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Studies Leading to the Development of a Single-Electron Transfer (SET) Photochemical Strategy for Syntheses of Macrocyclic Polyethers, Polythioethers, and Polyamides

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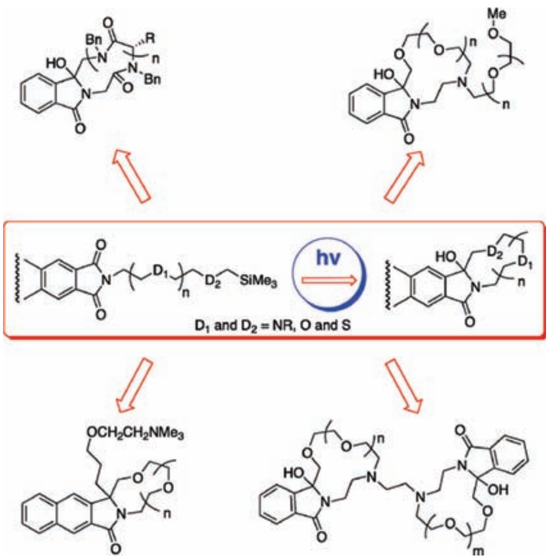
CONSPECTUS



Organic photochemists began to recognize in the 1970s that a new mechanistic pathway involving excited-state single-electron transfer (SET) could be used to drive unique photochemical reactions. Arnold's seminal studies demonstrated that SET photochemical reactions proceed by way of ion radical intermediates, the properties of which govern the nature of the ensuing reaction pathways. Thus, in contrast to classical photochemical reactions, SET-promoted excited-state processes are controlled by the nature and rates of secondary reactions of intermediate ion radicals. In this Account, we discuss our work in harnessing SET pathways for photochemical synthesis, focusing on the successful production of macrocyclic polyethers, polythioethers, and polyamides.

One major thrust of our studies in SET photochemistry has been to develop new, efficient reactions that can be used for the preparation of important natural and non-natural substances. Our efforts with α-silyl donor-tethered phthalimides and naphthalimides have led to the discovery of efficient photochemical processes in which excited-state SET is followed by regioselective formation of carbon-centered radicals. The radical formation takes place through nucleophile-assisted desilylation of intermediate α-silyl-substituted ether-, thioether-, amine-, and amide-centered cation radicals.

Early laser flash photolysis studies demonstrated that the rates of methanol- and water-promoted bimolecular desilylations of cation radicals (derived from α-silyl electron donors) exceeded the rates of other cation radical α-fragmentation processes, such as α-deprotonation. In addition, mechanistic analyses of a variety of SET-promoted photocyclization reactions of α-silyl polydonor-linked phthalimides and naphthalimides showed that the chemical and quantum efficiencies of the processes are highly dependent on the lengths and types of the chains connecting the imide acceptor and α-silyl electron donor centers. We also observed that reaction efficiencies are controlled by the rates of desilylation at the α-silyl donor cation radical moieties in intermediate zwitterionic biradicals that are formed by either direct excited-state intramolecular SET or by SET between the donor sites in the intervening chains.

It is important to note that knowledge about how these factors govern product yields, regiochemical selectivities, and quantum efficiencies was crucial for the design of synthetically useful photochemical reactions of linked polydonor—acceptor substrates. The fruits of these insights are exemplified by synthetic applications in the concise preparation of cyclic peptide mimics, crown ethers and their lariat- and bis-analogs, and substances that serve as fluorescence sensors for important heavy metal cations.

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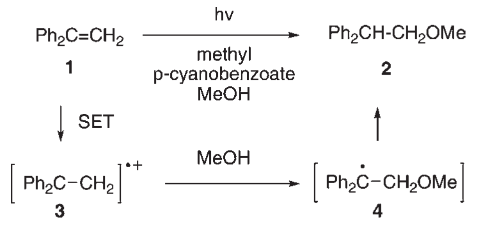
Phthalimide Single-Electron Transfer Photochemistry

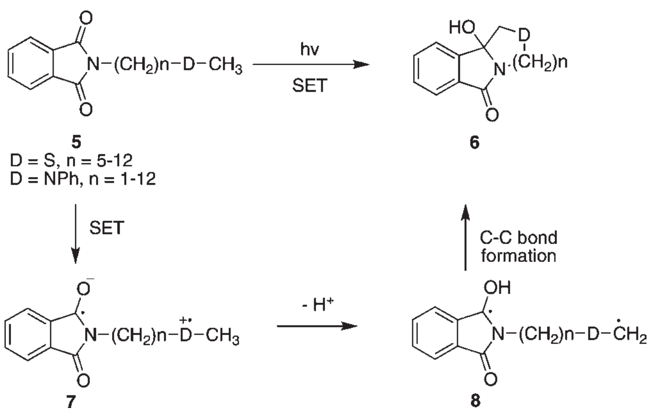
Beginning in the 1970s, a number of organic photochemists recognized that a new mechanistic pathway involving excited-state single-electron transfer (SET) could be used to drive unique photochemical reactions.[1] The seminal studies in this area by Arnold demonstrated that SET-promoted photochemical reactions proceed by way of ion radical intermediates whose properties govern the nature of reaction pathways followed. The novel transformation of 1,1-diphenylethylene (**1**) to the corresponding ether **2**[2] under SET-photosensitized reaction conditions (Scheme 1) stimulated the interest of a wide range of mechanistic and synthetic organic chemists.

Early studies by Kanaoka[3] and Coyle[4] showed that phthalimides participate in a number of different types of interesting SET-photochemical reactions. As a consequence of high singlet and triplet excited-state reduction potentials ($E_1^{S1}(-) = 2.3$ V; $E_1^{T1}(-) = 1.6$ V), these substances participate in SET-promoted excited-state reactions when paired with appropriate electron donors. Early investigations with linked phthalimide−thioethers[5] and −amines[6,7] (**5**, Scheme 2) showed that when phthalimide excited states are partnered with donors that have oxidation potentials less than ca. 2.3 V, SET takes place more rapidly than typical photoinduced H-atom abstraction processes.[8,9] Zwitterionic biradical intermediates **7** produced in the SET pathways were observed to undergo proton transfer to form biradical precursors of heterocyclic products **6**. Thus, even though the consequences of H-atom abstraction and SET pathways are similar, the regiochemical outcomes of the latter reactions are governed by the location of electron donor sites rather than the relative positions of hydrogen and the phthalimide carbonyl oxygen.

