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The Synthetic Potential of Phthalimide SET Photochemistry†

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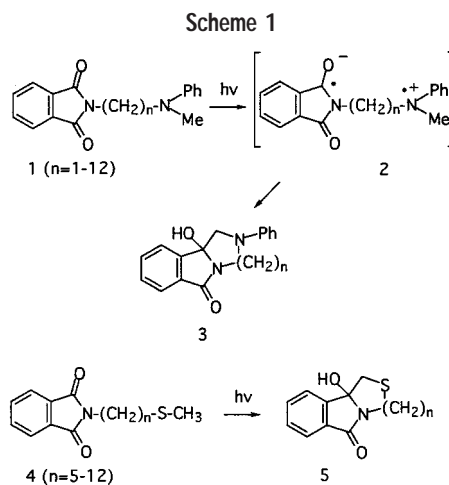
ABSTRACT

The authors' studies in the area of phthalimide photochemistry are discussed in the context of the development of new methods for N-heterocycle synthesis. Emphasis is given to reactions which are initiated by both intermolecular and intramolecular SET from silicon-containing electron donors to excited states of phthalimides and related maleimides and conjugated imides. The photoaddition and photocyclization processes which ensue follow mechanistic pathways, in which efficient desilylation of initially formed radical cation occurs to generate radical pair and biradical intermediates that serve as precursors of the products. Several examples that demonstrate the preparative potential of these reactions are presented. These are taken from the authors' investigations of (1) phthalimido-alkylsilane photocyclization reactions, (2) azomethine ylide-forming excited-state processes of *N*-(trimethylsilylmethyl)-phthalimide, and (3) photoaddition and photocyclization reactions of phthalimide α -silyl ether, thioether, amine, and amide systems.

Introduction

Extensive studies begun in the 1970s by Kanaoka¹ and co-workers have demonstrated that phthalimides undergo a number of interesting photochemical reactions. Like their aromatic ketone counterparts, phthalimide excited states participate in hydrogen atom abstraction. Numerous

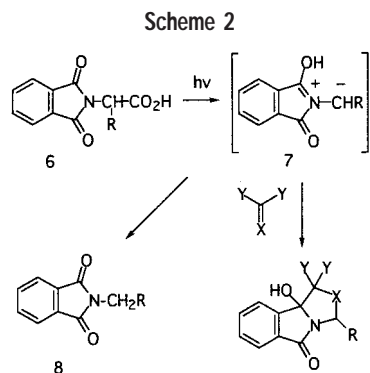
Ung Chan Yoon received his B.S. and M.S. degrees in pharmacy at the Seoul National University. After working for one year at the Natural Product Research Institute of Seoul National University, Professor Yoon came to the United States to conduct his doctoral studies in the Chemistry Department at Fordham University. Following postdoctoral work in the Chemistry Department at the University of Maryland, he joined the faculty at Pusan National University, where he is now professor of chemistry. His research interests are in the areas of organic photochemistry, medicinal chemistry, and materials chemistry.



examples of photochemical processes, initiated in this manner, have been uncovered in investigations of phthalimide photochemistry.² In addition, irradiation of *N*-alkylphthalimides leads to preferential γ -hydrogen atom abstraction as part of N-heterocyclic ring-forming reactions.^{3,4} Kanaoka's pioneering work in this area led to the discovery of another interesting excited-state property of phthalimides. As illustrated by photochemical transformations of the phthalimido-amines **1**^{5,6} and phthalimido-thioethers **4**⁷ (Scheme 1), the normal preference for γ -hydrogen atom abstraction is not adhered to in excited states of phthalimides which contain good electron donors in their N-tethers. As a consequence of their large excited-state reduction potentials ($E^{S1(-)} = 2.1$ V, $E^{T1(-)} = 1.6$ V),⁸ phthalimides of this type participate in photoinduced,

† The authors dedicate this contribution to the memory of Arthur G. Schultz, a generous person who, through elegantly designed and carefully executed studies, made major contributions to the area of synthetic organic photochemistry.

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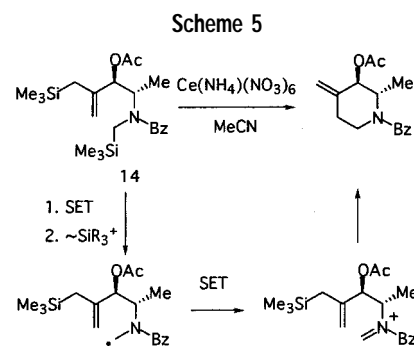
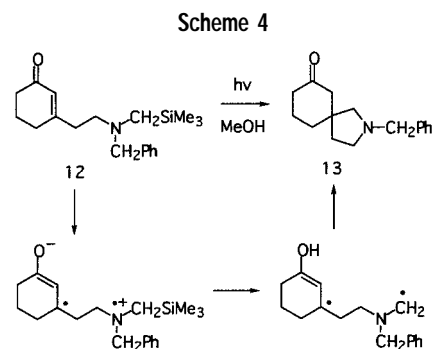
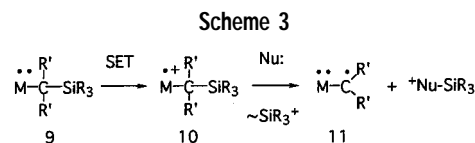
inter- and intramolecular single-electron-transfer (SET) reactions. When phthalimide excited states interact with donors that have oxidation potentials less than ca. 2.1 V, the free energy for SET is negative and, consequently, SET occurs rapidly (ca. $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$).⁹ In substrates that contain N-linked thioether and amine electron donors, SET dominates other pathways for excited-state decay, and it generates intermediate zwitterionic biradicals (e.g., **2**) that serve as precursors of the heterocyclic products **3** and **5**.

