,** *40,* 128−140

Photoinduced-Electron-Transfer Chemistry: From Studies on PET Processes to Applications in Natural Product Synthesis

AXEL G. GRIESBECK,*,†
NORBERT HOFFMANN,*,‡ AND
KLAUS-DIETER WARZECHA†

Institute of Organic Chemistry, University of Cologne, Greinstr. 4, 50939 Köln, Germany, and CNRS, Université de Reims, UFR Sciences, UMR 6519, B.P. 1039, 51687 Reims, France

Received June 2, 2006

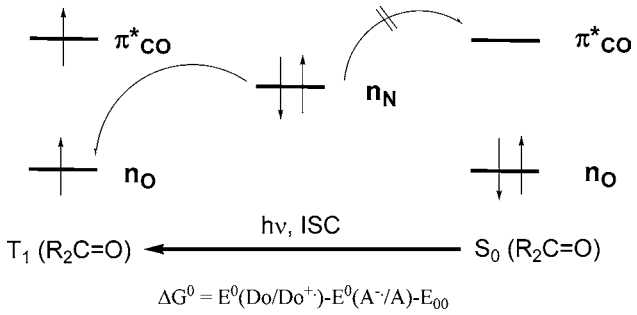
ABSTRACT

The application of photoinduced electron transfer (PET) for the construction of heterocyclic ring systems is an appealing route in synthetic organic photochemistry. Electronically excited carbonyl chromophors in ketones, aldehydes, amides, or imides are strong electron acceptors that oxidize alkenes, amines, thioethers, or carboxylates. In subsequent steps, the radical anions formed thereof either are operating as secondary electron donors and initiate a photon-driven chain reaction or combine with electrophilic species and form products. These reactions are applied in the synthesis of heterocyclic compounds. The basic structures of these target molecules are bicyclic tertiary amines from the pyrrolizidine, benzopyrrolizidine, and indolizidine families, cyclic oligopeptides, macrocyclic ring systems, and many more.

Introduction

Electronically excited states feature, at the same time, significantly increased reduction and oxidation properties, as compared to ground states. The recognition of photo-induced electron transfer (PET) as a key step in many photochemical reactions was fueled by the Nobel Prize awarded work of Marcus[1] and has, in recent decades, not only led to new synthetic applications[2] but also to a general paradigm change in photochemistry. As has been described in detail in several reviews,[3] the energetics of light-induced electron transfer can be estimated by use of a simplified version of the Rehm−Weller equation.[4] Unlike many other physical equations, this relationship immediately displays its chemical relevance: electronically excited states are concurrently much better reductants and oxidants, and the actual redox behavior depends on the reaction partner. This concept is shown for a carbonyl−amine system, which will play a major role for the chemistry described in this review. The high-lying lone pair at N and the low-lying antibonding π_{CO}* render the amine−carbonyl combination suitable for frontier molecular orbital (FMO)-controlled nucleophile−electrophile ground-state interaction. However, only after electronic excitation to the n→π* carbonyl state does an exergonic electron transfer become feasible. The same is true for

Scheme 1. Pictorial Description of a Photoinduced-Electron-Transfer Process



less active electron donors like alkyl carboxylates (vide infra), unsaturated or strained hydrocarbons, aromatic compounds, and many more. In this Account, we describe the use of photoinduced electron transfer (PET) to the carbonyl chromophore as the key step in synthesis. In subsequent steps, the radical anions formed thereof are either operating as secondary electron donors and initiating a photon-driven chain reaction or combining with electrophilic species and forming products. In both cases, these reactions are applied in the synthesis of nitrogen-containing natural target molecules. The basic structures of the target molecules are bicyclic tertiary amines from the pyrrolizidine and indolizidine families and from the group of aristolactams.

Target Structures. Pyrrolizidine alkaloids (PA) are secondary plant metabolites found in various geographical regions of the world. About 3% of the world's flowering plants contain toxic PA, the genera *Senecio*, *Crotalaria*, *Heliotropium*, and *Amsinckia* being the major sources.[5] These PA almost exclusively belong to the necines, having

Axel G. Griesbeck was born in 1958, received his Ph.D. from the University of Munich with Professor Klaus Gollnick, was postdoc with Waldemar Adam (Würzburg, Germany), Dieter Seebach (ETH Zürich, Switzerland), and Ernst Fischer (Rehovot, Israel), and is currently Professor at the University of Cologne. He is interested in multiple aspects of organic photochemistry with emphasis on spin phenomena, especially CH-activation, cycloaddition, photooxygenation, and decarboxylation reactions. He has coauthored 200 scientific publications and two textbooks on organic photochemistry (with Jochen Mattay).

Norbert Hoffmann was born in 1960 and received his Ph.D. from the Technical University (RWTH) of Aachen (Germany) with Hans-Dieter Scharf. He obtained a research position at CNRS (Chargé de Recherche) in Reims (France) and was appointed Directeur de Recherche at CNRS in 2004. His research interests are in the field of organic photochemistry: electron transfer, photoinduced radical reactions, cycloadditions of aromatic compounds, and application of these reactions to organic synthesis. Further research activities concern the use of renewable resources from agricultural origin for the production of fine chemicals and the synthesis of new organic semiconductor materials for microelectronics.

Klaus-Dieter Warzecha was born in 1962 and received his diploma from the University of Münster in 1988 for a study on the synthesis of naphthylisoquinoline alkaloids with Gerhard Bringmann. He performed his Ph.D. thesis in the research group of Martin Demuth at the Max Planck Institute of Bioinorganic Chemistry in Mülheim where he graduated in 2002 on photoinduced electron transfer domino cyclizations of steroid model systems. He is interested both in the synthetic applications of organic photochemistry and in time-resolved spectroscopy. Since 2003, he has been a research associate at the University of Cologne in the group of A. Griesbeck.

* To whom correspondence should be addressed.
† University of Cologne.
‡ CNRS, Université de Reims.

10.1021/ar068148w CCC: $37.00
Published on Web 01/27/2007

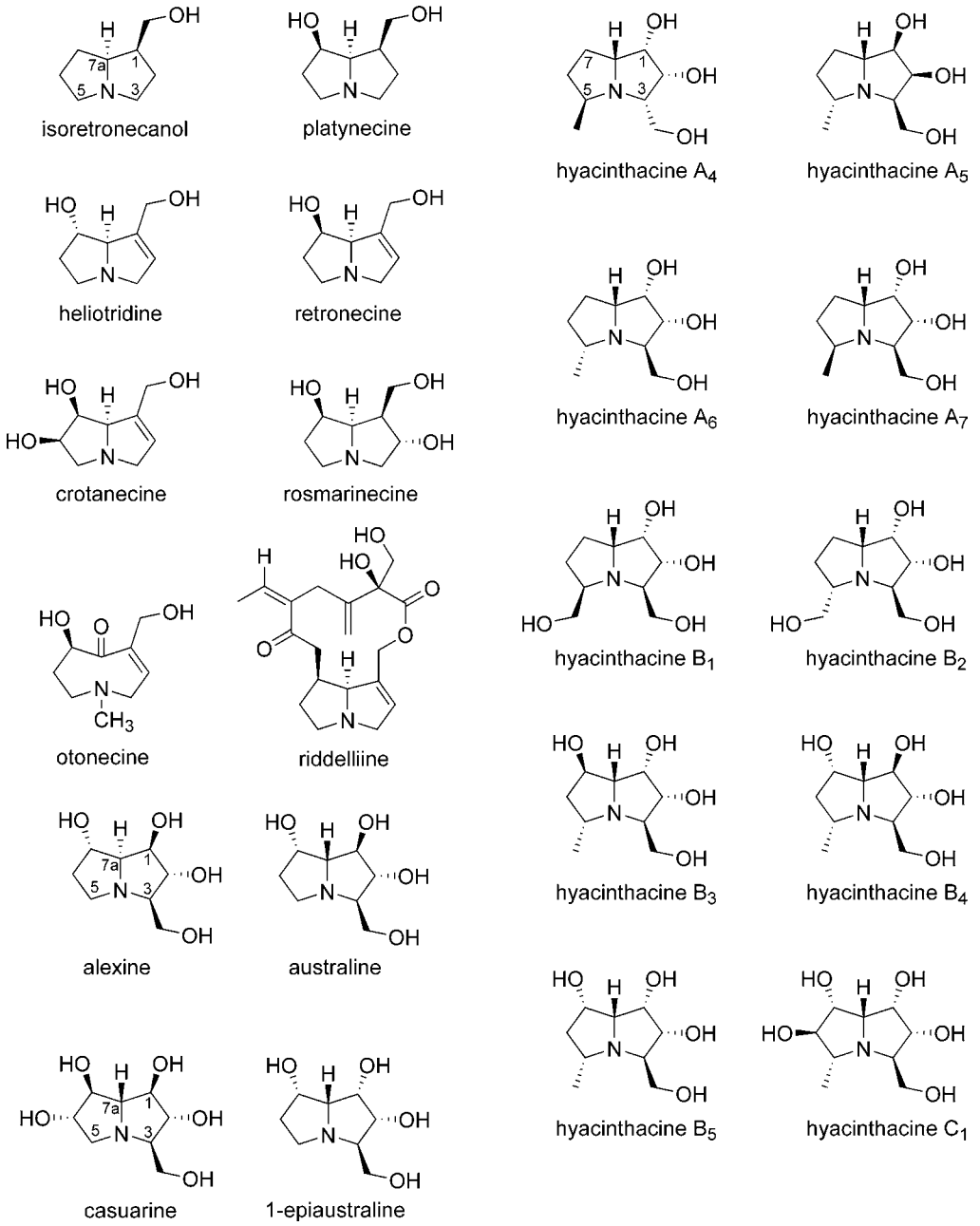


FIGURE 1. Naturally occurring pyrrolizidines.