SCHEME 1



SCHEME 2



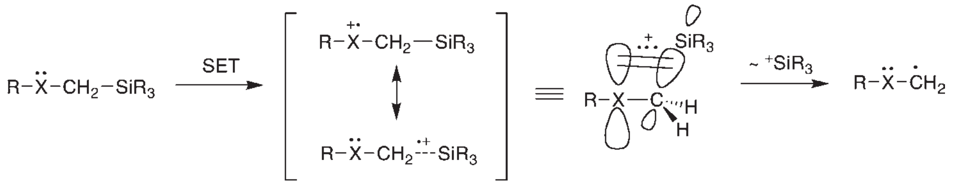
Organosilane Electron Donor in SET Photochemistry

In contrast to classical photochemical reactions, SET-promoted excited-state processes are controlled by the nature and rates of secondary reactions of intermediate ion radicals. Secondary reactions open to cation radicals formed by one-electron oxidation of n-electron donors include α-deprotonation, α-decarboxylation, α-retro-aldol fragmentation, and α-desilylation. Among the electron donors probed to date, α-trialkylsilyl substituted n-electron donors have several notable features that make them highly useful in the design of SET photochemical reactions. First, substances in this family are readily oxidized by SET to acceptor excited states owing to their low oxidation potentials arising from cation radical stabilization by overlap of high energy σ_{C-Si} orbitals and the half-filled p-orbitals at donor sites in the cation radicals (Scheme 3).[10−13] Moreover, the σ_{C-Si-p} orbital overlap weakens the C−Si bond and makes the Si center highly electropositive. Consequently, these cation radicals undergo fast desilylation reactions in the presence of silophiles to form carbon-centered radicals.

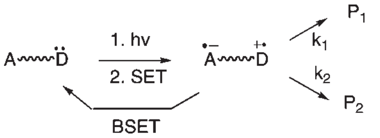
Information about the dynamics of cation radical fragmentation reactions is crucial for the design of novel and efficient SET photochemical processes. The importance of the rates of these processes is demonstrated by using an intramolecular photoinduced SET reaction of a hypothetical linked acceptor−donor substrate (Scheme 4). It can be seen by viewing this process that the rates of two competing cation radical reactions (k_1 and k_2) open to the intermediate zwitterionic biradical govern both the yields of products P_1 and P_2 ($\%P_1/\%P_2 \propto k_1/k_2$) and the quantum efficiency ($\Phi \propto [(k_1 + k_2)/(k_1 + k_2 + k_{BSET})]$). In the latter instance, the competition between reaction of the intermediate zwitterionic biradical and its decay by back-SET (BSET) influences the quantum yield, which is a measure of the efficiency for utilization of photons in bringing about reaction.

Laser flash photolysis (LFP) investigations carried out in our laboratories provided data that show that desilylation

SCHEME 3



SCHEME 4

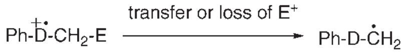


reactions of donor-derived cation radicals take place at higher rates than deprotonation (Scheme 5).[14,15] For example, methanol-promoted desilylation of α-silylanilinium **13** and the related amide **14** cation radicals have bimolecular rate constants as high as 6×10^7 M^{-1} s^{-1} in contrast to deprotonation (e.g., for **9**). In addition, Baciocchi[16] observed that the bimolecular rate constant for methanol-induced desilylation of the α-silylthioanisole cation radical **15** is 3.5×10^6 M^{-1} s^{-1}. In addition, the rates of heterolytic cleavage of the C–Si bond in radical cations derived from structurally similar α-silyl-substituted electron donors depend upon the stabilities of the charged radicals reflected in oxidation potentials of the corresponding electron donors. Thus, the rates for nucleophile-assisted desilylation of cation radicals arising by SET oxidation of the related donors fall in the order $ROCH_2SiMe_3 \approx RNMsCH_2SiMe_3 > RNAcCH_2SiMe_3 > RSCH_2SiMe_3$.

Owing to the properties of α-trialkylsilyl-substituted n-electron donor-derived cation radicals, it is possible to design substrates that will undergo sequential SET–α-desilylation to furnish radicals or biradicals in a highly regioselective fashion. This conclusion is demonstrated by the results of early investigations probing SET photochemical reactions of substrates containing linked α-silylamine donors and ketone acceptors (Scheme 6).[17,18]

α-Decarboxylation of n-electron donor-derived cation radicals is also a very rapid process (see **10** and **11** in Scheme 5), a property that has been employed in the design of photochemical reactions that rely on sequential SET–decarboxylation pathways. One of several interesting examples of this chemistry, coming from studies by Griesbeck,[19–22] is found in the efficient formation of tricyclic thioethers **17** promoted by irradiation of the α-thiocarboxylate-tethered phthalimides **16** (Scheme 7).[23]

SCHEME 5



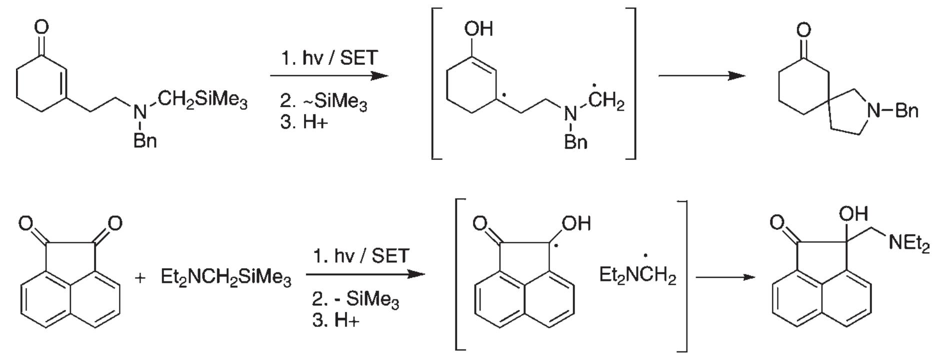
9 (D = NMe, E = H, TBAA/MeCN, 2.0×10^5 $M^{-1}s^{-1}$)
10 (D = NMe, E = CO_2NnBu_4, MeCN, 1.7×10^6 s^{-1})
11 (D = NAc, E = CO_2NnBu_4, MeCN, 3.6×10^7 s^{-1})
12 (D = NMe, E = CH_2CH_2OH, TBAA/MeCN, 4.4×10^4 $M^{-1}s^{-1}$)
13 (D = NMe, E = $SiMe_3$, MeOH/MeCN, 7.5×10^5 $M^{-1}s^{-1}$)
14 (D = NAc, E = $SiMe_3$, MeOH/MeCN, 6.0×10^7 $M^{-1}s^{-1}$)
15 (D = S, E = $SiMe_3$, MeOH/MeCN, 3.5×10^6 $M^{-1}s^{-1}$)