Another unique excited-state reaction, discovered by Kanaoka and his co-workers, is photodecarboxylation of *N*-phthalimido- α -amino acids (**6** \rightarrow **8**, Scheme 2).¹⁰ This process proceeds via the intermediacy of azomethine ylides **7**.^{11,12} We have shown that these ylide intermediates **7** can be trapped by cycloaddition with carbonyl and alkene dipolarophiles.¹³ Recent laser flash photolysis (LFP) investigations have provided evidence for the existence of azomethine ylides in *N*-phthalimido- α -amino acid photoreactions and rate data for cycloaddition and intramolecular proton-transfer reactions of these intermediates.¹⁴

Set Photochemistry with Silicon-Containing Electron Donors

Our relatively recent interest in this area of photochemistry grew out of investigations conducted over the past two decades probing SET-promoted excited-state and ground-state reactions of silicon-containing substrates. In early studies of iminium SET photochemistry,^{15–17} we predicted and then observed that cation radicals **10**, arising by SET oxidation of α -trialkylsilyl-substituted electron donors **9**, undergo efficient, nucleophile-induced desilylation to form carbon-centered radicals **11** (Scheme 3). This simple concept, based upon an evaluation of the degree of overlap between filled $\sigma_{\text{C-Si}}$ and half-occupied n or π orbitals, has led to the design of a number of synthetically applicable photochemical and ground-state reactions.¹⁸ Two examples are the regioselective photoconversion of silylamino enone **12** to the spirocyclic amino ketone **13**¹⁹ (Scheme 4) and the Ce(IV)-induced Mannich cyclization of the α -silylamido-substituted allylsilane **14** (Scheme 5).²⁰

The efficiencies of these SET-promoted processes are a consequence of highly regioselective desilylation reactions of the key cation radical intermediates. Data gained



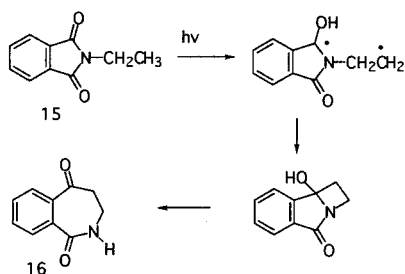
from parallel LFP studies^{21,22} show that the rates of α -desilylation of cation radicals derived from aniline derivatives are ca. 2 orders of magnitude larger than those for base-induced α -deprotonation. Thus, carbon-centered radical formation in these processes is highly regioselective.

These findings suggested that phthalimides would participate in related SET-promoted photoreactions with silicon-containing substrates and that these processes would serve as the foundation for unique methods of heterocycle synthesis. An evaluation of phthalimide excited-state reduction potentials indicates that a variety of α -silyl electron donors, including α -silyl amines, amides, olefins, arenes, ethers, and thioethers, can be used in these reactions. Since excited phthalimides are potent electron acceptors, even SET from alkylsilanes might be thermodynamically/kinetically efficient. Below,²³ we discuss the results of investigations we have carried out in the area of phthalimide photochemistry which have shown that the mechanistic analyses outlined above translate into synthetically useful excited-state reactions.

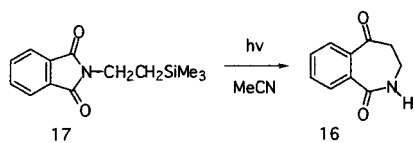
Photoreactions of ω -Phthalimido-alkylsilanes

Hydrogen atom abstraction dominates the excited reactivity profiles of *N*-alkylphthalimides. This is exemplified by the photochemistry of *N*-ethylphthalimide **15**, where irradiation leads to formation of the benzazepinedione **16** (Scheme 6).³ Here, initial γ -hydrogen abstraction is followed by biradical coupling and ensuing amidol ring opening. However, the yield of this process (ca. 5%), as

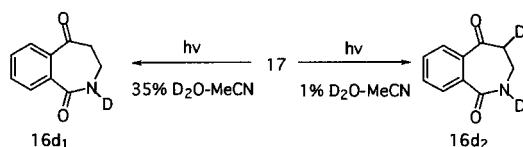
Scheme 6



Scheme 7



Scheme 8



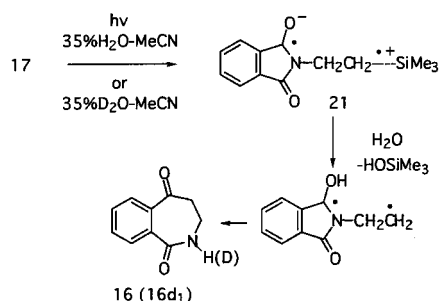
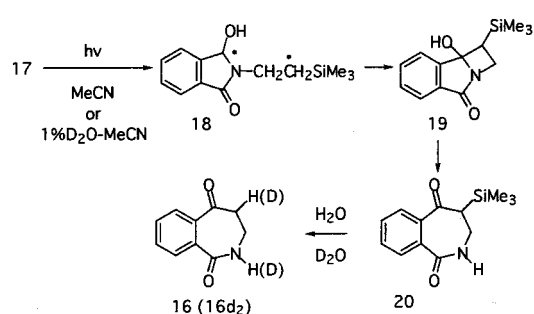
well as those of related *N*-alkylphthalimide photocyclizations, is not preparatively acceptable.

In contrast, *N*-(silylethyl)phthalimide **17** efficiently (68%) produces benzazepinedione **16** (Scheme 7) when irradiated in MeCN solution.²⁴ Introduction of the trimethylsilyl substituent transforms a minor photoreaction into one that has synthetic value. Insight into the factors responsible for the yield enhancement was gained from the results of experiments in which photoreaction solvent was varied. Irradiation of **17** in 35% D₂O–MeCN leads to exclusive production of the mono-*N*-deuterated product **16-d**, while photoreaction of **17** in 1% D₂O–MeCN yields the *N,C*-dideuterated benzazepinedione **16-d₂** (Scheme 8). In addition, ¹H NMR monitoring of the photoreaction of **17** in CD₃CN shows that the α -silyl product **20** is produced initially and that this substance is converted to **16** or **16-d₂** when treated with H₂O or D₂O, respectively (Scheme 9).

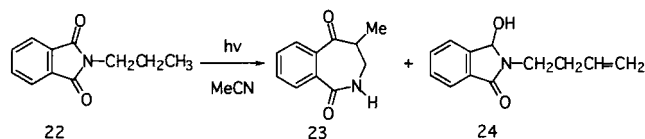
The results suggest that two pathways (Scheme 9) are responsible for the photochemical transformation of (silylethyl)phthalimide **17** to benzazepinedione **16**. In low-water-content solvents (e.g., 1% D₂O–MeCN), the reaction is initiated by γ -hydrogen atom transfer, which yields sequentially the silicon-containing tricyclic amidol **19** and silyl-azepinedione **20**. In contrast, desilylation must precede C–C bond formation in the reaction of **17** in the highly polar-silophilic solvent systems 35% D₂O–MeCN. In this case, intramolecular SET from the σ_{C-Si} bond ($E_{p/2} = 2.5$ V vs SCE)^{25a} to the singlet excited phthalimide leads to the solvent-stabilized but transient^{25a,b} zwitterionic biradical **21**. Desilylation of **21** then generates the precursor of the non-silicon-containing benzazepinedione **16** (or **16-d**).