a 1-hydroxymethyl substituent as the common structure element. Typical representatives of the necine group are isoretronecanol as well as monohydroxylated (e.g., platynecine, retronecine) and dihydroxylated (e.g., rosmarinecine, crotanecine) species and the open otonecine-type alkaloids and ansa-PA (e.g., riddelliine)[6] with a bridging substituent connecting the hydroxymethyl group at C1 and a hydroxyl group at C7. Necine-type PA, which play a role in the defense strategy of certain insects,[7] pose a health risk to grazing animals (livestock poisoning) and (via contaminated food and milk) to humans. They exhibit acute and chronic toxicity and genotoxicity and are proven to be cancerogenic. In 1988, australine,[8] the first representative of the so far unknown alexines, 3-hydroxymethyl PA, was isolated from the seeds of *Castanospermum australe*. Subsequent reports on the finding of several hyacinthacines[9] did not only prove that this new class of polyhydroxylated carbohydrate-mimetic pyrrolizidine alkaloids was less rare than believed but also showed that the alexines are potent glycosidase inhibitors with antiviral, anti-HIV, and anti-cancer properties.Indolizidine alkaloids[10] are typically associated with colorful "poison frogs", for the most part of the genera *Dendrobates*, *Epipedobates*, *Phyllobates*, and *Mantella*. Interestingly, dendrobatid frogs are not able to biosynthesize the alkaloids isolated from their skin but depend on a dietary of leaf-litter arthropods.[11] However, some species are capable to enantioselectively hydroxylate pumiliotoxins to the more toxic allopumiliotoxins,[12] thus achieving an enhanced antipredator protection. As in the case of the pyrrolizidines, carbohydrate-mimetic hydroxylated indolizidines have received particular interest because of

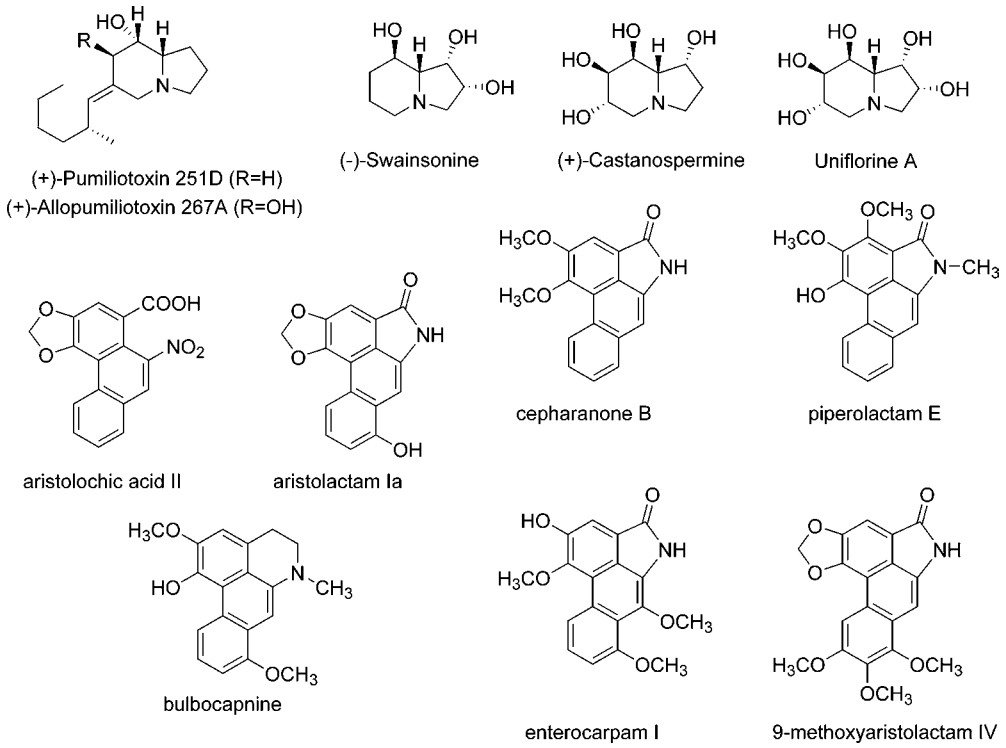


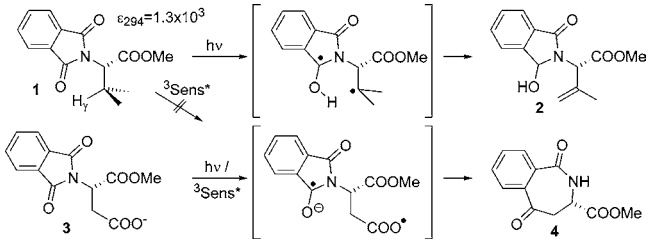
FIGURE 2. Naturally occurring indolizidines and phenanthrene lactams.

their pharmacological properties, for example, as antidiabetics and antiviral and anticancer agents as well as immunosuppressants in transplantation medicine.

Aristolactams[13] constitute a class of phenanthrene lactam alkaloids structurally and biologically related to aristolochic acids and aporphines. While the richest natural source of the aristolactams are plants of the *Aristolochia* genus, further representatives of this group of alkaloids have been isolated from *Piperaceae, Saururaceae*, and various genera of the *Annonaceae* family. The chemical variations among the natural aristolactams mostly involve hydroxy, methoxy, and methylendioxy substituents at different positions of the phenanthrene skeleton.

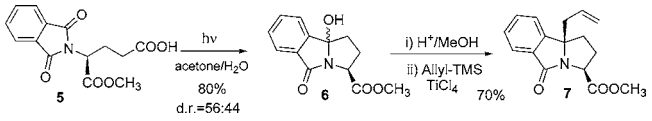
Phthalimide Photochemistry. Isoindoline-1,3-diones (phthalimides), easily available either via solvent-free condensation of phthalic anhydrides with amines or via coupling methods under less drastic conditions,[14] are versatile electron acceptors in PET reactions. N-Substituted phthalimides typically absorb in the 295 nm range with extinction coefficients around 10^3. The quantum yields for intersystem crossing Φ_{ISC} significantly change with the substitution on the imide nitrogen, for example, $\Phi_{ISC} = 0.5$ for *N*-isobutylphthalimide and $\Phi_{ISC} < 0.01$ for *N*-arylphthalimides.[15] Nevertheless, efficient population of the triplet state is possible by sensitization. With a triplet energy E_T of 293−300 kJ mol^{-1} and a ground-state reduction potential around $E^\circ = -1.85$ V versus Fc/Fc$^+$, electronically excited phthalimides are potent electron acceptors.[16] The rich photochemistry of this chromophore has recently been reviewed.[17,18] The intramolecular hydrogen abstraction is an archetype process for electronically excited carbonyl groups (Norrish-Type-II reaction).

Scheme 2. Photochemistry of Phthaloyl Derivatives of Valine and Aspartate

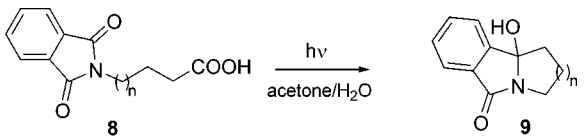


The 1,4-biradicals formed by γ-CH transfer can undergo several subsequent reactions, including secondary H transfer, cyclization, or fragmentation. Furthermore, the excited imido group is an efficient electron acceptor and can be reduced by numerous electron donors. These two routes are demonstrated for amino acid derivatives of phthalimides, for example, **1** and **3** from valine and aspartate.The photophysical and photochemical properties of the *N*-phthaloylvaline methyl ester **1** were studied by nanosecond laser flash photolysis ($\lambda_{exc} = 248$ or 308 nm).[19] The quantum yield of fluorescence is low ($\Phi_F = 10^{-2}$), whereas that of phosphorescence at −196 °C is large (0.5). Formation of singlet molecular oxygen ($^1\Delta_g$−$^1O_2$) was observed in several aerated solvents at room temperature with substantial quantum yields ($\Phi_\Delta = 0.47$ in acetonitrile). The triplet properties were examined at room temperature and in ethanol at low temperatures: triplet acetone, acetophenone, and xanthone in acetonitrile are quenched by **1** via energy transfer; the rate constant is almost diffusion-controlled and somewhat smaller for benzophenone. However, no products were formed when the spectroscopically observable π,π^* triplet state of **1** is generated with these sensitizers, while direct irradiation

Scheme 3. Photochemistry of *N*-Phthaloyl Methyl Glutamic Acid



Scheme 4. Decarboxylative Photomacrocyclization



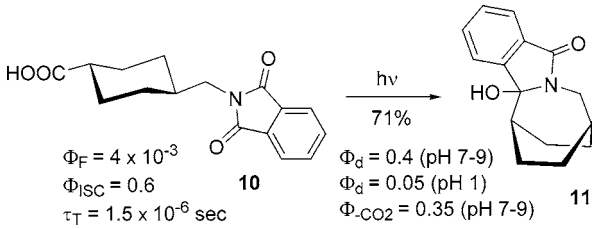
for n = 1-8: yields: 75, 89, 88, 78, 73, 81, 80, 72%

furnishes the isodehydrovaline derivative **2** with a quantum yield of 0.2, most likely via an n,π^* singlet or an upper excited n,π^* triplet pathway. In contrast, the aspartate derivative **3** gives the benzazepine-1,5-dione **4** in good yield both by direct excitation and by triplet sensitization. This ring enlargement most probably involves the formation of an intermediate hydroxyazetidine that converts to the seven-membered heterocycle. Following this first example of intramolecular photodecarboxylation, we have developed this route into a powerful tool.[20] Because of the plethora of ω-amino acids from the pool of natural compounds or available by synthetic methods, structurally diverse substrates can be easily converted into imides. The phthaloyl derivatives of α-amino acids undergo efficient photodecarboxylation resulting in the corresponding amines (for the exception methionine see later); β-amino acids are converted to benzazepines, and γ-amino acids are converted to benzopyrrolizidines. The glutamic acid derivative **5** resulted in the formation of a diastereomeric mixture of benzopyrrolizidinones **6** that were converted via acyliminium cation chemistry into the allylated pyrrolizidine **7** in diastereomerically pure form (with ee > 98%).[21]

Medium and large rings were obtained from higher ω-amino acids in good yields by the same protocol beside secondary reduction.[22] No apparent ring-size dependence was observed; even eight- and nine-membered rings were formed without a drop in efficiency via direct electron transfer or via sulfur-mediated electron transfer (vide infra).