α-Silyl Monodonor-Linked Phthalimides

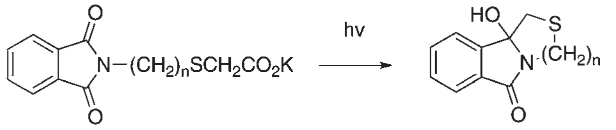
Preliminary information about the factors governing the efficiencies of SET-promoted reactions of linked acceptor–donor systems arose from an investigation of the SET photochemistry of tethered monodonor phthalimide substrates.[15,24,25] The results of this study provided information about how the fragmentation rates of zwitterionic biradicals, generated by intramolecular excited-state SET, influence the nature and efficiencies of reactions. In these reactions, SET from amine, amide, ether, and thioether donor sites to the phthalimide excited states produces zwitterionic biradicals **27**, which undergo proton transfer, methanol-promoted desilylation, or decarboxylation to form biradicals **28**, which serve as precursors of cyclic amidol products **26** (Scheme 8). Importantly, high chemical and quantum efficiencies are observed for reactions of substrates that contain α-silyl- and α-carboxy-substituted N, O, and S donors. For example, in contrast to the inefficient reactions of simple amine- and amide-tethered substrates **18** and **19**, photocyclizations of the silyl- and carboxylate-containing phthalimides **21–23** proceed with high chemical or quantum yields. In addition, reactions of the analogous α-silylether- and α-thioether-tethered phthalimides **24** and **25** take place efficiently to generate bicyclic amidols **26**.

In the photocyclization reactions displayed in Scheme 8, loss of an electrofugal group from the intermediate zwitterionic biradicals **27** should compete with energy-wasting BSET. Thus, as the results show, photoreactions of substrates that proceed via zwitterionic biradical intermediates that have the capability of undergoing fast desililylation or decarboxylation have the largest quantum yields.

SCHEME 6

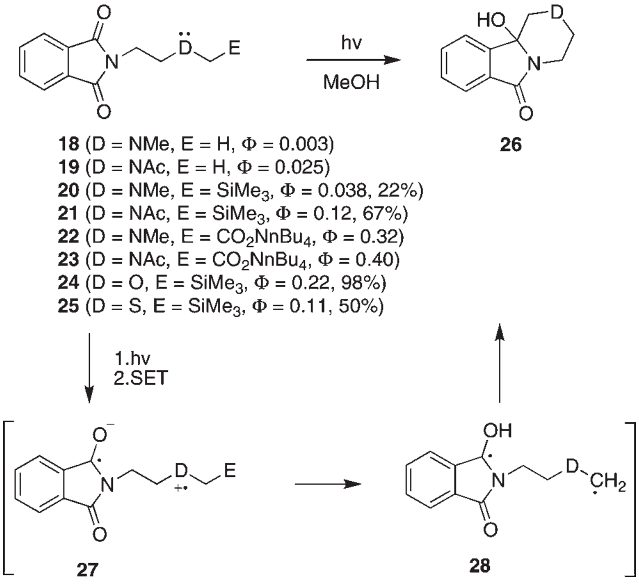


SCHEME 7



16 **17**

SCHEME 8



26 **27** **28**

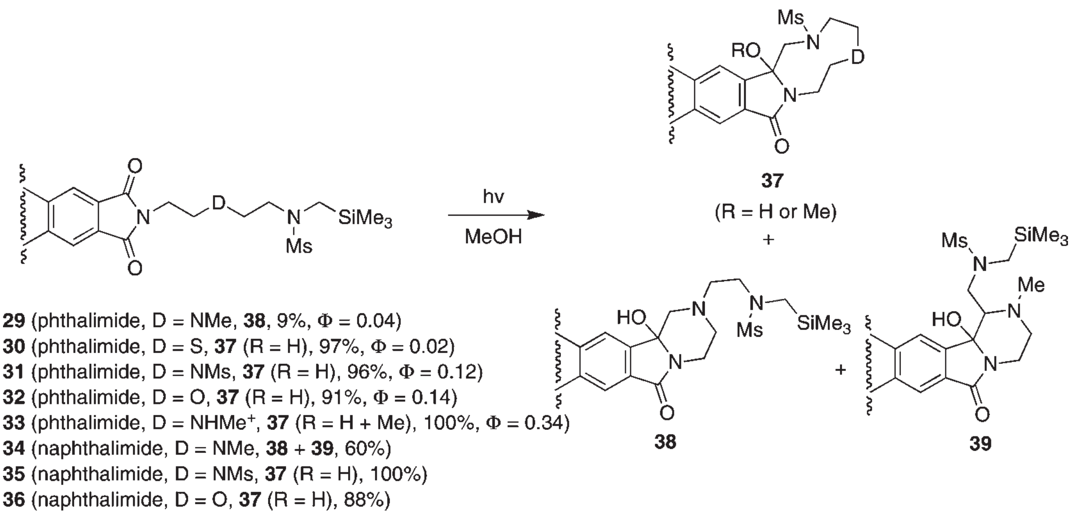
18 (D = NMe, E = H, Φ = 0.003)
19 (D = NAc, E = H, Φ = 0.025)
20 (D = NMe, E = SiMe$_3$, Φ = 0.038, 22%)
21 (D = NAc, E = SiMe$_3$, Φ = 0.12, 67%)
22 (D = NMe, E = CO$_2$NnBu$_4$, Φ = 0.32)
23 (D = NAc, E = CO$_2$NnBu$_4$, Φ = 0.40)
24 (D = O, E = SiMe$_3$, Φ = 0.22, 98%)
25 (D = S, E = SiMe$_3$, Φ = 0.11, 50%)