This mechanistic study provided practical insight into the design of conditions that can be used to enhance the

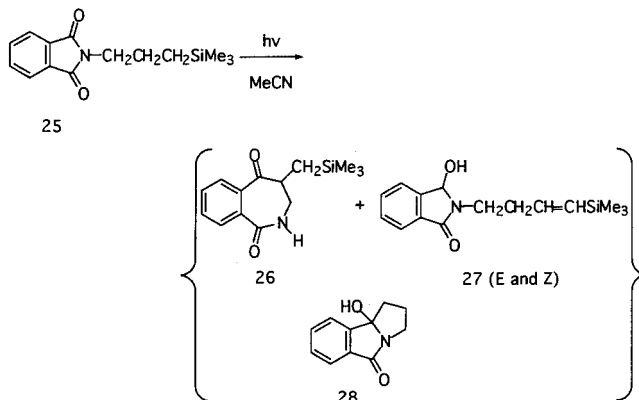
Scheme 9



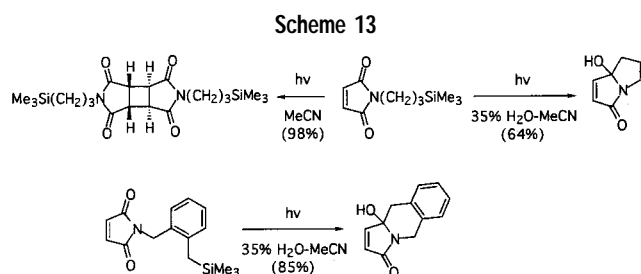
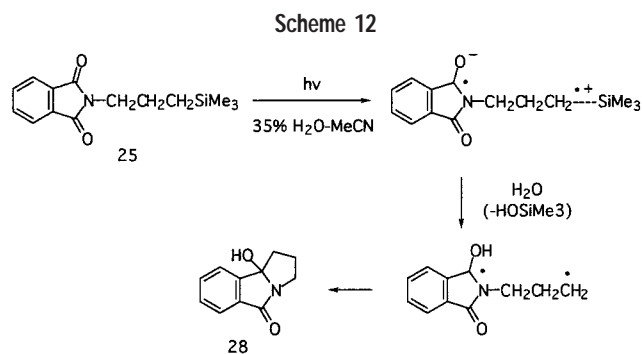
Scheme 10



Scheme 11



chemical and quantum efficiencies of *N*-(silylalkyl)phthalimide photoreactions. One example which demonstrates the level of control offered by solvent variation is found in the photochemistry of the (silylpropyl)phthalimide **25**. Kanaoka reported earlier that irradiation of the *N*-propyl substrate **22** leads to low-yield (29%) formation of methylbenzazepinedione **23**, along with the unsaturated amidol **24** (18%) (Scheme 10).³ Similarly, irradiation of the silicon analogue **25** in MeCN gives rise to a mixture of products including benzazepinedione **26** (28%), amidol **27** (18%), and benzopyrrolizidinone **28** (21%) (Scheme 11).²⁴ The major products generated in both of these photoreactions arise by initial γ -hydrogen atom abstraction. The formed biradicals cyclize or disproportionate to produce the respective benzazepinedione and unsaturated amidol products.

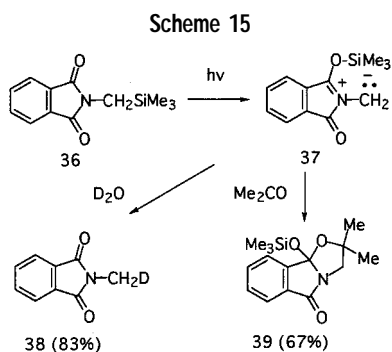
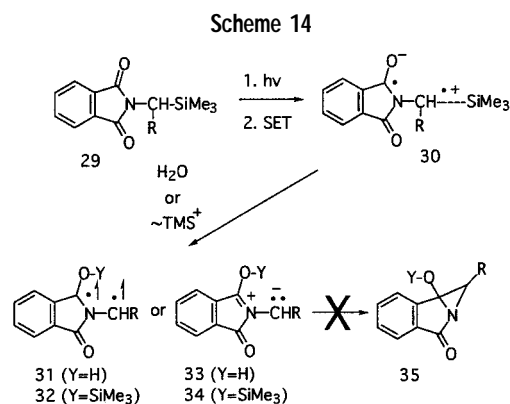


In contrast, irradiation of the (silylpropyl)phthalimide **25** in 35% H₂O–MeCN results in nearly quantitative (96%) formation of the benzopyrrolizidinone **28** (Scheme 12). In addition, the quantum efficiency for photoreaction of **25** in the aqueous solvent system is ca. 20-fold greater than that for the process in MeCN. As in the case of **17**, a change to the aqueous solvent system produces a dramatic change in the excited-state reactivity of the (silylpropyl)phthalimide. Under the high-polarity/silophilicity aqueous MeCN condition, SET occurs to the total exclusion of hydrogen atom abstraction.

As demonstrated by the examples included in Scheme 13, the “water effect” profoundly impacts the photochemistry of a number of silicon-substituted maleimides.²⁶ In these systems, pyrrolizidine product formation in the aqueous solvent system, via sequential desilylation–diradical coupling routes, dominates over [2 + 2] photodimerization, the exclusive pathway followed when photoreactions are conducted in MeCN. The results of our studies exemplify how knowledge gained from a detailed scrutiny of the mechanisms of excited-state reactions can be used to design preparatively useful photochemical processes.

Azomethine Ylide-Forming Photoreactions of *N*-(Trimethylsilylmethyl)phthalimides and Related Conjugated Imides

The studies described above show that the unique redox properties of alkylsilanes and conjugated imide excited states serve to drive synthetically interesting photoreactions. The efforts also have uncovered interesting reactions of excited states of *N*-(silylalkyl)phthalimides in which 1,ω-biradicals are produced as reactive intermediates by SET and subsequent desilylation of σ_{C–Si} cation radicals. Consideration of how this reactivity pattern might be applied to (silylmethyl)phthalimides **29** results in the prediction that 1,3-biradicals or azomethine ylides would

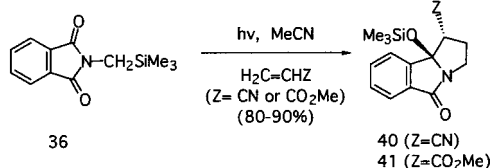


be formed as reactive intermediates (Scheme 14). In this case, the zwitterionic biradicals **30** generated by SET in the triplet or singlet excited states of **29** could undergo nucleophile-induced desilylation to form 1,3-biradicals **31** (if triplets) or azomethine ylides **33** (if singlets). Alternatively, the oxyanion center in **30** could serve as an internal nucleophile for desilylation at the σ_{C–Si} cation radical site in **30**. This process, being both energetically and entropically favored, would result in production of the silicon-containing biradical or dipolar intermediates, **32** or **34**. Unlike the related 1,>3-biradicals produced in photoreactions of longer chain (silylalkyl)phthalimides, cyclizations of **31**–**34** would generate strained bicyclic aziridines **35**. Consequently, we anticipated that these transients would be long-lived and, thus, capable of reacting with trapping agents.