Mechanism of Intra-Photodecarboxylation: *COO*$^-$ → *C*═O*. Bearing a diequatorial arrangement of the functional groups that can be converted into electron donor and acceptor functionalities, the antifibrinolytic tranexamic acid, available in high stereoisomeric purity, constitutes a versatile starting material for the investigation of intramolecular electron-transfer processes. In the chair conformation of the phthalimide derivative **10**, the donor−acceptor distance of about 7.5 Å prevents contact electron transfer. The photolysis of **10** in acetone/water mixtures gave the tetracyclic product **11** in high yields.The quantum yield of substrate decay ϕ_d depends on the pH of the reaction medium, demonstrating the relevance of the carboxylate anion as electron donor. The ϕ_d/pH correlation shows sigmodial behavior with an inversion point corresponding to the pK_a of the substrate. A time-resolved

Scheme 5. Photochemistry of the Tranexamic Acid Derivative 10



conductometry study was performed with **10** and other substrates.[23] In aqueous solutions at pH 8−11, the conductivity strongly increases within <1 μs after the laser pulse (20 ns) and then slowly decreases. The fast increase is due to the formation of the imide radical anion which is rapidly protonated and delivers OH^- which shows a distinct higher equivalent conductivity. Thus, CO_2 and OH^- are formed within the laser pulse. The absolute values for decarboxylation of **10** (ϕ = 0.35) were determined by using 2-naphthylglyoxylic acid as reference.

In Figure 3, the changes in UV-absorption are shown for the substrate **10**: the absorption at 300 ± 10 nm disappears and a new band in the 255 nm region appears (imide→amide conversion). The right box shows the pH-dependence of the decay quantum yields for several substrates: the tranexamic acid derivative **10** (circles) and three sulfur-substituted compounds **14** (triangle and squares). The moderate quantum yields (<0.12) that were determined for the latter compounds are due to the incorporation of an electron-transfer-mediating thioether

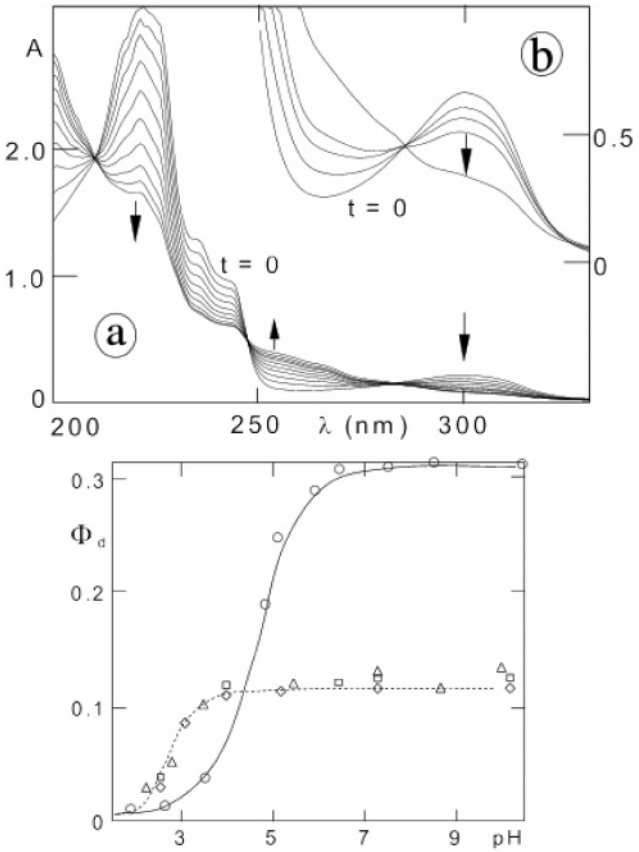
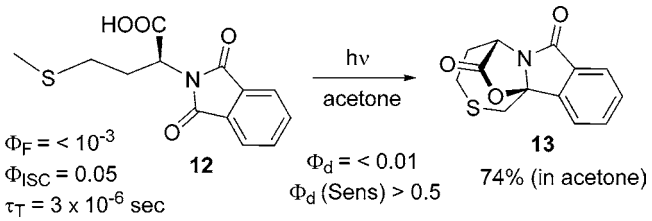
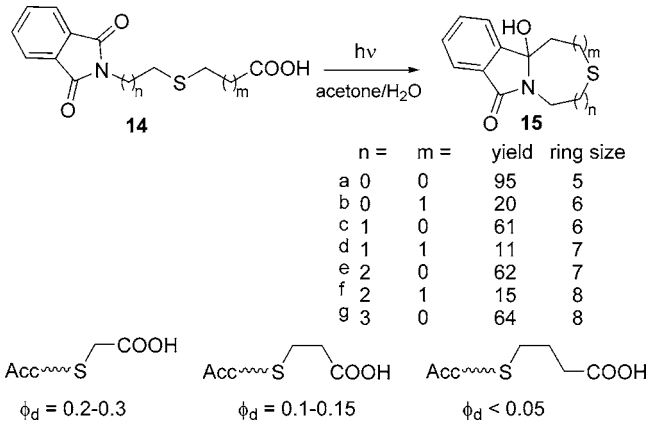


FIGURE 3. UV-absorption change for **10** (top) and pH-dependence of decay quantum yields.

Scheme 6. Photochemistry of the Methionine Derivative 12, Sulfur-Priented Electron Transfer



Scheme 7. Sulfur-Mediated Decarboxylative Photomacrocyclization



group that reduces the efficiency of carboxylate oxidation in comparison with an unperturbed acceptor−donor system.

***S*-Mediated Electron-Transfer Decarboxylation: $R_2S \rightarrow C{=}O^*$.** The concept of electron-transfer-initiated macrocyclization, originally developed by Kanaoka and coworkers[24] for thioalkyl-substituted phthalimides, follows the reaction principle described in Figure 1. We became interested in these processes when trying to develop a method for the synthesis of cyclopeptides from sulfur-containing oligopeptides. An obvious prerequisite for such a method is that other potential electron-donating substituents are unreactive under photochemical conditions. An illustrative negative example is the photocyclization of *N*-phthaloyl methionine (**12**) (Scheme 6). When irradiated in pure acetone, this compound gave the tetracyclic lactone **13** in high yields.[25] This reaction is unusual in the sense that photolysis of unprotected *N*-acyl amino acids normally leads to efficient α-decarboxylation. Thus, electron-transfer reactions involving thioalkyl groups can efficiently compete with carboxylate activation.

From the investigation of other sulfur-substituted ω-amino acids, it became clear that the linker separating the primary electron donor (Do^1, i.e., the thioether group) and the terminal donor (Do^2, i.e., the carboxylate) is crucial. In **12**, a three-carbon chain separates Do^1 and Do^2 in the thioalkylcarboxylates **14**, and two-carbon and one-carbon chains separate the two donor groups (Scheme 7). A distance dependence of the decarboxylation efficiency can be extracted from the data for 10 different sulfur-substituted substrates. This becomes also apparent from the yields of the photocyclization products indicating that for compounds with longer spacers between sulfur and the carboxylate anion, alternative photochemistry competes with or (in case of the methionine derivative **12**) completely supresses decarboxylation.

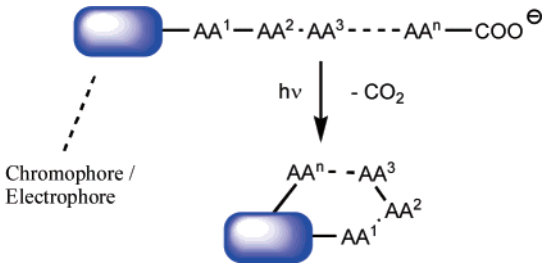


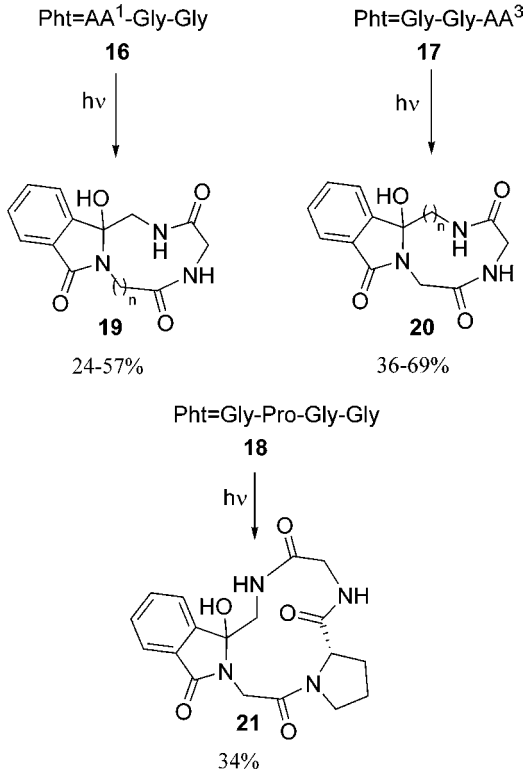
FIGURE 4. Photodecarboxylation/macrocyclization concept.

Synthesis of Cyclopeptides: $COO^- \rightarrow C{=}O^*$. Synthetic cyclic oligopeptides can depict reactive conformational motifs of bioactive oligopeptides[26] and are thus intensively investigated as peptidomimetica, as pharmaceutically active low molecular weight analogues,[27] or as artificial arrays with defined nanostructures.[28] The avenues to these target structures are numerous taking advantages of the highly developed techniques in peptide synthesis. Photochemical macrocyclizations constitute a relevant class of reactions which often are controlled by excited-state rather than ground-state properties.[29] From our studies on the intramolecular photodecarboxylation of ω-phthalimido alkyl carboxylates, this concept evolved as a route to macrocyclic products (Figure 4).

A series of C-unprotected di- and tripeptides activated by the N-terminal phthalimide functionality was investigated with the basic concept shown schematically for a cyclic peptide incorporating a tripeptide motif.[30] As primary spacers AA^1, unbranched ω-amino acids were applied with increasing $(CH_2)_n$ spacer lengths with $n = 1$, 2, 3, 5, 10, and 11. Initially, we suspected that a secondary amide is not applicable as primary functional group in the peptide tether because of the hydrogen-bonding hypothesis.[31] Photochemical reactivity was, however, observed for longer secondary spacer chains: the Gly-βAla couple gave the decarboxylation/hydrogen transfer product and longer amino acids as second components also restored the cyclization activity, for example, the Gly-Aca substrate gave the 10-membered product in 69%. Thus, hydrogen-bonding deactivation can be overwritten by using appropriate substitution pattern.

Another way to improve the photocyclization efficiency is to increase the chain lengths of the primary amino acid tether: whereas the βAla-Gly substrate gave only 24% of the corresponding 7-membered lactam, the βAla-βAla couple gave the 8-membered lactam already in 32% yield and the ϵAca-βAla substrate resulted in the 11-membered lactam in 55% yield (Scheme 8). The chain elongation concept proved to be also successful for tripeptide substrates: the photocyclization path was still active when longer amino acid spacers were used as the first (i.e., AA^1-Gly-Gly **16**) or third (i.e., Gly-Gly-AA^3 **17**) component. Elongating the primary linker chain stepwise increased the cyclization efficiacy from βAla ($m = 2$, 24%) to ϵAca ($m = 5$, 42%) and Auda ($m = 10$, 57%). Likewise, the glycine-linked tripeptides Pht = $GlyGlyAA^3$ became reactive for chain-elongated amino acids as the internal tethers.