α-Silyl Bis-donor-Linked Phthalimides

Our studies with bis-donor-tethered phthalimides provided further information about the factors that govern the efficiencies of SET-promoted photocyclization reactions.[26] The goal of this effort was to elucidate how the nature of second donors, located in the chain separating the α-silyl-substituted donor and phthalimide reaction centers would influence the nature and chemical and quantum efficiencies of SET-promoted photocyclization reactions. We believed that this information would be key to the design of photocyclization reactions that can be employed in the preparation of poly-electron-donor containing macrocyclic ring systems. For this purpose, the photochemistry of systems containing a common terminal α-silyl donor group (NMsCH$_2$SiMe$_3$) and internal donor sites that have varying oxidation potential and that contain only α-hydrogens was explored (Scheme 9). Several interesting trends were observed. First, phthalimides and naphthalimides that contain other heteroatom donor sites with slightly higher or nearly equal oxidation potentials (e.g., O, NMs) compared with the terminal α-silylsulfonamide undergo efficient and highly regioselective photocyclization reactions via sequential SET−desilylation pathways. Second, substrates that possess N−Me (e.g., **29** and **34**) internal donors with greatly lower oxidation potentials than the α-silylsulfonamide group undergo low yielding, unselective, and quantum-inefficient photoreactions. In these cases, the major reaction pathway involves α-proton transfer from the internal tertiary aminium radical center in the initially formed zwitterioninc biradical followed by biradical cyclization or disproportionation. However, the unselective photoreactions of the tertiary amine containing substrates can be made efficient and highly regioselective by irradiation in acidic solutions where the amine groups are protonated. Third, the findings showed that the thioether-containing phthalimide−sulfonamide **30** is an intermediate case where chemically efficient photocyclization takes place in a quantum-inefficient manner.

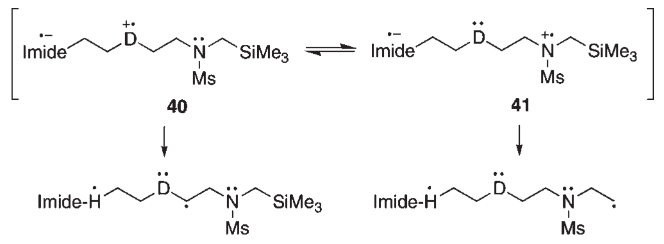
The trends observed in this effort can be best understood by considering the fates of competitively formed and rapidly interconverting pairs of zwitterionic biradicals, **40** and **41** (Scheme 10), generated by either initial or intrachain SET. One factor contributing to the efficiencies and regioselectivities of these photocyclization reactions is the intrinsic rates of α-heterolytic fragmentation processes ($\sim SiMe_3^+ > \sim H^+$) that can occur at each cation radical site. A second factor is the relative energies of the zwitterionic biradical intermediates, which control not only the final populations

SCHEME 9

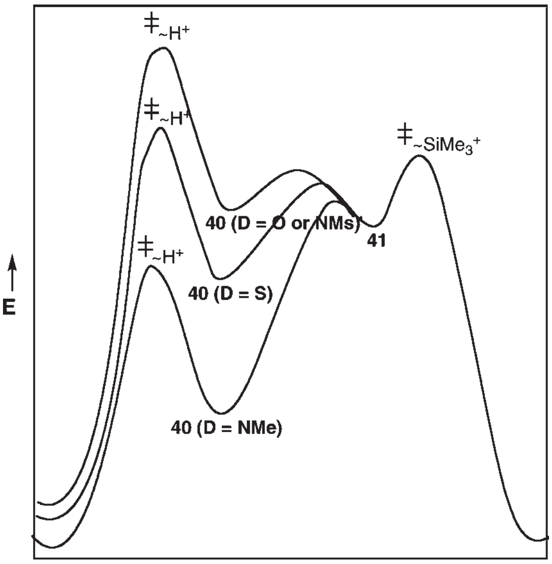


29 (phthalimide, D = NMe, **38**, 9%, Φ = 0.04)
30 (phthalimide, D = S, **37** (R = H), 97%, Φ = 0.02)
31 (phthalimide, D = NMs, **37** (R = H), 96%, Φ = 0.12)
32 (phthalimide, D = O, **37** (R = H), 91%, Φ = 0.14)
33 (phthalimide, D = NHMe$^+$, **37** (R = H + Me), 100%, Φ = 0.34)
34 (naphthalimide, D = NMe, **38** + **39**, 60%)
35 (naphthalimide, D = NMs, **37** (R = H), 100%)
36 (naphthalimide, D = O, **37** (R = H), 88%)

SCHEME 10



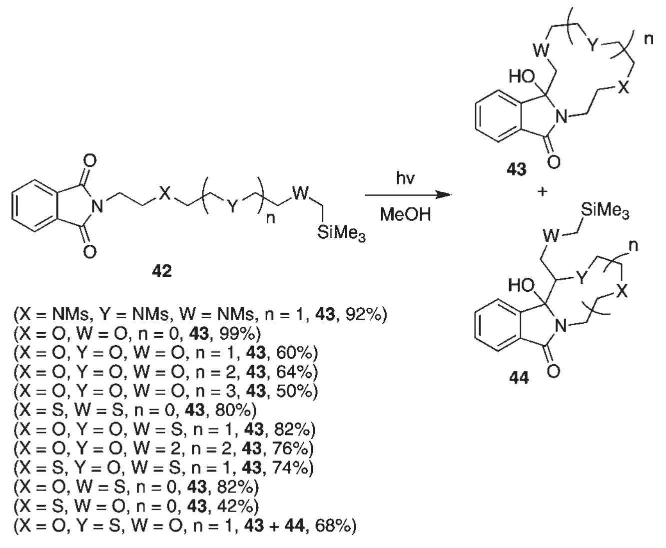
SCHEME 11



of **40** and **41** but also the energy barriers for the competing α-heterolytic fragmentation processes. Consequently, fast desilylation at α-silylsulfonamide sites of zwitterionic biradicals **41** dominates reactions of competitively formed, near equal or higher energy zwitterionic biradicals **40**, which can only undergo slow α-deprotonation. However, when the internal zwitterionic biradicals **40** have significantly lower energies, α-deprotonation pathways can predominate.

A pictorial representation of the energies involved in reactions of zwitterionic biradicals derived from bis-donor-substituted phthalimides is given in Scheme 11. The assignments of relative energies of the zwitterionic biradicals in this diagram are made based on the known oxidation potentials of α-silylmethansufonamides and simple methansulfonamide, thioethers, ethers, and tertiary amines.[25,27−30] The relative intrinsic barriers for competing desilylation and deprotonation reactions are estimated by using the kinetic data obtained for these processes using simple model systems (see, for example, Scheme 5). Thus, three distinctive situations exist in the reactions probed in this effort. In one case (exemplified by **31**−**33**), reactions proceed by way of near equal energy zwitterionic biradicals that have greatly different rates of α-fragmentation. Here, reactions occur with high yields and quantum efficiencies to yield products arising by the sequential SET−desilylation pathway. The other extreme corresponds to the process in which the less reactive internal zwitterionic biradical is of much lower energy (exemplified by **29**). In this situation, the barrier for desilylation is insurmountably high and, thus inefficient reaction takes place by a deprotonation pathway. Finally, an intermediate case exists (**30**) in which the barrier for desilylation is lower than that for deprotonation but is lower than that for BSET. Here, regioselective reaction takes place in high chemical yield but low quantum efficiency.