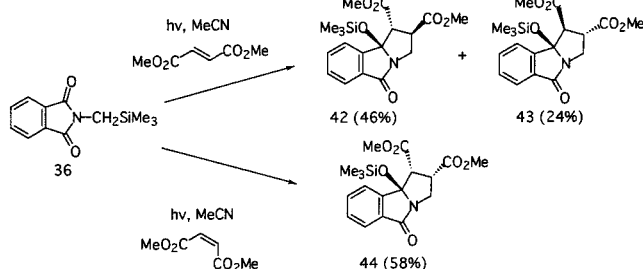
Observations made in studies with the parent (silylmethyl)phthalimide **36** confirm the operation of this unique excited-state process involving sequential SET silyl transfer.^{14,27} We found that irradiation of **36** in D₂O–MeCN results in efficient production of *N*-(methyl-*d*)phthalimide **38**, while excited-state reaction of this phthalimide in acetone gives rise to the adduct **39** (Scheme 15). The intermediate in these processes is the azomethine ylide **37**, which reacts by C-deuteration with D₂O or dipolar cycloaddition with acetone to form **38** and **39**, respectively.

LFP techniques were used to gain evidence for the intermediacy of azomethine ylides in these processes.¹³ Excitation (266 nm) of **36** in MeCN gives rise to a 392-nm-absorbing transient which undergoes second-order decay (1.4 × 10⁶ A⁻¹ s⁻¹). Added dipolarophiles, e.g., methyl acrylate and acrylonitrile, enhance the decay of the 392 nm transient, with second-order rate constants

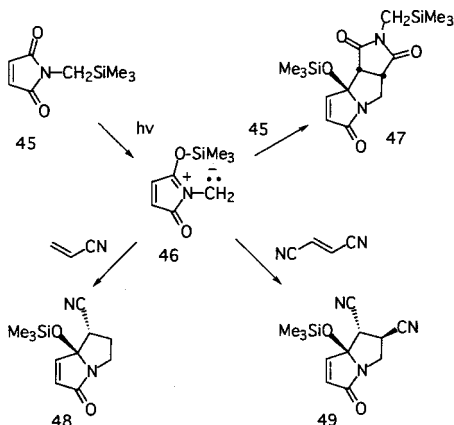
Scheme 16



Scheme 17



Scheme 18

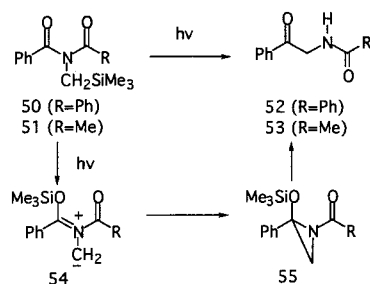


around $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. The results are in accord with assignment of the 392-nm-absorbing transient as azomethine ylide **37** and the bimolecular decay pathways promoted by methyl acrylate and acrylonitrile as dipolar cycloadditions, processes.

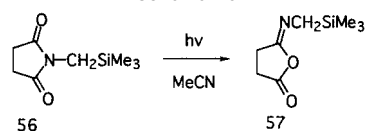
Preparative photochemical experiments have provided supporting evidence for this proposal.^{14,27} Irradiation of **36** in MeCN solutions containing 10 mM acrylonitrile or methyl acrylate leads to efficient (80–90%) formation of the respective benzopyrrolizidines **40** and **41** (Scheme 16). The ylide trapping reactions are endo selective and stereospecific (preferential production of **42** + **43** and **44** from photoreactions of **36** with dimethyl fumarate and dimethyl maleate, respectively (Scheme 17)).

This novel and preparatively useful azomethine ylide-forming photoreaction is not restricted to phthalimide substrates.²⁸ Other conjugated imides that contain *N*-silylmethyl substitution are transformed to their corresponding azomethine ylides by a photoinduced C-to-O silyl migration reaction. For example, irradiation of *N*-(trimethylsilylmethyl)maleimide **45** in MeCN results in efficient formation of the adduct **47** (Scheme 18) arising from self-trapping of the intermediate ylide **46**. This intermediate can be competitively trapped by cycloaddition with added dipolarophiles such as acrylonitrile (\rightarrow **48**) and fumaronitrile (\rightarrow **49**).

Scheme 19



Scheme 20



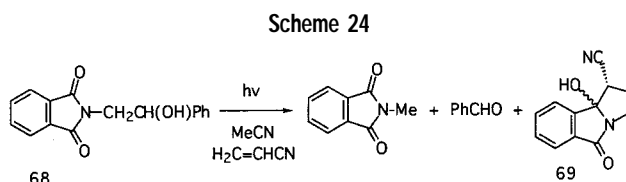
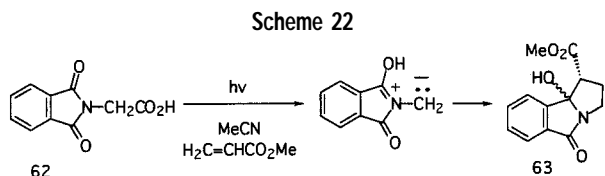
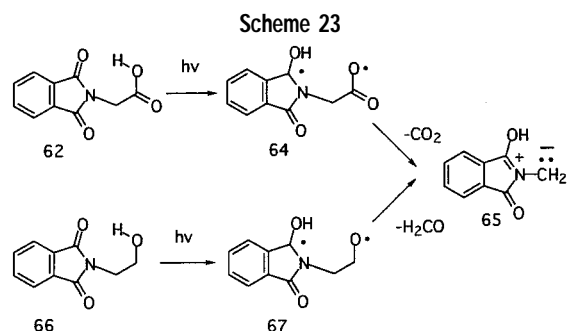
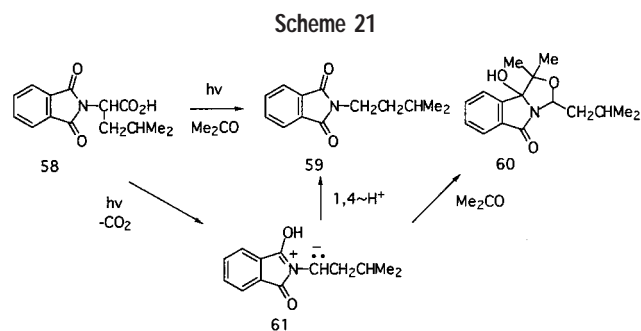
Azomethine ylide formation also occurs from the excited states of symmetric and mixed benzimides **50** and **51** (Scheme 19).²⁸ Irradiation of these substrates in MeCN leads to generation of the respective α -amido ketones **52** and **53**. In these processes, excited-state C-to-O silyl migration is followed by 4π -electrocyclization of the formed ylide intermediate **54**. The unstable, aziridinyl ethers **55** formed in this manner can be detected by ¹H NMR monitoring of photoreactions conducted under rigorously anhydrous conditions. Desilylative ring opening then occurs on exposure of these substances to water, yielding the amido ketone products. Interestingly, the acyclic azomethine ylides **54** are not trapped by even high concentrations of highly reactive dipolarophiles, e.g., fumaronitrile.