Scheme 8. Synthesis of Medium-Sized Cyclopeptides by Photodecarboxylation

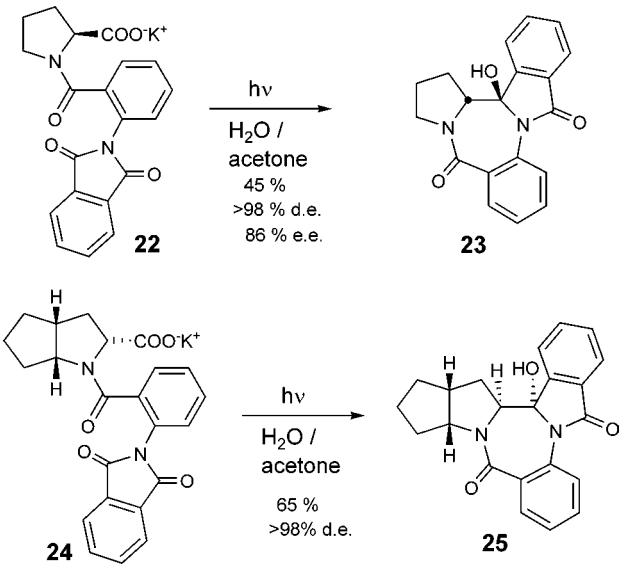


Diglycine-containing cyclopeptides are thus available in flexible chain modifications which appear important for the design of new β-turn mimetica.[32]

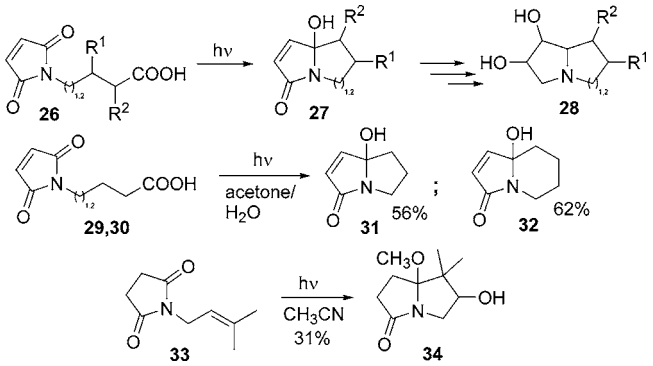
One step further in this protocol, the *N*-phthaloyl derivative of the tetrapeptide Gly-Pro-Gly-Gly (**18**) was synthesized by standard coupling procedures. The irradiation of this substrate resulted in the 12-membered cyclopeptide **21** in 34% yield. Whereas photosolvolysis or solvolysis in general resulted in a slight decrease in pH (because of the formation of a phthalamide acid), photocyclization went parallel with a strong increase in pH.[33] The latter effect is due to the charge shift from the carboxylate oxygen to give the alkoxide oxygen which leads to an increase in hydroxide concentration.

Photodecarboxylation with Memory of Chirality: Benzodiazepines. The concept of memory of chirality was originally defined by Fuji and Kawabata.[34] In the course of our investigations, we have detected the first example of high memory of chirality for a photochemical reaction which involves most probably a 1,7-triplet biradical. As a substrate, we used the proline-based acceptor−linker−donor couple **22** which, after electronic excitation and decarboxylation, cyclized to give the [1,4]-pyrrolobenzodiazepine **23** with 86% ee (Scheme 9).[35] This process serves as a new approach to these highly active DNA-alkylating reagents. The stereogenic center in **22** is planarized after CO_2 extrusion, but a remarkable high degree of chirality memory was retained. The simple diastereoselectivity of the radical combination process was very high (>98%) and only the cis-fused diastereoisomer was detected in the crude reaction mixture. With the stereolabeled substrate **24** derived from (all-R)-2-azabicyclooctanoate, the in-

Scheme 9. Memory of Chirality in *N*-Phthaloyl Anthranilic Acid Amide Photochemistry



Scheme 10. Synthesis of the Pyrrolizidine Skeleton by Photoinduced Electron Transfer

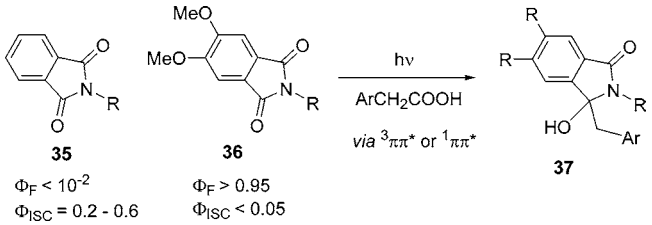


duced as well as the simple diastereoselectivity was remarkably high. From the X-ray structures of products **23** and **25** and from the comparison of their respective CD-exciton chirality behavior, it was concluded that the photodecarboxylation/cyclization had occurred with inversion of configuration at the stereogenic α-center. From a more detailed investigation of linker-extended substrates, it became clear that the bond formation step is not concerted with CO_2 extrusion, which is a prerequisite for a memory effect.[36]

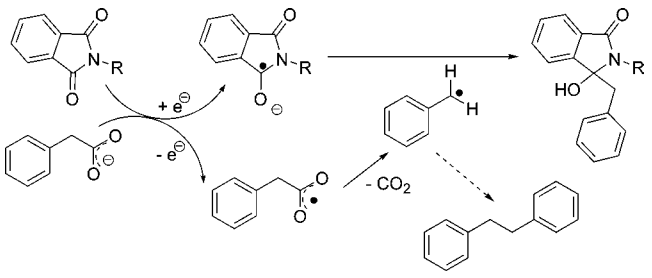
Synthetic Approaches to Pyrrolizidines, Indolizidines, and Aristolactam Precusors: $COO^- \rightarrow C{=}O^*$. Two different PET-based approaches toward the pyrrolizidine skeleton have been developed by us on the basis of donor-substituted imides. On the one hand, the intramolecular decarboxylative cyclization of suitably substituted ω-carboxyalkyl maleimides **26** both gives rise to pyrrolizidines and indolizidines **27** and allows the construction of the hydroxylation pattern in **28** by functionalization of the imide double bond (Scheme 10). The transformation of the parent substrates **29** and **30** resulted in the pyrrolizine **31** and the indolizidine **32** in good yields.

The second concept ties in with our previous research on the PET-induced functionalization and cyclization of

Scheme 11. Photobenzylation of Phthalimides and 4,5-Dimethoxyphthalimides



Scheme 12. Mechanism of the Photobenzylation and Homocoupling



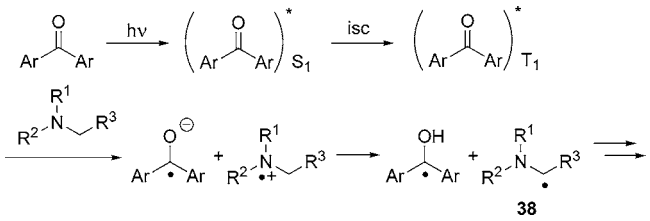
alkenes in the presence of nucleophiles.[37] Intramolecular photoinduced electron transfer from a trialkyl-substituted alkene **33** to the excited state of the succinimide chromophore followed by anti-Markovnikov addition of the nucleophilic solvent (methanol) and subsequent radical cyclization furnishes the pyrrolizidine **34** in moderate yield.

The nature of the excited state for intramolecular electron-transfer decarboxylation (vide supra) cannot be unambigously assigned (see before). This situation changes for the intermolecular version. In this case, only the lowest excited triplet of unsubstituted phthalimides is the reactive species. When, however, substituting the phthalimide by electron-donating groups, the lifetime of the first excited state increases and the fluorescence quantum yields approach unity (Scheme 11).[38] The addition of numerous alkyl carboxylates,[39] α-ketoalkylcarboxylates,[40] or α-heterosubstituted alkylcarboxylates[41] is possible when phthalimides are irradiated in the presence of slight excess of the corresponding carboxylate salts in aqueous media.

The irradiation of N-substituted phthalimides **35** in the presence of phenylacetic acid in aqueous acetone furnishes benzylated 3-hydroxyisoindolinones with yields in the 90% range. Likewise, the dimethoxy-substituted phthalimides **36** gave benzylation products **37** (R=OMe) and showed strong fluorescence quenching with electron-rich arylacetates.

With respect to the results from the laser flash photolysis and the preparative irradiations,[15] the following mechanism is conceivable: PET between the ^{3}A* state of the phthalimide and the phenylacetate yields the observable phthalimide radical anion and the acyloxy radical of the electron donor, that is, the oxidation takes place with the carboxylate as the electrophore (Scheme 12). The acyloxy radical thus formed instantaneously decarboxylates in a photo-Kolbe reaction to give a benzyl radical which eventually adds to the acceptor radical anion. In preparative photolyses (5−100 mM scale), a significant shortening of the irradiation times until complete conversion of the phthalimides was observed when replacing the parent phenylacetic acid with electron-rich methoxy-substituted derivatives. This improvement originates in a 1000-fold increase of the triplet quenching rates (i.e., the initial electron-transfer step) and reflects a fundamentally different mechanism under these conditions. With dimethoxy-substituted phenylacetates, the primary electron transfer no longer involves the carboxylate but takes place at the electron-rich (di)methoxyarene electrophore in a pseudo-photo-Kolbe process. Regardless the mechanistic details, the photodecarboxylative benzylation of phthalimides seemingly is compatible with a variety of substituents on the imide nitrogen as well with different methoxygenation patterns on the electron donor; in all cases examined, the reaction could be brought to full conversion and furnished the benzylation product with yields in the 90% range. The products thus obtained in a reaction that constitutes a clean alternative to the Grignard reaction are of quite some importance: elimination under acidic condition furnishes building blocks in the oxidative stilbene-phenanthrene cyclization on route to the aristolactam skeleton.