SCHEME 12



(X = NMs, Y = NMs, W = NMs, n = 1, **43**, 92%)
(X = O, W = O, n = 0, **43**, 99%)
(X = O, Y = O, W = O, n = 1, **43**, 60%)
(X = O, Y = O, W = O, n = 2, **43**, 64%)
(X = O, Y = O, W = O, n = 3, **43**, 50%)
(X = S, W = S, n = 0, **43**, 80%)
(X = O, Y = O, W = S, n = 1, **43**, 82%)
(X = O, Y = O, W = 2, n = 2, **43**, 76%)
(X = S, Y = O, W = S, n = 1, **43**, 74%)
(X = O, W = S, n = 0, **43**, 82%)
(X = S, W = O, n = 0, **43**, 42%)
(X = O, Y = S, W = O, n = 1, **43** + **44**, 68%)

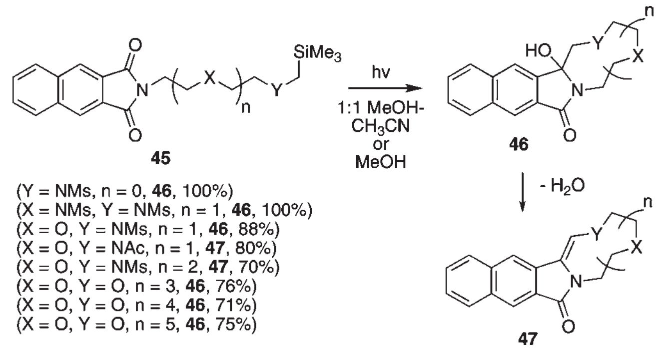
α-Silyl Polydonor-Linked Phthalimides

In further studies, we observed that the factors outlined above also control SET-promoted photochemical reaction of other bis- and polydonor-containing α-silyl-ether, -thioether, -sulfonamide, and -amide terminal linked phthalimides (Scheme 12).[26,31] The high efficiencies of these SET-promoted processes, caused by regioselective cation radical desilylation, suggest that the reactions would serve as the foundation for novel methods for the preparation of interesting macrocyclic compounds.

It should be noted that SET-promoted photocyclization reactions take place with silyl-terminated polydonor-linked naphthalimides, exemplified by **45** (Scheme 13).[26] Irradiation of methanol solutions of these substances, which contain a long-wavelength absorbing chromophore, brings about efficient formation of the corresponding macrocyclic amidols **46** and enamides **47**.

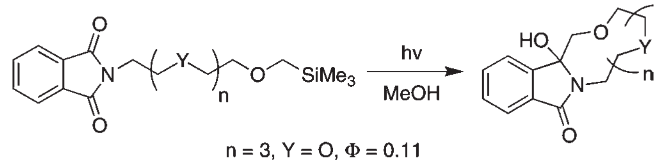
An important observation made in our investigations[32] was that significant differences exist between the efficiencies of photocyclization reactions of polyethylenoxy- vs polymethylene-tethered α-silyl ether tethered phthalimides and naphthlimides. Also, chain length plays a role in governing photocyclization efficiencies. In all cases studied, shorter chain containing, polyethylenoxy-linked substrates react to form the corresponding macrocyclic products with higher quantum yields than their long-chain polymethylene counterparts (Scheme 14). We have postulated that these differences are a consequence of the enhanced rates of formation of the key ω-zwitterionic biradical intermediates relative to BSET that are mediated by the length and the presence or absence of oxygen donor sites in the chains connecting the reactive centers.

SCHEME 13



(Y = NMs, n = 0, **46**, 100%)
(X = NMs, Y = NMs, n = 1, **46**, 100%)
(X = O, Y = NMs, n = 1, **46**, 88%)
(X = O, Y = NAc, n = 1, **47**, 80%)
(X = O, Y = NMs, n = 2, **47**, 70%)
(X = O, Y = O, n = 3, **46**, 76%)
(X = O, Y = O, n = 4, **46**, 71%)
(X = O, Y = O, n = 5, **46**, 75%)

SCHEME 14



n = 3, Y = O, Φ = 0.11
n = 3, Y = CH_2, Φ = 0.04
n = 4, Y = O, Φ = 0.07
n = 4, Y = CH_2, Φ = 0.02

Branched α-Silyl Polydonor-Linked Phthalimides

Another approach used to probe factors governing the chemical and quantum yields of photomacrocyclization reactions, and one that has the potential of yielding information about the preparative utility of these processes, focuses on product distributions in reactions of branched α-trimethylsilyl-substituted polydonor-tethered phthalimides. For this purpose, photochemical studies were carried out with the amine branched mixed polyethylenoxy–polymethylene-linked phthalimides **48** and **49** (Scheme 15), promoted by irradiation of MeOH solutions containing $HClO_4$.[32] The choice of this condition was guided by the desire to prevent SET from the amine donor in the chain through protonation. These reactions can potentially follow two sequential SET–desilylation pathways via the intermediacy of competitively formed zwitterionic biradicals having cation radical centers located at the ends of near equal length polymethylene and polyethylenoxy chains. In fact, photoreactions of **48** and **49** occur cleanly to form the cyclic amidols **50** and **51** or ether **52** predominantly or exclusively. This observation suggests that the availability of oxygen centers in the polyethylenoxy chain leads to more efficient production of zwitterionic biradicals **53**. Additional support was gained from photochemical studies with the bis-phthalimide-substituted α-silylether **54** (Scheme 16), which show that irradiation of a methanol solution of this substance containing perchloric acid results in exclusive formation of **55**, arising via selective SET−desilylation from the silylether center connected to the phthalimide chromophore by the oxygen-containing chain.