In contrast to phthalimide and conjugated imide analogues, *N*-trimethylsilylmethyl derivatives of simple, nonconjugated imides, as well as *N*-trimethylsilylmethyl amides, do not participate in excited-state C-to-O silyl migration reactions. An example is found in the photochemistry of the *N*-(silylmethyl)succinimide **56**, where irradiation promotes a well-known acyl migration to produce the unstable imidate derivative **57** (Scheme 20).²⁸

Observations made in these studies suggest that the novel C-to-O silyl migration reaction of conjugated imides is a general excited-state process. It is reasonable to propose that these reactions occur in imides that have low-energy $\pi-\pi^*$ singlet or triplet excited states. As suggested above, the driving force for silyl migration could reside in both the respective redox potentials of the conjugated imide acceptor and $\sigma_{\text{C-Si}}$ donor sites and the entropic favorability of silyl transfer in the intermediate zwitterionic biradicals. In the case of nonconjugated imide counterparts, low-energy $n-\pi^*$ states exist, and these react via acyl cleavage rather than SET pathways.

Ylide-Forming Photoreactions of *N*-Phthaloyl Derivatives of α -Amino Acids and β -Amino Alcohols

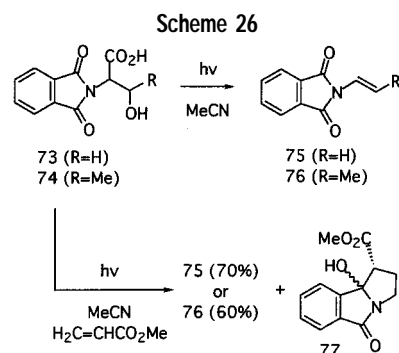
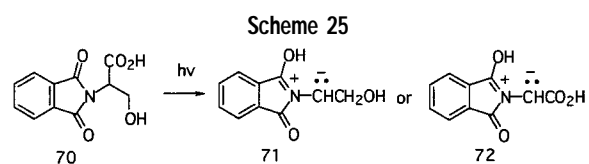
A number of years ago, Kanaoka and co-workers¹⁰ reported that *N*-phthaloyl- α -amino acids undergo high-yielding photodecarboxylation reactions to produce the



corresponding *N*-alkylphthalimides. Although dismissed by these workers as being unlikely, the existence of azomethine ylides as intermediates in these excited-state processes is hinted at by Kanaoka's observation that adduct **60** is formed as a minor product when *N*-phthaloyl-leucine **58** is irradiated in acetone (Scheme 21). We felt that **60** might arise in this process by dipolar cycloaddition of acetone to the ylide **61** in competition with its decay by proton transfer (\rightarrow **59**). The acetone cycloaddition is reminiscent of the similar reaction of the (silylmethyl)phthalimide-derived azomethine ylide **37** (see Scheme 15).

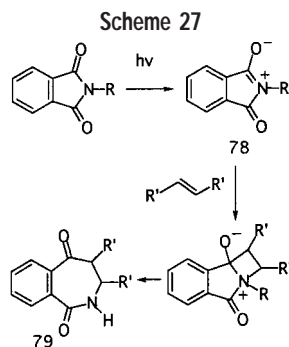
Recent mechanistic and exploratory investigations in our laboratories have demonstrated that azomethine ylides definitely are intermediates in *N*-phthaloyl- α -amino acid photodecarboxylation reactions. Evidence for this conclusion comes in part from the results of laser flash photolysis studies of *N*-phthaloyl-glycine.¹³ Flash excitation of this substance gives rise to a 392-nm-absorbing transient characterized as the HO ylide (Scheme 22). Like its similarly absorbing (silylmethyl)phthalimide-derived, TMSO counterpart, this transient undergoes methyl acrylate- or acrylonitrile-induced decay with second-order rate constants around $3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. In addition, irradiation of *N*-phthaloyl-glycine **62**, as well as other phthalimido- α -amino acid derivatives, in MeCN solutions containing the dipolarophiles methyl acrylate and acrylonitrile results in clean formation of benzopyrrolizidine adducts (e.g., **63**).¹⁴

The transformation of *N*-phthaloyl- α -amino acids to HO-azomethine ylides could be initiated by hydrogen atom abstraction. Transfer of the carboxylic acid hydroxyl hydrogen to the excited phthalimide carbonyl oxygen would generate the carboxy radical-containing diradical **64**, a direct precursor of the azomethine ylide intermediate **65** (Scheme 23). *N*-Phthaloyl derivatives of β -amino alcohols **66** participate in a very similar hydrogen atom-transfer reaction to produce biradicals **67**, which serve as precursors of the HO-azomethine ylides **65**.²⁶ In both cases, azomethine ylide formation occurs by way of carbonyl-forming, C–C bond-cleaving homolytic processes (Scheme 23). The conversion of the phthalimido



alcohol **68** to benzaldehyde, phthalimide, and benzopyrrolizidine **69** by irradiation in an MeCN solution containing acrylonitrile (Scheme 24) exemplifies the operation of the latter ylide-forming photofragmentation pathway.