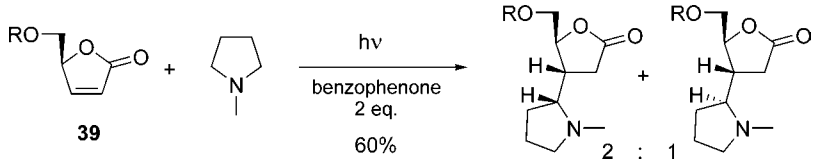
Scheme 13. Formation of α-Aminoalkyl Radicals via Photoinduced Electron Transfer



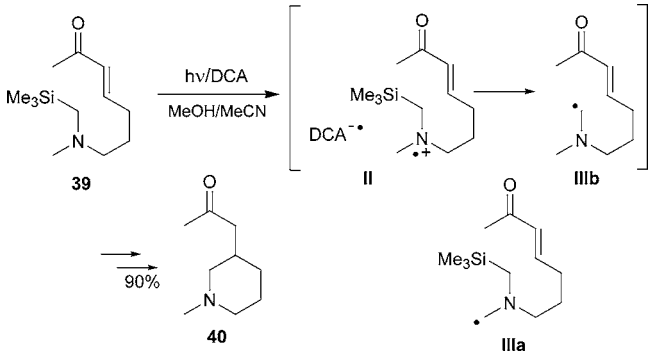
Electron-Transfer-Induced Radical Addition of Tertiary Amines to C=C Double Bonds: *R*$_3$*N* → *C*=O*. The addition of α-aminoalkyl radicals to alkenes constitutes a pivotal step in the synthesis of biologically active nitrogen-containing compounds. Photoinduced-electron-transfer oxidation of tertiary amines provides an elegant access to these radicals, since radical cations initially generated upon PET to an electronically excited redox sensitizer (acceptor), such as an aromatic ketone, undergo proton exchange with the acceptor radical anion to eventually yield a pair of neutral radicals. Nucleophilic α-aminoalkyl radicals **I** thus generated preferentially add to electron-deficient C=C double bonds, such as those in α,*β*-unsaturated lactones (Scheme 13). The only downside of the overall process, exemplified for the addition of *N*-methylpyrrolidine to α,*β*-unsaturated furanones **38** (Scheme 14), is the rather moderate yield (max 60%) with acetophenone or benzophenone as sensitizers.[42]

To overcome this drawback, two different approaches have been proposed. A series of studies address the reactivity of silylated tertiary amines. The basic concept underlying these experiments is that the radical cation desilylates more easily than deprotonates.[43] It was indeed found that a competition between deprotonation and desilylation exists.[44] In less polar aprotic solvents such as acetonitrile, deprotonation is favored leading to intermediate **IIIa** and silylated products are obtained. In the

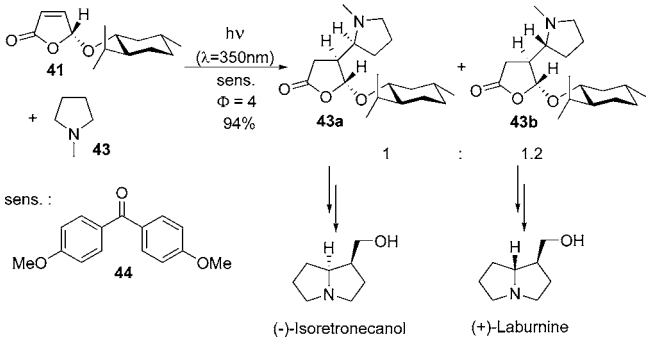
Scheme 14. Radical Addition of a Tertiary Amine to a Furanone Derivative via Photochemical Electron Transfer



Scheme 15. Intramolecular Radical Addition of Tertiary Amine Carrying a Silyl Leaving Group



Scheme 16. Efficient Radical Addition of *N*-Methylpyrrolidine 42 to Menthyloxyfuranone 41 with Electron-Donor-Substituted Aromatic Ketones as Sensitizer



presence of more polar, protic solvents such as methanol, desilylation dominates (Scheme 15). The strategy was successfully applied to intermolecular reactions such as in the transformation of **39**.[43] After formation of a radical ion pair **II** via photoinduced electron transfer, desilylation occurred and the α-aminoalkyl radical **IIIb** was generated. Efficient intramolecular addition of the nucleophilic radical to the electron-deficient double bond results in the piperidine derivative **40** in high yield. The silylalkyl-substituted tertiary amines were frequently used in the synthesis of nitrogen-containing heterocycles.[45]

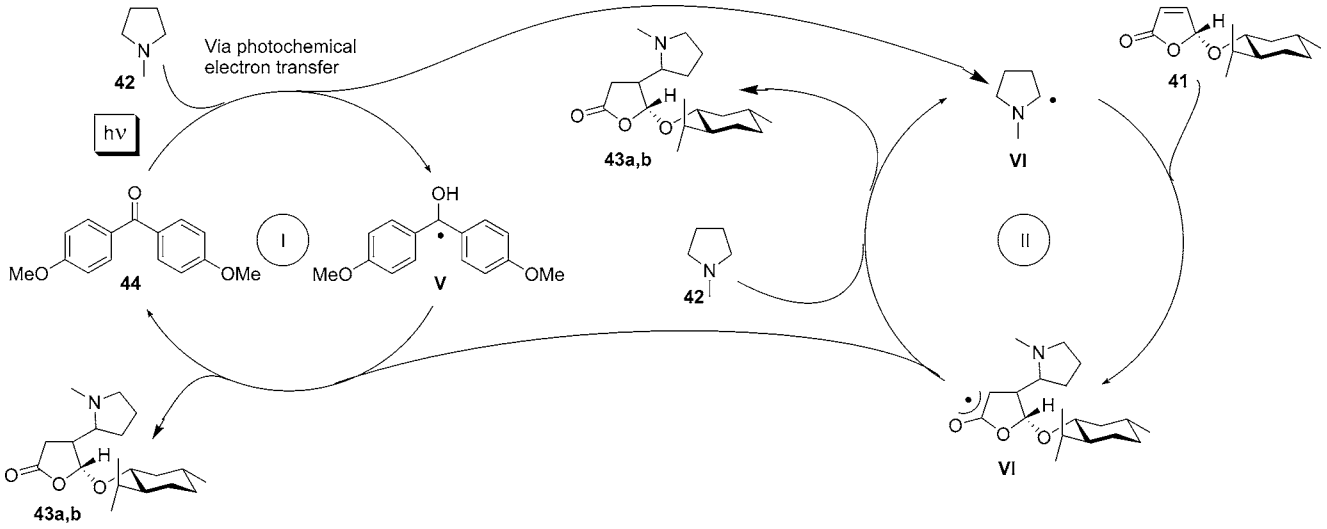
Another approach addresses the optimization of the sensitizer. A considerable improvement of the intermolecular reaction (compare Scheme 14) was observed when conventional sensitizers such as benzophenone or acetophenone were replaced by electron-donor-substituted aromatic ketones such as **44** (Scheme 16):[46] under these conditions, *N*-methylpyrrolidine **42** adds to menthyloxyfuranone **41** in high yields. The radical attack occurred stereoselectively anti with respect to the alkoxy substituent. The configuration of the stereogenic center in the α position of the nitrogen, however, was not controlled. Therefore, two diastereoisomers **43a**, **b** were obtained; in contrast to the conventional ones, the new sensitizers were only used in catalytic amounts and could be recovered up to 80% after the reaction. To explain these observations, the radical chain mechanism shown in Scheme 17 was proposed: in a photoinduced-electron-transfer process (compare Scheme 13), α-aminoalkyl **IV** and ketyl radicals **V** were generated. The nuclecophilic radical **IV** adds easily to the electron-deficient double bond of menthyloxyfuranone **41** leading to electrophilic oxoallyl radicals **VI**. The latter intermediates abstract a hydrogen atom from the tertiary amine to form the products **43a**, **b**. By this chain process, α-aminoalkyl radicals **IV** are formed. This radical chain process is rather inefficient since the product quantum yield is only 4. The termination step thus plays an important competitive role. The electrophilic oxoallyl radicals **VI** also react with the ketyl radicals **V** of the aromatic ketone **44**. By this route, additional product is formed and the sensitizer is regenerated, thus efficiently linking the starting and the termination step in a second efficient radical cycle; for a similar mechanism, see ref 47. The efficiency of the reaction can be rationalized by the fine-tuning of the various steps of a complex radical reaction. In these reactions, polarity effects alternate in the radical addition steps as well as in the hydrogen abstractions.[48] Nucleophilic radicals add to electron-deficient double bonds generating electrophilic radicals. The latter abstract hydrogen from an electron-rich reaction partner (amine) leading to nucleophilic radicals and so on.

The reaction was also performed on a large scale, for example, 15 g of the starting material **41** was transformed in 5 min of irradiation. The diastereoisomers were easily separated by chromatography and were transformed into the pyrrolizidine alkaloids (-)-isoretronecanol and (+)-laburnine. Different electron-deficient alkenes were successfully applied in the same way.

The reaction was particularly efficient with cyclic tertiary amines such as pyrrolidine derivatives **45** (Scheme 18, Table 1). The process always involved activation of the ring and not of the alkyl side chain. This was observed even for *N*-isopropylpyrrolidine (entry 3) where a thermodynamically more stable tertiary radical would be formed via hydrogen abstraction from the isopropyl substituent. This regioselectivity can be explained by the fact that deprotonation of the radical cations occurs under kinetic control[49] and is particularly fast when the bonding orbital of the corresponding C−H bond is orientated in a parallel way with respect to the single occupied orbital at the nitrogen (Figure 5). Apparently, such orientation is more easily established inside the heterocyclic ring.

When compared with reactions of conventional sensitizers such as benzophenone (Scheme 14) that involve

Scheme 17. Mechanism of the Photoinduced Radical Addition



Scheme 18. Efficient Radical Addition of Cyclic Tertiary Amines to Menthyloxyfuranone 41 via Photochemical Electron Transfer

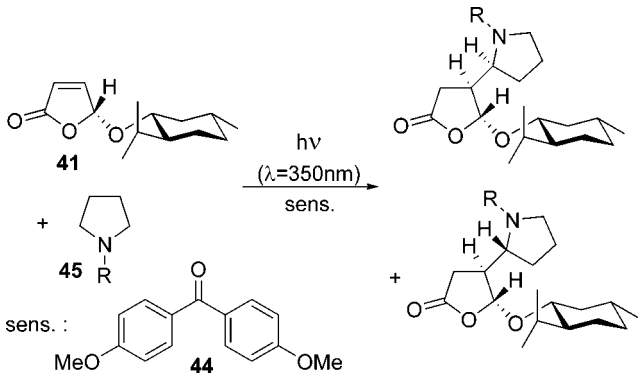


Table 1.

entry	R	irradiation time (min)[a]	isolated yield (%)
1	Me	5	94
2	Et	5	81
3	*i*-Pr	5	82
4	*t*-Bu	5	81
5	*t*-BuMe$_2$Si	12	77

[a] Solutions of **41** (0.5 mmol), the amine **45** (10 mmol), and **44** (0.05 mmol) in 25 mL acetonitrile were irradiated in a Rayonet photochemical reactor RPR200 (16 lamps, $\lambda = 350$ nm).