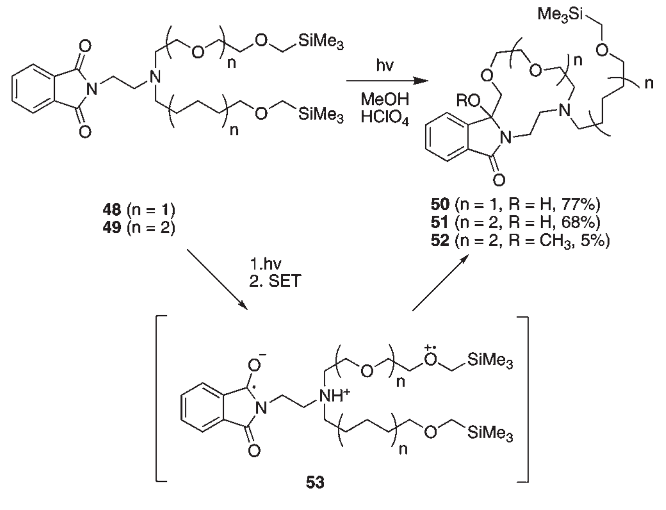
Another observation that relates to synthetic applications of SET-promoted photocyclization reactions of polydonor-linked phthalimides comes from an investigation with branched mixed α-silylether and α-silylthioether substrates **56** and **57** (Scheme 17).[33] Contrary to earlier results[25] that demonstrated that the quantum efficiency for photocyclization of a α-silylthioether-tethered phthalimide is lower than that of an α-silylether analog, reactions of these substances take place exclusively through formation and desilylation of the zwitterionic biradicals **58**, arising by SET from the sulfur rather than oxygen donors.

Applications of SET-Promoted Photocyclization Reactions to the Synthesis of Interesting Macrocyclic Targets

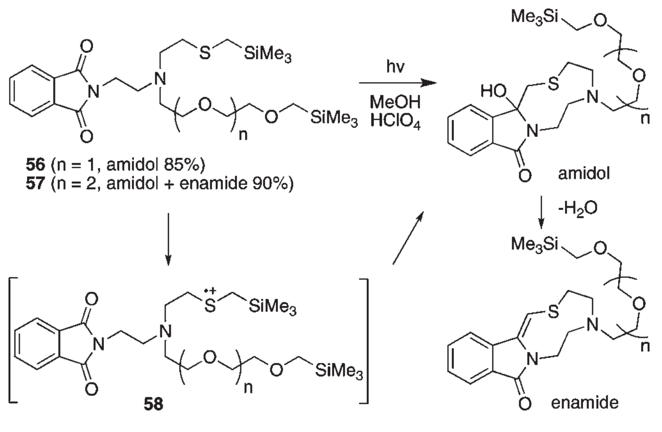
Substances that possess macrocyclic, polyheteroatom-containing ring systems play a central role in investigations aimed at discovering new chemically and biologically interesting materials. Crown ethers and their analogs, prime examples of members of this large family, have attracted great attention as a consequence of their selective metal and ammonium cation binding properties.[34] In addition, naturally occurring and synthetic cyclic peptides have been used in efforts aimed at exploring conformationally defined and hydrolytically stable polypeptide mimetics.[35−37] Several general methods have been developed to construct the macrocyclic ring systems present in members of the cyclic peptide and crown ether families. In some procedures, high dilution techniques are required to maximize cyclization reaction efficiencies. In addition, methods relying on preorganization of linear precursors have found use in routes for the synthesis of crown ethers.[38,39] In cyclic peptide synthesis, incorporation of conformationally biasing *N*-alkyl amino acid and proline units is known to facilitate macrocyclization processes. Also, several interesting processes, including backbone cyclizations[40] and cyclization−ring contractions,[41] have been used to generate cyclic peptide mimetics. Owing to the significance of crown ethers and cyclic peptides, new synthetic methods for their preparation are still in demand.

The unique features of SET-promoted photocyclization reactions of polydonor-linked imides make them suitable for the construction of macrocyclic polypeptides. In an investigation probing the feasibility of this approach, we observed that irradiation of the phthalimido-peptides **59**−**66** (Scheme 18) promotes macrocyclization reactions that produce the cyclic peptides, each as a single diastereomer (i.e., single configurations at the amidol carbons) in low to moderate yields.[42]

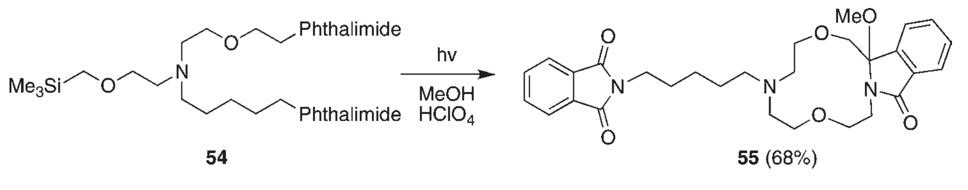
SCHEME 15



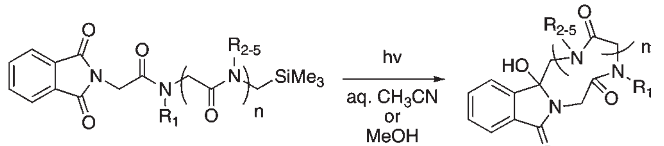
SCHEME 17



SCHEME 16

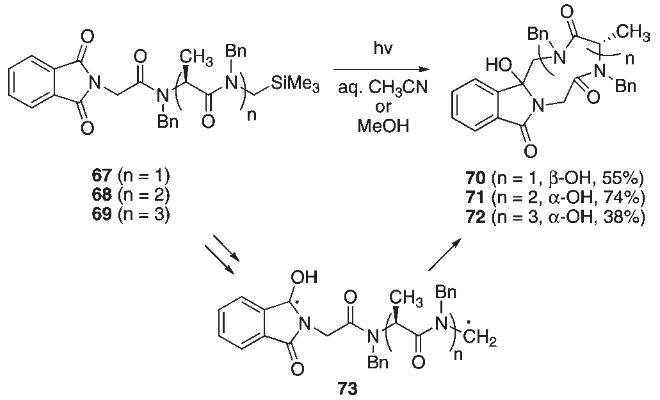


SCHEME 18



59 (n = 0, R_1 = H, 18%)
60 (n = 0, R_1 = Bn, 60%)
61 (n = 1, R_1 = R_2 = Bn, 40%)
62 (n = 1, R_1 = Me, R_2 = Bn, 40%)
63 (n = 2, R_1 = R_2 = R_3 = Bn, 55%)
64 (n = 2, R_1 = R_2 = Me, R_3 = Bn, 15%)
65 (n = 3, R_1 = R_2 = R_3 = R_4 = Bn, 70%)
66 (n = 4, R_1 = R_2 = R_3 = R_4 = R_5 = Bn, 61%)

SCHEME 19



67 (n = 1)
68 (n = 2)
69 (n = 3)

70 (n = 1, β-OH, 55%)
71 (n = 2, α-OH, 74%)
72 (n = 3, α-OH, 38%)