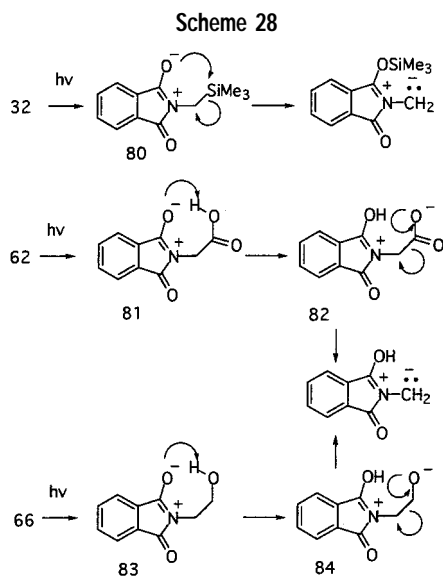
A priori, the excited states of *N*-phthaloyl derivatives of β -hydroxy amino acids **70** can react by either of the two azomethine ylide-forming routes described above. Photodecarboxylation of these substrates would yield β -hydroxy ylides **71**, while retro-aldol-like cleavage would form carboxy ylides **72** (Scheme 25). To evaluate the relative efficiencies of these two potentially competitive processes and to determine the chemical properties of the unusually substituted ylides generated by these routes, we investigated the photochemistry of *N*-phthaloyl derivatives of serine **73** and threonine **74**.²⁹ Irradiation of MeCN solutions of **73** and **74** gives rise, in each case, to a mixture of products in which the respective *N*-vinylphthalimides **75** and **76** are major products (Scheme 26). The presence of 65 mM methyl acrylate has little effect on the nature of these photoreactions. Accordingly, irradiation of MeCN solutions of **73** and **74**, each containing methyl acrylate, results in predominant formation of the vinylphthalimides **75** and **76** along with only minor amounts of the benzopyrrolizidine adduct **77**.



Two important conclusions can be drawn from the results of these studies. First, photodecarboxylation is the major reaction pathway followed by excited states of *N*-phthaloyl α -amino- β -hydroxy acids. Second, β -hydroxy-azomethine ylides, formed in the photochemistry of these substrates, are exceptionally short-lived intermediates (i.e., not readily trapped). This is a consequence of the existence of a facile β -elimination route which efficiently transforms these ylides into *N*-vinylphthalimides.

It is instructive to question whether the azomethine ylide-forming photoreactions of *N*-(silylmethyl)phthalimides and those of the *N*-phthaloyl α -amino acids and β -amino alcohols share any potentially common mechanistic features. Earlier in this Account, we discussed these processes in terms of SET-silyl-transfer and hydrogen abstraction mechanisms. However, from another perspective, these reactions can be viewed as originating from a common polarized phthalimide excited state. Dipolar structures **78** can be invoked to explain photoinduced cycloaddition reactions which occur when phthalimides are irradiated in the presence of non-electron-rich alkenes (Scheme 27).³⁰ Addition of an alkene to **78** is believed to be the key mechanistic step in these processes, which lead to formation of benzazepinedione products **79**.

By using the dipolar description of phthalimide excited states, it is possible to develop an alternate and perhaps more encompassing picture of the ylide-forming photoreactions. For example, the conversion of (silylmethyl)phthalimide excited states **80** to the corresponding TMSO



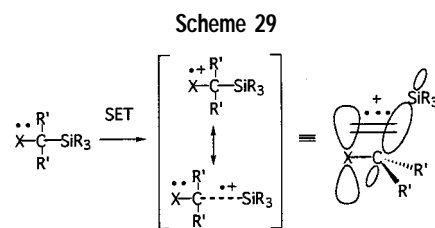
ylide can be viewed as a 1,4-sigmatropic rearrangement or a two-step internal nucleophilic substitution at silicon (Scheme 28). Similarly, rearrangement of acid- and alcohol-derived dipolar excited states **81** and **83** by proton transfer would set the stage for polar fragmentation of the resulting zwitterions **82** and **84** to form the HO ylide.

Independent of which mechanistic description one adopts for the ylide-forming photoreactions, it is clear that the process can serve as the foundation for novel methods to prepare interestingly structured and functionalized *N*-heterocyclic products.

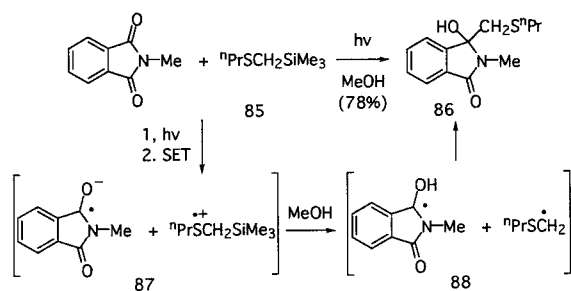
Photoadditions and Photocyclizations of Phthalimide with α -Silyl Ether, Thioether, Amine, and Amide Substrates

α -Trialkylsilyl substitution in heteroatom-containing substances has a profound effect on their oxidation potentials. As demonstrated by the comprehensive theoretical and experimental studies reported by Yoshida and his co-workers,^{31,32} this effect results in thermodynamic stabilization of the cation radicals, derived by one-electron oxidation of these substrates. Overlap of the relatively high energy, doubly occupied σ_{C-Si} orbital with the half-filled heteroatom orbital in the cation radical results in lowering of the energy of the charged radical (Scheme 29). From this view, the delocalized silicon-stabilized cation radical can be pictured as a species with positive charge and odd electron density distributed over the heteroatom, α -carbon, and silicon centers. This thermodynamic stabilization also instills kinetic instability in these high-energy intermediates. The orbital interaction weakens the C-Si bond and makes the silicon center even more electropositive than it is in neutral alkylsilanes. Consequently, nucleophile/silophile-induced α -heterolytic fragmentation of these intermediates is a facile process that results in production of heteroatom-stabilized, carbon-centered radicals. Our studies of SET-induced excited-state reactions of phthalimides with α -trialkylsilyl-substituted ethers, thioethers, amines, and amides have shown that cation radical desilylation drives a host of interesting processes which proceed by pathways involving generation and carbon-carbon bond-forming coupling of radical intermediates.

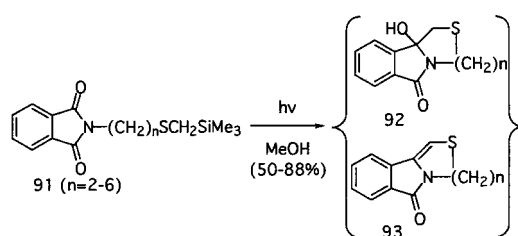
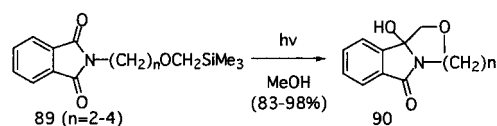
In an early effort, we observed that simple α -silyl ethers, thioethers, and amines undergo modestly efficient photoaddition to phthalimide and its *N*-methyl derivative.³³ The highest yields in this series of closely related reactions were obtained with the (silylmethyl)propyl thioether **85**, which undergoes photoaddition to *N*-methylphthalimide to produce the adduct **86** in 78% yield (Scheme 30). The general mechanistic pathway followed in this and related