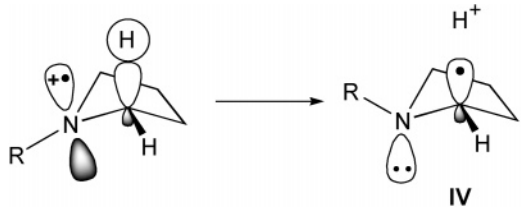
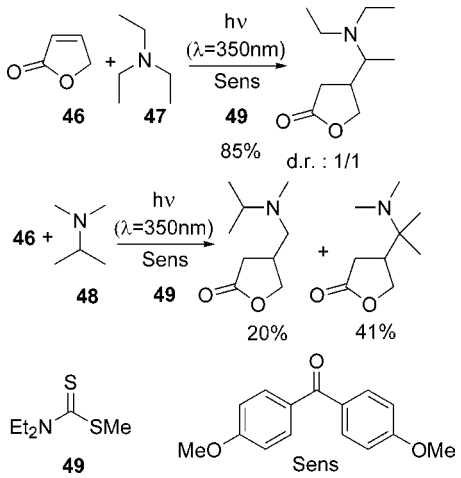


FIGURE 5. Transition state of the radical cation deprotonation of tertiary amines.

significant catalyst decomposition, one can conclude that the stability of the electron-donor-substituted ketyl radicals plays an important role. As it is well-established that electron-donor-substituted aromatic ketones such as 4,4′-dimethoxybenzophenone **44** possess T_1 states with $\pi\pi^*$ character, while the conventional sensitizers such as acetophenone or benzophenone have T_1 states with $n\pi^*$

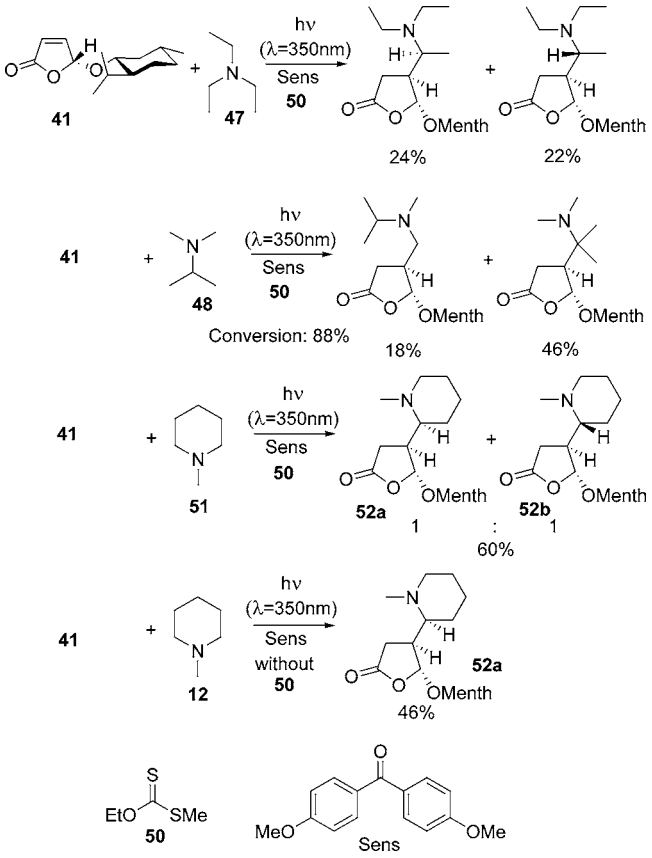
Scheme 19. Efficient Radical Addition of Acyclic Tertiary Amines in the Presence of the Dithiocarbonyl Derivative 49



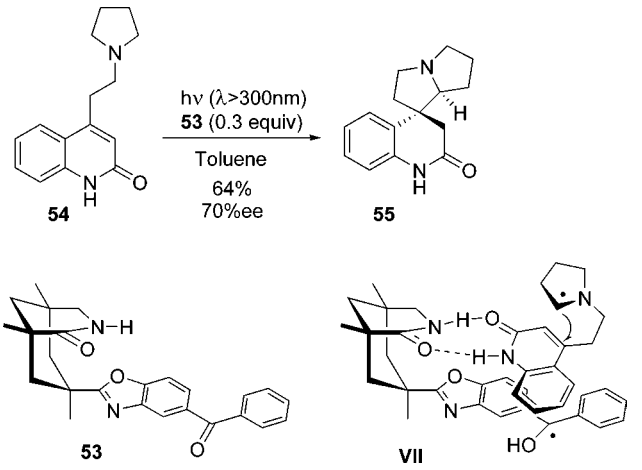
character, it was also probed whether photophysical properties such as triplet quenching are significantly altered.[50] However, this study revealed that the electron-donor-substituted aromatic ketones are not significantly different from the classical sensitizers such as benzophenone or acetophenone.[51] In particular, the triplet quenching rates were in the same order of magnitude. Further optimization of the structure of the sensitizer to improve the results of the reaction therefore appeared to be less promising.

Although the reaction was performed with numerous electron-deficient alkenes, the scope of the tertiary amines was rather limited. Mainly cyclic tertiary amines were successfully transformed, while acyclic tertiary amines such as triethylamine were generally less reactive. To extend the scope, the interplay of various radical intermediates involved in the mechanism was studied. The addition of thiocarbonyl compounds such as a thiocarbamate (e.g., **49**) or a xanthate accelerated significantly the transformation of various tertiary amines which otherwise were almost unreactive. Under these conditions, triethylamine **47** and dimethylisoproylamine **48** were successfully added to the furanone **46** (Scheme 19).[52] **48**

Scheme 20. Efficient Radical Addition of Tertiary Amines in the Presence of the Xanthate 50



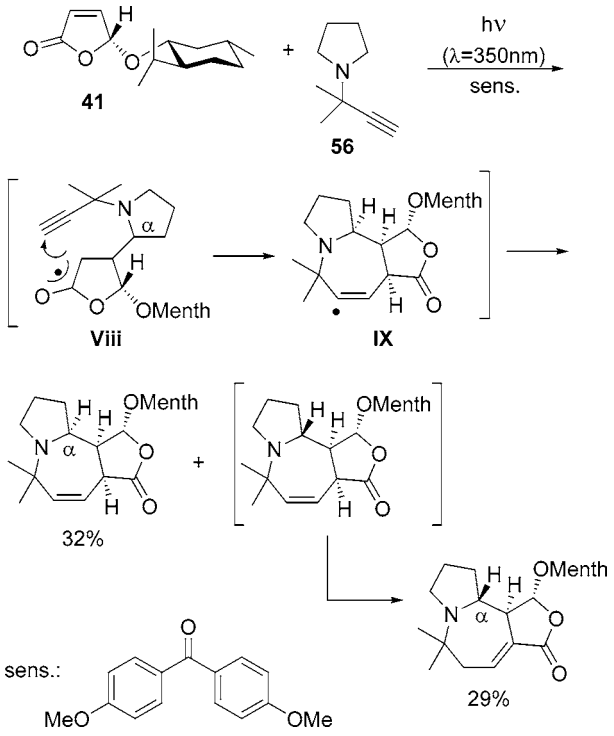
Scheme 21. Intramolecular Radical Addition of Tertiary Amines Using Enantioselective



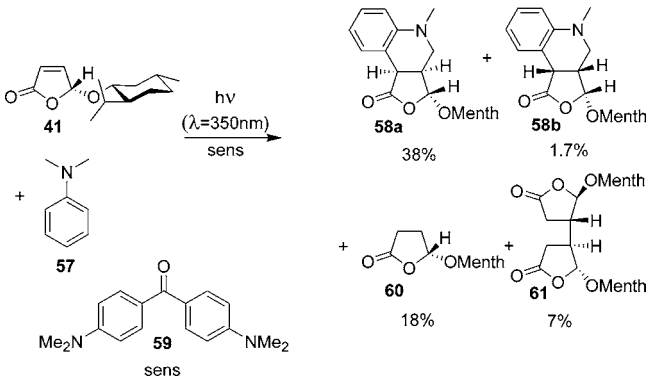
reacted preferentially at the isopropyl substituent which means that the thermodynamically more stable tertiary radical was added more easily. This observation is in contrast to previous results.[46,49] Detection of thiocarbamate-containing intermediates by mass spectrometry proved that the thiocarbonyl compound is capable of trapping radical intermediates. Such trapping steps play also an important role in the radical addition of xanthates to alkenes.[53]

The corresponding transformations with the more complex furanone **41** could not be performed since decomposition of the products occurred during workup.

Scheme 22. Photochemically Induced Radical Tandem Addition Cyclization Reaction with Unsaturated Amines



Scheme 23. Photochemically Induced Radical Tandem Addition Cyclization Reaction with the Aromatic Amine 57

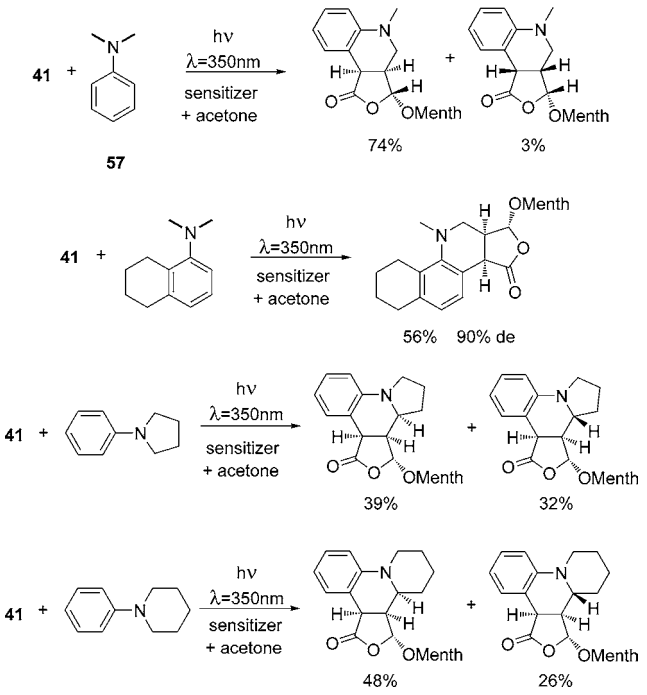


Therefore, the xanthate **50** was used in this case. In the case of *N*-methylpiperidine **51**, two diasteroismers **52a**, **b** were obtained (Scheme 20). In absence of the xanthate, only one diastereoisomer **52a** was isolated.