73

The highest efficiencies were seen in reactions of *N*-benzyl blocked peptides owing to the greater stabilities of the products. In addition, photocyclization reactions of the α-silyl-terminated glycine-((*S*)-alanine) peptides **67**−**69** were studied to show that the SET-photocyclization-based methodology can be used to synthesize stereoregular cyclic peptide analogs (Scheme 19). An important feature of photoreactions of these substrates is that a new chiral center is created at the amidol carbon in the products. Earlier studies with related phthalimide-derived photoproducts demonstrated that configurational inversion at amidol centers of this type via reversible formation of either *N*-acyliminium ions or amido-ketones occurs slowly under neutral conditions. Thus, stereochemical preferences in photocyclization reactions of alaninyl peptides would be determined by kinetic factors governing the rates of cyclization of biradical intermediates **73**. In light of this, it is interesting that irradiation of peptides **67**−**69** in 35% H_2O−MeCN leads to modestly efficient formation of the corresponding cyclic peptide mimics **70**−**72**.

The results of the investigation described above demonstrate the feasibility of the photochemical based strategy for preparation of cyclic peptide analogs. Moreover, the modestly high yields observed for the photocyclization reactions suggest that SET from amide donor sites in the peptide chains to the excited phthalimide chromophore, as expected, occurs more rapidly than other excited state reaction modes (e.g., H-atom abstraction). In addition, the fact that the efficiencies of these processes are not significantly affected by the length of the polypeptide chain indicates that, following the initial SET event, migration of the radical cation center to the position where the reactive α-trimethylsilyl group is located takes place at rates that are competitive with back-SET (BSET) and proton loss from benzylic sites in intervening cation radicals.[43−45] Furthermore, the apparent chain length independence of the efficiencies of these processes suggests that the rates of the final biradical cyclizations are not significantly retarded by entropy. Interestingly, a closely related photochemical approach to the preparation of cyclic peptide mimics has been developed in elegant studies by Griesbeck.[19,20] The methodology, exemplified in Scheme 20 by the conversion of **74** to **75**, relies on cyclization processes that operate by sequential excited state SET−decarboxylation pathways.

Direct and Indirect Approaches for the Preparation of Novel Lariat-Type Crown Ethers

Lariat-type crown ethers that contain a macrocyclic polyether core to which a cation complexing donor side chain is appended tend to more tightly bind cations than do their simple crown ether analogs.[34] This is a consequence of the complexing properties of their flexible side arms. A number of different methodologies have been employed to prepare these substances. A direct route for this purpose that has arisen from our studies involves the preparation and photocyclization reactions of nitrogen branched bis-polyethylenoxy-tethered phthalimides (**76**−**80**, Scheme 21).[32,33] As can be seen by viewing the results, these photocyclization reactions can be employed to directly and efficiently generate a wide variety of lariat crown ethers, starting with readily accessible substrates.

Another route that we developed for synthesis of lariat-type crown ethers takes advantage of facile secondary reactions of amidol-containing macrocyclic ethers that are produced by irradiation of polyethylenoxy-linked α-silylether-terminated phthalimides and 2,3-naphthalimides.[46−48] Examples of this approach are displayed in Scheme 22. As described above, irradiation of the polyether-linked naphthalimides results in highly efficient photocyclization reactions that produce a polyether ring containing cyclic amidols **42**.

Introduction of a variety of donor-containing side chains into these substances can be readily accomplished by using Lewis acid catalyzed allylation reactions of the amidol moiety with allyltrimethylsilane. Hydroboration–oxidation then forms intermediates **81** that possess hydroxypropyl groups to which a variety of different donor functionality can be appended. By using this approach, a number of lariat crown ethers, exemplified by **82**–**84**, that contain aminoether and thioether side arms have been produced.

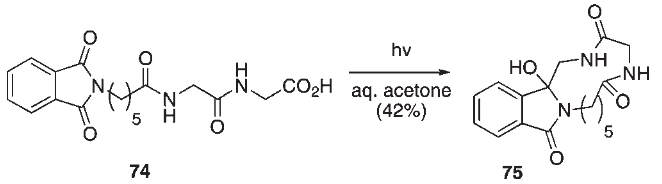
A variety of sensors have been developed using a SET–fluorescence quenching strategy in which guest binding is signaled through blocking SET quenching of fluorophore excited states[47,48] by appended donors. Beginning with the pioneering work of Sousa in the 1970s, a large effort was given to the development of crown ether based fluorescence sensors for the detection of metal cations.[49] Novel fluorescence sensors for the important environmental contaminant Hg^{2+} based on crown ether frameworks have come from recent studies.[50,51]

The practical utility of the efficient photochemical and side arm attachment methods we have developed for lariat-type crown ether synthesis has been explored in the context of metal ion fluorescence sensors. The amine and thioether side chains present in **82**–**84** (Scheme 22) and related substances, prepared in our efforts, serve as SET donors to promote efficient quenching of fluorescence from the naphtahalene chromophore when metal ion guests are absent. If the pendant electron donors in these substances were to participate in metal ion binding, less efficient fluorescence quenching would take place. As anticipated, fluorescence enhancements of these and related substances were observed in the presence of a variety of heavy metal cations (in some case selectively) including Mg^{2+}, Cu^{2+}, Hg^{2+}, and Pb^{2+}, as well as Ag^{+}.[46,56]

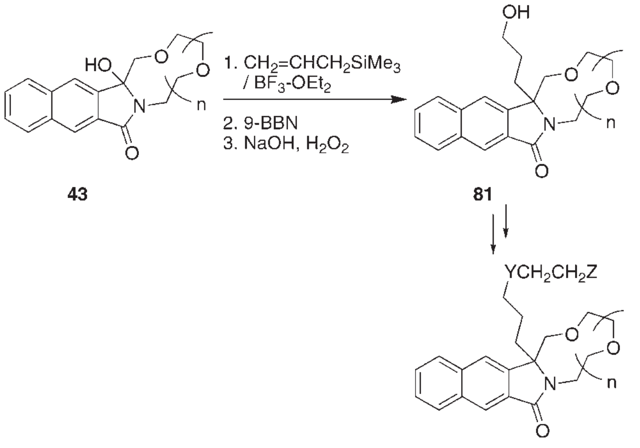
An Application of SET-Promoted Photocyclization Reaction of Phthalimides to the Preparation of Biscrown Ethers

Biscrown ethers,[52] which possess two macrocyclic polyether rings linked by a connecting unit, have been shown to display unique binding profiles as a consequence of the formation of sandwich-type complexes with metal cations.[53] Methods used for the preparation of biscrown ethers have relied on traditional procedures most commonly involving formation of monocrowns by nucleophilic substitution induced macrocyclic ring formation and subsequent coupling to form the biscrown framework.