Scheme 30



Scheme 31

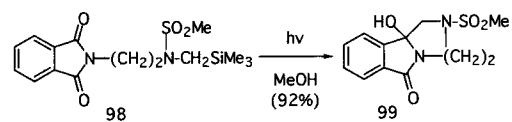
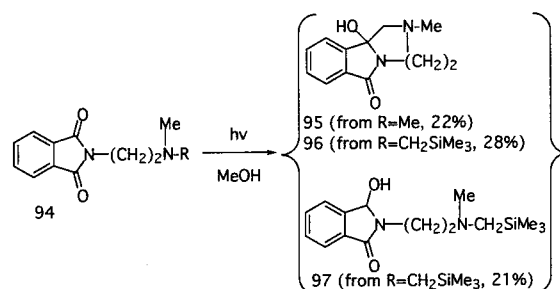


processes is shown in Scheme 30. Thermodynamically/kinetically driven SET from **85** to the phthalimide excited state leads to formation of the ion radical pair **87**. Solvent (MeOH)-promoted desilylation of the cation radical and protonation of the anion radical then provides the radical pair **88**, the direct precursor of adduct **86**.

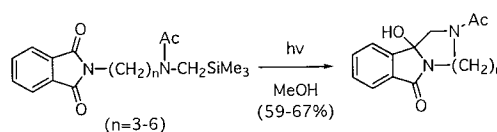
Intramolecular photoreactions of phthalimides containing N-tethered α -silyl donors proceed with high chemical efficiencies to generate a variety of novel heterocyclic products. For example, irradiation of MeOH solutions of the phthalimido silyl ethers **89** leads to formation of the amidol-containing oxygen heterocycles **90** in excellent yields (Scheme 31).³⁴ Analogous photocyclization reactions are observed with the phthalimido thioethers **91**.³⁵ Although dehydration of the primary photoproducts (**92** \rightarrow **93**) occurs with varying ease in these systems, the overall yields of the reactions remain high, even when the size of the ring that is formed in the ultimate diradical cyclization steps is large.

A parallel investigation of the photochemistry of α -silylamine- and α -silylamide-linked phthalimides has provided a more in-depth understanding of the factors that govern both the chemical and quantum yields of SET-promoted photocyclization reactions.^{36,37} We observed that irradiation of a MeOH solution of the (silylamino)-phthalimide **94** leads to nonselective formation of a mixture of products, including the fused diazines **95** and **96** and amidol **97** (Scheme 32). In stark contrast, the tricyclic sulfonamide **99** is formed in high yield when the (silylamido)phthalimide **98** is irradiated in MeOH (Scheme 32). These divergent results suggest that the preparative utility of photocyclization reactions, operating by sequential SET desilylation pathways, could be enhanced by using substrates that contain α -silylamide rather than α -silyl-

Scheme 32



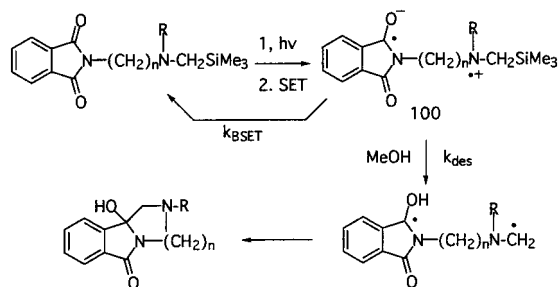
Scheme 33



amine donor sites. Support for this proposal is found in photoinduced cyclization of the acetamide derivatives shown in Scheme 33. Quantitative studies showed that the quantum yields of photocyclization reactions of the linked phthalimides **94** and **98** are also greatly dependent on the nitrogen substituent, with the amide substrate reacting with a greater efficiency ($\phi = 0.12$) than the amine ($\phi = 0.04$).

When first viewed, the results presented above appear counterintuitive, and they lead one to question why the SET-promoted photoreactions are more efficient when they involve poorer electron donors (oxidation potentials of amines are often ca. 0.5 V lower than those of the corresponding amides). The answer to this question comes from an analysis of the key factors involved in determining the chemical and quantum efficiencies of excited-state reactions that proceed via pathways in which initial SET is followed by secondary reaction of charged radical intermediates. In the case at hand, SET from both α -silylamide and α -silylamine donors to the singlet excited state of the phthalimide chromophore should be highly exothermic. As a result, both intramolecular SET processes should occur at rates ($>1 \times 10^{10} \text{ s}^{-1}$)⁹ that are highly competitive with other pathways responsible for decay of the excited phthalimide. In this respect, Coyle and co-workers^{8c} have suggested that the $n-\pi^*$ singlet excited state of phthalimides is quenched by SET from pendant amino groups and that this quenching process is on the pathway for cyclization reaction of these substrates. The intermediate zwitterionic biradicals **100** (Scheme 34) formed by excited-state SET in (silylamino)- and (silylamido)phthalimides can react by several different routes. For example, exothermic back-SET would generate the ground-state starting materials with rates which are essentially independent of the nitrogen substituent. Competitive with this are secondary fragmentation reactions such as methanol-induced α -desilylation. Our earlier laser

Scheme 34

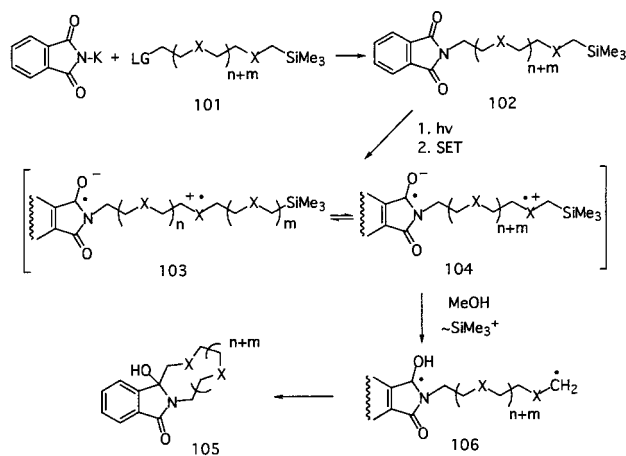


flash photolysis studies^{21,22} demonstrated convincingly that the rates of aminium radical fragmentation are highly dependent on the nitrogen substituent. Specifically, methanol-induced desilylation of silylamine cation radicals is 2 orders of magnitude slower than the analogous reaction of α -silylamide cation radicals. In more general terms, the rates of ion radical reactions are directly proportional to the stability of these short-lived intermediates, as judged from the redox potentials of neutral precursors. In summary, the large rate constants for desilylation of zwitterionic biradicals derived by photoinduced, intramolecular SET in α -(silylamido)phthalimides translates into a larger rate constant ratio, $k_{des}/(k_{des} + k_{BSET})$. Consequently, larger quantum efficiencies are observed for diradical and product formation.