Recently, Bach et al. have attached the same type of sensitizers to a chiral derivative of Kemps acid (**56**) (Scheme 21).[54] The system was used to induce the intramolecular radical addition of tertiary amines with electron-deficient double bonds in analogy to the intermolecular reaction with transformation of the quinolinone derivative **54** into the spirocyclic compound **55**. Chirality is induced in a catalytic way via complexation of the substrate (**VII**). The aromatic ketone acts as sensitizer and shielding group.

Electron-Transfer-Induced Radical Tandem Addition/Cyclization Reactions of Tertiary Amines: $R_3N \rightarrow C{=}O^*$. Using the same electron-donor-substituted aromatic ketones as sensitizer, more complex reactions such as radical

Scheme 24. Application of the Radical Tandem Addition Cyclization Reaction with Aromatic Amines to the Asymmetric Synthesis of Nitrogen-Containing Heterocycles



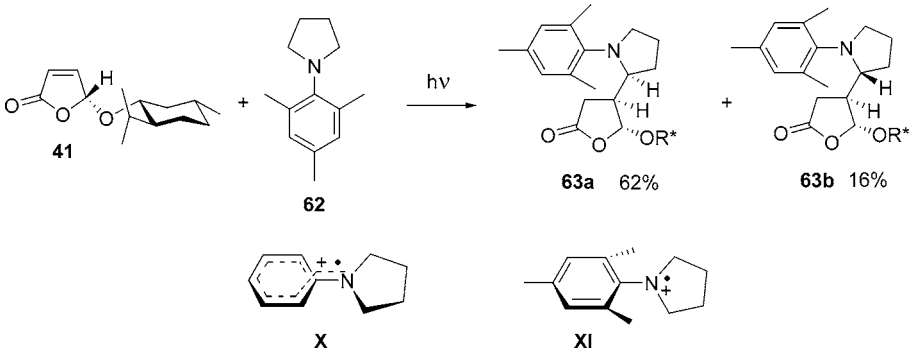
tandem addition/cyclization reactions have been performed. In this way, the pyrrolidine derivative **56** was added to menthyloxyfuranone **41** (Scheme 22).[55] α-Aminoalkyl radicals are generated via photochemical electron transfer at the ring (compare with Scheme 13), and these intermediates add to **41** leading to oxoallyl radicals **VIII**. Intramolecular radical addition to the alkyne bond took place exclusively in an endo cyclization way (**IX**). As in the previous cases, the radical attack is highly stereoselective anti with respect to the menthyloxy substituent, however, the configuration of the α position of the nitrogen could not be controlled. Under the reaction conditions, one of the stereoisomers underwent double-bond isomerization. Both exo and endo cyclizations were observed in the reaction with a corresponding alkene derivative.

An interesting tandem addition cyclization reaction was also observed with aromatic tertiary amines. When the reaction was performed with *N,N*-dimethylaniline **57**, tetrahydroquinoline derivatives such as **58a**, **b** were obtained with about 90% diastereoselectivity (Scheme 23).[55,56] In this case, Michler's ketone **59** was used as sensitizer and the yields were rather low with considerable formation of reduction side products **60** and **61**.

Isotopic-labeling experiments revealed that the partial reduction of the furanone **41** is connected to a rearomatization step which leads to the final products **58a**, **b**. In this step, a hydrogen atom is transferred onto **41**. The partial reduction of **41** could be completely suppressed when ketones such as acetone as mild oxidant were added to the reaction mixture. Under these conditions, the yields of the desired tetrahydroquinoline derivatives were doubled and the reaction was applied to the synthesis of a variety of nitrogen-containing heterocycles (Scheme 24). A similar transformation was also observed as a side reaction in a photochemical electron-transfer reaction between α,β-unsaturated ketones and *N,N*-dimethylaniline.[57] In this case, the main reaction results from combination of the corresponding radical ion pair.

An interesting observation was made with an aniline derivative possessing substituents in both ortho positions (**62**) (Scheme 25).[55] In this case, no cyclization occurred and the two diastereoisomeric adducts **63a**, **b** were isolated. As in previous cases, only the configuration of the stereogenic center in the α position of the nitrogen was not completely controlled. However, in the present case, this diastereoselectivity was improved with respect to earlier cases. Qualitatively, this observation can be attributed to the highly steric encumbrance of the mesityl substituent in **62**. Generally, under the same reaction conditions, tandem addition cyclizations are significantly slower than the simple addition reactions. Conversion was completed after several hours of irradiation while addition reactions only need up to 10 min. The diminished reactivity of simple aniline derivatives is certainly linked to the mesomeric stabilization of the radical cation intermediate **X**. In the corresponding intermediate **XI**, such a delocalization is not possible. For steric reasons, the SOMO of the radical cation is orientated in an orthogonal manner with respect to the π system of the aromatic ring. Therefore, the reaction of compound **62** resembles to that one of *N*-alkylpyrrolidine derivatives.

Scheme 25. Radical Addition of the *N*-Mesitylpyrrolidine 62



Conclusions

Photoinduced-electron-transfer reactions have found highly useful applications for organic synthesis as demonstrated for several prime examples. In this Account, we have shown that, starting mostly from simple substrates, electronically excited carbonyl components are able to oxidize amines, thioethers, and carboxylates generating radical ion pairs that can undergo a multitude of secondary reactions resulting in highly interesting nitrogen-containing heterocycles. Various ways of stereocontrol (classic auxiliary based chiral induction, memory of chirality, or enantioselective catalysis) have been applied.

We are grateful for support form the CNRS, the Ministère de l'Education Nationale de l'Enseignement Supérieur et de la Recherche, the Région Champagne-Ardenne, and Syngenta Crop Protection AG. Our research activities in this field were also funded by the CNRS and the Deutsche Forschungsgemeinschaft in the context of bilateral French−German projects. The contributions by our co-workers over the last 10 years that are mentioned in the references are gratefully acknowledged.