SCHEME 20

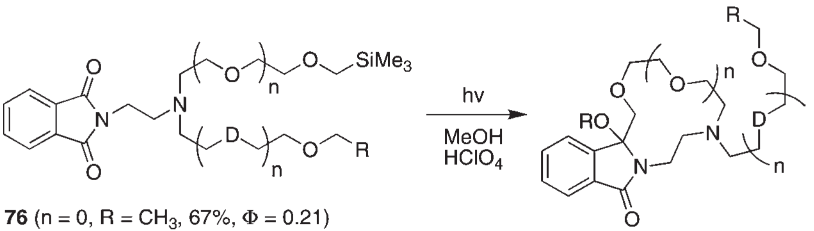


SCHEME 22



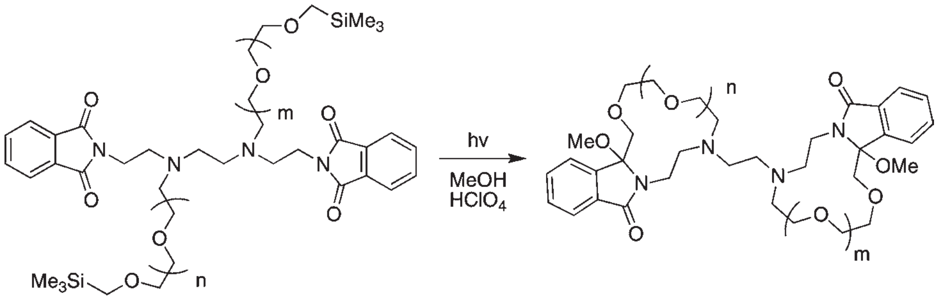
82 (n = 3-5, Y = O, Z = NMe_2)
83 (n = 4, Y = S, Z = Me)
84 (n = 4, Y = S, Z = SEt)

SCHEME 21



76 (n = 0, R = CH_3, 67%, $\Phi = 0.21$)
77 (n = 1, D = O, R = CH_3, 48%, $\Phi = 0.14$)
78 (n = 1, D = CH_2, R = CH_3, 52%, $\Phi = 0.15$)
79 (n = 0, R = H, 62%, $\Phi = 0.21$)
80 (n = 1, D = CH_2, R = H, 58%, $\Phi = 0.19$)

SCHEME 23



85 (n = m = 1)
86 (n = m = 2)
87 (n = m = 3)
88 (n = 3, m = 2)

89 (n = m = 1, 67%)
90 (n = m = 2, 65%)
91 (n = m = 3, 62%)
92 (n = 3, m = 2, 63%)

The results of our studies of SET-promoted photocyclization reactions of polydonor−imide acceptor systems have given rise to the design of a novel strategy for biscrown ether synthesis.[54] The methodology takes advantage of selective photocyclization reactions of bis-tethered substrates (Scheme 23). From a mechanistic perspective, irradiation of these substances would result in the production of a number of interconverting zwitterionic biradicals, formed by SET from donor sites in either chain to either phthalimide acceptor. Implications drawn from the results of earlier distance-dependence studies (see above)[32,33] are that the most efficient reaction pathways followed by the bis-tethered phthalimides should involve SET between the proximal rather than distant acceptor−silyl-terminated polydonor moieties. In order to test this prediction and explore the general strategy for biscrown synthesis, the α-silyl-terminated polyethylenoxy branched bis-phthalimides **85**−**88** were prepared and subjected to photochemical studies. The results demonstrate that photomacrocyclization reactions of these substrates take place with high efficiencies and high degrees of chemoselectivity to generate the interesting biscrown ethers **89**−**92**, derived by routes in which C−C bond formation occurs between the close rather than distant α-silylether and phthalimide centers.

Summary

A multidirectional approach has been used to probe the scope and limitations of SET-promoted photomacrocyclization reactions of polydonor-containing α-silyldonor−phthalimide and −naphthalimide systems. Mechanistic studies, designed to gain information about the factors that govern chemical yields and quantum efficiencies of these processes, have provided a foundation for predicting the chemoselectivities, regioselectivities and efficiencies of these excited-state reactions. The observations made in these investigations demonstrate that the efficiencies of SET-promoted reactions of α-silyl polydonor linked phthalimide/naphthalimides depend on the length, number, types, location, and reactivity of ion radical centers formed by either initial SET or intrasite SET. The unique features of the cyclization reactions have been used advantageously in the design of synthetically useful photochemical strategies for the preparation of novel cyclic peptide mimetics, crown ethers, and their lariat- and bis-type analogs. It should be noted that, although limitations exist for the use of photochemical reactions in organic synthesis associated with scale up issues, several features make them suited to potential applications in unique situations. Perhaps of greatest importance in this regard is the ability to promote photochemical reactions in a highly temporally and spatially controlled manner. Few other types of chemical reactions can be initiated by a simple external stimulus (photons) in small confined environments (nanoscale). Thus, the ability to generate macrocyclic substances that interact selectively with guests in a timed way in a specific location has potential significance.

This Account is dedicated to the late Donald R. Arnold whose pioneering studies of SET photochemical reactions served as the foundation for this field of science and an inspiration for our earlier work. The studies described in this Account were supported by Nation Research Foundation of Korea Grant funded by the Korean Government (Nos. KRF-2008-521-C00156 and KRF-2009-0072585, for U.C.Y.) and the National Science Foundation (Grant CHE-0550133) (for P.S.M.). The diligent work of a large number of undergraduate and doctoral students and postdoctoral associates, described in references to our studies, is greatly appreciated.

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Dae Won Cho received his Ph.D. degree from the Chemistry Department at the Pusan National University in Korea under the direction of Ung Chan Yoon. He is currently a postdoctoral research fellow with Patrick S. Mariano in the Department of Chemistry and Chemical Biology at the University of New Mexico. His research interests lie in the fields of organic photochemistry, materials chemistry, and biomass deconstruction.

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Patrick S. Mariano received his undergraduate education at Fairleigh Dickinson University and his doctoral degree at the University of Wisconsin under the direction of Howard Zimmerman. Following postdoctoral studies at Yale University, he was on faculty at the University of Maryland. His current research work focuses on mechanistic photochemistry and bioorganic chemistry.

FOOTNOTES

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