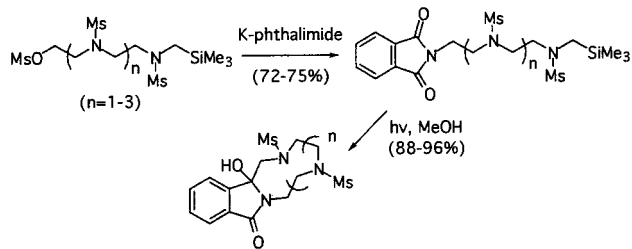
The Use of Phthalimide Photochemistry in Macrocyclic Polyamide, Polyether, and Polythioether Synthesis

The chemical yields of photoaddition and photocyclization reactions of systems comprised of phthalimides and α -silyl heteroatom donors are in the range normally deemed acceptable for synthetic applications. On the basis of this conclusion, we have recently designed strategies for the preparation of families of macrocyclic substances that rely on the use of this excited-state chemistry as the principal ring-building methodology. As depicted in Scheme 35, irradiation of phthalimides **102**, which have N-linked, silylmethyl-terminated polyheteroatom chains, should result in regioselective production of macrocyclic polyamides, -ethers, and -thioethers **105**. Accordingly,

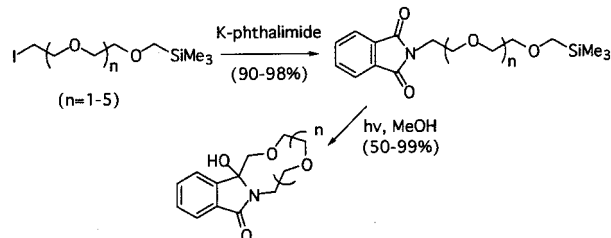
Scheme 35



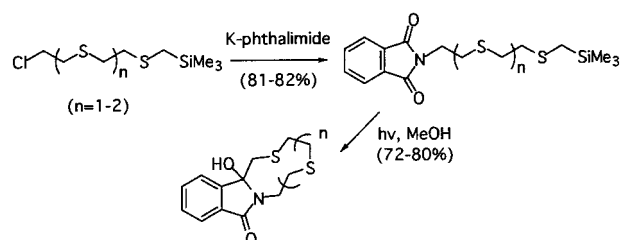
Scheme 36



Scheme 37



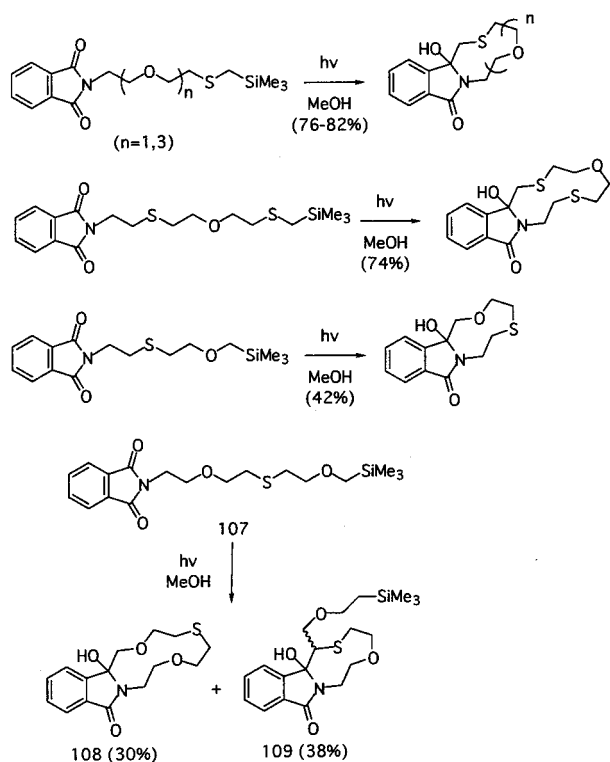
Scheme 38



photoinduced SET in these substrates would yield a mixture of rapidly interconverting zwitterionic biradicals **103** + **104**, whose relative abundance would be governed by the relative energies of the cation radicals (as judged from the oxidation potential at each heteroatom center). Importantly, the rates of secondary α -deprotonation and α -desilylation adjacent to each of the rapidly interconverting cation radical sites will not depend on their relative populations. Rather, the relative rates of these processes and, thus, the relative yields of 1, n -biradicals will be determined by the rates of the competing fragmentation reactions. Since desilylation of the terminal cation radical **104** should be the most rapid process,^{21,22} selective generation of the diradical precursors (**106**) of the macrocyclic products **105** should be observed.

The phthalimides **102**, which serve as starting materials for these photomacrocyclization reactions, are readily prepared by N-alkylation of potassium phthalimide with polyamide-, -ether-, and -thioether-linked mesylates or halides **101**. A wide variety of substrates (Schemes 36–39) in these families have been synthesized in this manner. As can be seen from the processes included in Schemes 36–38, irradiation of the phthalimido-silylpolyamides, -ethers, and -thioethers in MeOH solution does, indeed, result in modestly to highly efficient production of the corresponding macrocyclic products.^{38,39} The only exception to this general trend is seen in the excited-state reaction of the mixed ether–thioether substrate **107** (Scheme 39), where the macrocycle **109**, arising from a

Scheme 39



cation radical deprotonation route, is formed competitively.

Overview

In the above discussion, we have attempted to show how SET-promoted photoreactions of substituted phthalimides can be used to efficiently construct a number of interesting heterocyclic structures. Although the impetus for our efforts in this area has been mechanistic in nature, the studies have led to the development of a better understanding of how the chemical and quantum efficiencies of these excited-state processes can be enhanced. Finally, our investigations, along with parallel studies guided by Griesbeck,²³ have broadened the foundation of knowledge about phthalimide photochemistry so adeptly laid by Kanaoka and his co-workers some years ago.

The authors thank all of their enthusiastic and productive co-workers who contributed to the investigations described in this review. Financial support for the studies, provided by grants from the National Institutes of Health (GM-27251 to P.S.M.), the International Program of the National Science Foundation (INT-9796064 to P.S.M.), the Korea Research Foundation (1999-015-DI-0064 to U.C.Y.) and the Korea Science and Engineering Foundation (Basic Research Program, 2000-1-12300-006-3 to U.C.Y.), is gratefully acknowledged.

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