References

(1) Marcus, R. A. Electron Transfer Reactions − Theory and Experiment (Nobel Lecture) *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1111−1121.
(2) Griesbeck, A. G.; Mattay, J. Synthetic Organic Photochemistry, *Mol. Supramol. Photochem.* **2005**, *14*, 1−9.
(3) Kavarnos, G. J. Fundamental Concepts of Photoinduced Electron-Transfer. *Top. Curr. Chem.* **1990**, *156*, 21−58.
(4) Rehm, D.; Weller, A. H. Kinetics and Mechanism of Electron Transfer During Fluorescence Quenching in Acetonitrile. *Ber. Bunsen-Ges. Phys. Chem.* **1969**, *73*, 834−839.
(5) Fu, P. P.; Xia, Q.; Lin, G.; Chou, M. W. Genotoxic Pyrrolizidine Alkaloids − Mechanisms Leading to DNA Adduct Formation and Tumorigenicity. *Int. J. Mol. Sci.* **2002**, *3,* 948−964.
(6) Adams, R.; van Duuren, B. L. Riddelliine, the alkaloid from *Senecio riddellii*. II. The Structure of Riddellic Acid and the Total Structure of Riddelliine. *J. Am. Chem. Soc.* **1953**, *75*, 4638−4642.
(7) Bezzerides, A.; Yong, T.; Bezzerides, J.; Husseini, J.; Ladau, J.; Eisner, M.; Eisner, T. Plant-derived Pyrrolizidine Alkaloid Protects Eggs of a Moth (*Utetheisa ornatrix)* Against a Parasitoid Wasp (Trichogramma ostriniae). *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9029−9032.
(8) Molyneux, R. J.; Benson, M.; Wong, R. Y. Australine, A Novel Pyrrolizidine Alkaloid Glycosidase Inhibitor from *Castanospermum Australe*. *J. Nat. Prod.* **1988**, *5*, 1198−1206.
(9) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. New Polyhydroxylated Pyrrolidine, Piperidine, and Pyrrolizidine Alkaloids from *Scilla sibirica*. *J. Nat. Prod.* **2002**, *65,* 1875−1881.
(10) Michael, J. P. Indolizidine and quinolizidine alkaloids. *Nat. Prod. Rep.* **2005**, *22*, 603−626
(11) Clark, V. C.; Raxworthy, C. J.; Rakotomalala, V.; Sierwald, P.; Fisher, B. L. Convergent Evolution of Chemical Defense in Poison Frogs and Arthropod Prey Between Madagascar and the Neotropics. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11617−11622.
(12) Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Clark, V. C.; Ma, J.; Ziffer, H.; Cover, J. F. Evidence for an Enantioselective Pumiliotoxin 7-hydroxylase in Dendrobatid Poison Frogs of the Genus Dendrobates. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 11092−11097.
(13) Kumar, V.; Poonam Prasad, A. K.; Parmar, V. S. Naturally Occuring Aristolactams, Aristolochic Acids and Dioxoaporphines and Their Biological Activities. *Nat. Prod. Rep.* **2003**, *20*, 565−583.
(14) Casimir, J. R.; Guichard, G.; Briand, J.-P. Methyl 2-((Succinimidooxy)carbonyl)benzoate (MSB): A New, Efficient Reagent for *N*-Phthaloylation of Amino Acid and Peptide Derivatives. *J. Org. Chem.* **2002**, *67*, 3764−3768.
(15) Warzecha, K.-D.; Görner, H.; Griesbeck, A. G. Photoinduced Decarboxylative Benzylation of Phthalimide Triplets with Phenylacetates. *J. Phys. Chem. A* **2006**, *110*, 3356−3363.
(16) Wintgens, V.; Valat, P.; Kossanyi, J; Biczok, L.; Demeter, A.; Bérces, T. Spectroscopic Properties of Aromatic Dicarboximides. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 411−421.
(17) Yoon, U. C.; Mariano, P. S. The Synthetic Potential of Phthalimide SET Photochemistry. *Acc. Chem. Res.* **2001**, *34*, 523−532.
(18) Griesbeck, A. G.; Kramer, W.; Oelgemöller, M. New Tools in Organic Synthesis: PET-Decarboxylation: Scope and Limitations. *Synlett* **1999**, 1169−1178.
(19) Griesbeck, A. G.; Görner, H. Laser Flash Photolysis Study of N-alkyated Phthalimides. *J. Photochem. Photobiol., A* **1999**, *129*, 111−119.
(20) Griesbeck, A. G.; Henz, A.; Peters, K.; Peters, E.-M.; von Schnering, H. G. Photo Electron Transfer Induced Macrocyclization of N-Phthaloyl ω-Amino Carboxylic Acids. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 474−476.
(21) Griesbeck, A. G.; Nerowski, F.; Lex, J. Decarboxylative Photocyclization: Synthesis of Benzopyrrolizidines and Subsequent Transformations. *J. Org. Chem.* **1999**, *64*, 5213−5217.
(22) Griesbeck, A. G.; Henz, A.; Kramer, W.; Lex, J.; Nerowski, F.; Oelgemöller, M.; Peters, K.; Peters, E.-M. Synthesis of Medium- and Large-Ring Compounds Initiated by Photochemical Decarboxylation of ω-Phthalimido Alkylcarboxylates. *Helv. Chim. Acta* **1997**, *80*, 912−933.
(23) Görner, H.; Oelgemöller, M.; Griesbeck, A. G. Photodecarboxylation Study of Carboxy-Substituted N-Alkylphthalimides in Aqueous Solution. *J. Phys. Chem. A* **2002**, *106*, 1458−1467.
(24) Hatanaka, Y.; Sato, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Kanaoka, Y. Photochemistry of the Phthalimide System. Photoinduced Reactions. Regioselective Remote Photocyclization − Examples of a Photochemical Macrocyclic Synthesis with Sulfide-Containing Phthalimides. *Liebigs Ann. Chem.* **1992**, 1113−1123.
(25) Griesbeck, A. G.; Mauder, H.; Müller, I.; Peters, K.; Peters, E.-M.; von Schnering, H. G. Photochemistry of N-Phthaloyl Derivatives of Methionine. *Tetrahedron Lett.* **1993**, *34*, 453−456.
(26) Rizo, J.; Gierasch, L. M. Constrained Peptides − Models of Bioactive Peptides and Protein Substructures. *Ann. Rev. Biochem.* **1992**, *61*, 387−418.
(27) For example, the RGD-containing cyclopeptides: Thumshirn, G.; Hersel, U.; Goodman, S. L.; Kessler, H. Multimeric Cyclic RGD Peptides as Potential Tools for Tumor Targeting: Solid-phase Peptide Synthesis and Chemoselective Oxime Ligation. *Chem.—Eur. J.* **2003**, *9*, 2717−2725.
(28) Fernandez-Lopez, S.; Kim, H. S.; Choi, E. C.; Delgado, M.; Granja, J. R.; Khasanov, A.; Kraehenbuehl, K.; Long, G.; Weinberger, D. A.; Wilcoxen, K. M.; Ghadiri, M. R. Antibacterial Agents Based on the Cyclic D,L-alpha-peptide Architecture. *Nature* **2001**, *414*, 329−329.
(29) Griesbeck, A. G.; Henz, A.; Hirt, J. Photochemical Syntheses of Macrocycles. *Synthesis* **1996**, 1261−1276.
(30) Griesbeck, A. G.; Heinrich, T.; Oelgemöller, M.; Molis, A.; Lex, J. A Photochemical Route to Cyclopeptides with a Minimum of Activation and Protection Chemistry. *J. Am. Chem. Soc.* **2002**, *124*, 10972−10973.
(31) Oelgemöller, M.; Griesbeck, A. G.; Lex, J.; Haeuseler, A.; Schmittel, M.; Niki, M.; Hesek, D.; Inoue, Y. Structural, CV- and IR-Spectroscopic Evidences for Preorientation in PET-Active Phthalimido Carboxylic Acids. *Org. Lett.* **2001**, *3*, 1593−1596.
(32) See, for example: MacDonald, M.; Velde, D. V.; Aubé, J. Synthesis and Conformation of Gly-Gly Dipeptides Constrained with Phenylalanine-like Aminocaproic Acid Linkers. *Org. Lett.* **2000**, *2*, 1653−1655.
(33) Griesbeck, A. G.; Heinrich, T.; Oelgemöller, M.; Heidtmann, A.; Molis, A. Synthesis of Cyclic Peptides and Pseudopeptides by Photochemical Decarboxylation of ω-Phthalimido Peptides in Aqueous Solution. *Helv. Chim. Acta* **2002**, *85*, 4561−4578.
(34) Fuji, K.; Kawabata, T. Memory of Chirality − A new Principle in Enolate Chemistry. *Chem.—Eur. J.* **1998**, *4*, 373−376.
(35) Griesbeck, A. G.; Kramer, W.; Lex, J. Memory of Chirality in Triplet 1,7-biradicals: Diastereo- and Enantioselective Synthesis of Pyrrolo[1,4]-benzodiazepines by Decarboxylative Photocyclization of Anthranilic Acid Building Blocks. *Angew. Chem., Int. Ed.* **2001**, *40*, 577−579.
(36) Griesbeck, A. G.; Kramer, W.; Bartoschek, A.; Schmickler, H. Photocyclization of 2-Azabicyclo[3.3.0]octane-3-carboxylate Derivatives: Induced and Non-Induced Diastereoselectivity. *Org. Lett.* **2001**, *3*, 537−539.
(37) Warzecha, K.-D.; Görner, H.; Demuth, M. Photoinduced Electron Transfer from Isoprenoid Polyalkene Acetates to Dicyanoarenes. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 1701−1706.
(38) Griesbeck, A. G.; Schieffer, S. Intra- and Intermolecular Fluorescence Quenching of N-Activated 4,5-Dimethoxyphthalimides by Sulfides, Amines, and Alkylcarboxylates. *Photochem. Photobiol. Sci.* **2003**, *2*, 113−117.
(39) Griesbeck, A. G.; Oelgemöller, M. Photodecarboxylative Addition of Carboxylates and α-Keto Carboxylates to Phthalimides. *Synlett* **1999**, 492−494.

(40) Griesbeck, A. G.; Oelgemöller, M.; Lex, J. Photodecarboxylative Additions of α-Keto Carboxylates to Phthalimides: Alkylation, Acylation and Ring Expansion. *Synlett* **2000**, 1455−1457.
(41) Griesbeck, A. G.; Oelgemöller, M. Decarboxylative Photoaddition of Heteroatom-substituted Carboxylates to Phthalimides. *Synlett* **2000**, 71−72.
(42) Santiago de Alvarenga, E.; Mann, J. Photocatalyzed Addition of Pyrrolidines to Butenolides: a Concise Synthesis of the Pyrrolizidine Alkaloid Ring System. *J. Chem. Soc. Perkin Trans I* **1993**, 2141−2142.
(43) Yoon, U. C.; Mariano, P. S. Mechanistic and Synthesis Aspects of Amine-Enone Single Electron Transfer Photochemistry. *Acc. Chem. Res.* **1992**, *25*, 233−240.
(44) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. Dynamics of α-CH Deprotonation and α-Desilylation Reactions of Tertiary Amine Cation Radicals. *J. Am. Chem. Soc.* **1994**, *116*, 4211−4220.
(45) Jeon, Y. T.; Lee, C.-P.; Mariano, P. S. Radical Cyclization Reactions of α-Silyl Amine α,β-Unsaturated Ketone and Ester Systems Promoted by Single Electron Transfer Photosensitization. *J. Am. Chem. Soc.* **1991**, *113*, 8847−8863.
(46) Bertrand, S.; Hoffmann, N.; Pete, J. P. Highly Efficient and Stereoselective Radical Addition of Tertiary Amines to Electron Deficient Alkenes. Application to the Enantioselective Synthesis of Necine Bases. *Eur. J. Org. Chem.* **2000**, 2227−2238.
(47) Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. Synthesis of Mono Protected 1,4-diketones by Photoinduced Alkylation of Enones with 2-substituted 1,3-dioxolanes. *Tetrahedron* **2001**, *57*, 10319−10328.
(48) For polarity contributions in hydrogen abstractions: Roberts, B. Polarity-reversal Catalysis of Hydrogen-atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25−35.
(49) Lewis, F. D. Proton-Transfer Reactions for Photogenerated Radical Ion Pairs. *Acc. Chem. Res.* **1986**, *19*, 401−405.
(50) Cohen, S. G.; Parola, A.; Parsons, G. H., Jr. Photoreduction by Amines. *Chem. Rev.* **1973**, *73*, 141−161.
(51) Hoffmann, N.; Görner, H. Photoinduced Electron Transfer from N-methylpyrrolidine to Ketones and Radical Addition to an Electron-Deficient Alkene. *Chem. Phys. Lett.* **2004**, *383*, 451−455.
(52) Harakat, D.; Pesch, J.; Marinkovic, S.; Hoffmann, N. Thiocarbonyl Compounds as Regulating Reagent in the Radical Addition of Tertiary Amines with Alkenes Using Photoelectron Transfer Conditions. *Org. Biomol. Chem.* **2006**, *4*, 1202−1205.
(53) Zard, S. Z. On the Trail of Xanthates: Some New Chemistry from an Old Functional Group. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672−685.
(54) Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. Catalytic Enantioselective Reactions Driven by Photoinduced Electron Transfer. *Nature* **2005**, *436*, 1139−1140.
(55) Bertrand, S.; Hoffmann, N.; Humbel, S.; Pete, J. P. Diastereoselective Tandem Addition-Cyclization Reactions of Unsaturated Tertiary Amines Initiated by Photochemical Electron Tansfer (PET). *J. Org. Chem.* **2000**, *65*, 8690−8703.
(56) Marinkovic, S.; Brulé, C.; Hoffmann, N.; Prost, E.; Nuzillard, J. M.; Bulach, V. Origin of Chiral Induction in Radical Reactions with the Diastereoisomers (5R)- and (5S)-5-(l)-Menthyloxyfuran-2[5H]-one. *J. Org. Chem.* **2004**, *69*, 1646−1651.
(57) Zhang, X.-M.; Mariano, P. S. Mechanistic Details for SET-Promoted Photoadditions of Amines to Conjugated Enones Arising from Studies of Aniline-Cyclohexenone Photoreactions. *J. Org. Chem.* **1991**, *56*, 1655−1660.

AR068148W