Sequential two electron photooxidation of *t*-amines: generation of a regiospecific iminium cation and its application in organic synthesis

Ganesh Pandey* and Smita R. Gadre

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune – 411 008, India
E-mail: Pandey@ems.ncl.res.in

Dedicated to Dr. Sukh Dev on the occasion of his 80th birthday

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Abstract

PET activation of cyclic *t*-amines, utilizing 9, 10-dicyanonaphthalene (DCN) as light absorbing electron acceptor in aqueous acetonitrile solution, leads to the generation of iminium cation intermediate involving electron – proton – electron (E-P-E) transfer sequence. Iminium cation generation is found to be highly regiospecific and depends upon the kinetic acidity which is subject to the stereoelectronic factor of the α –C-H proton of the unymmetrical *t*-amines. Tetrahydro-1, 3-oxazines (**6**) are synthesized in complete regio-and stereoselective manner from the PET activation of the substrates of type **4**. Nucleophilic alkylation of **6** by alkyl Grignard reagents provides *cis*- α, α'-dialkyl cyclic amines (**8**). Similarly, chiral perhydropyrido[2,1-b][1, 3, 4]-oxadiazinone (**11**) is synthesized as a precursor for the synthesis of optically active α-alkyl piperidines. Both enantiomers of hemlock alkaloid coniine (**13**) are also synthesized. Furthermore, to broaden the scope of these reactions, precursor **16** is designed for the synthesis of various α –amino acids and their N-alkyl derivatives.

Keywords: Photoinduced electron transfer, iminium cation, α-amino radical, iminium cation cyclization

Introduction

The generation of radical ions, critical intermediates in the development of a modern concept of organic reactivity,[1,2] by photoinduced electron transfer (PET) processes has acquired prominence in the last two decades[3,4] as photoexcitation readily induces well-defined redox potential differences between interacting substrates– a prerequisite for electron transfer. Significant progress is made in understanding the reactivity profiles of these high-energy odd-electron species[5] which have facilitated the application of PET reactions in driving energetically uphill

processes in the chemical synthesis.[6-8] The product formation from PET reactions is dependant, among many other parameters, on the redox potentials of the donor-acceptor pairs and the solvent polarity[9-11] and therefore, change in any one of these parameters has a significant influence on the reaction dynamics of the radical reactions.[12]

For example *t*-amine radical cations, produced from an excited arene-amine pair, are known to undergo H^+ transfer from the α-C-H bond to the geminal ion radical within the solvent cage, resulting in an arene-amine adduct through coupling of the resultant radical species.[13] Detailed mechanistic studies by Lewis and co-workers[14] of stilbene-amine photoaddition reactions have suggested that the reaction occurs within the contact ion pair (CIP) and conclusive evidence to this fact is derived by observing stilbene anion radical by time resolved resonance Raman spectroscopy.[15] These studies have also provided predictive capabilities for the regioselectivity of unsymmetrical amine photoadditions. In sharp contrast, photoreaction[16] between cyanoarene, a potent electron acceptor, and *t*-amine in acetonitrile gives the addition product of acetonitrile to cyanoarene instead of amine, possibly due to the involvement of longer lived solvent separated ion pairs (SSIP) in these particular systems.

This difference in the reactivity pattern of the excited singlet cyanoarene with *t*-amines,[16] led us to explore further this fundamental reaction processes. It was argued that the SSIP formed between 1,4-dicyanonaphthalene (DCN) and *t*-amine after initial one electron exchange, in a solvent of high dielectric constant, would dissociate into free radical ion pair (FRIP) where the cyanoarene anion radical would be potentially less reactive towards the amino cation radical. Predominant deprotonation from these amino cation radicals in aqueous solvent would result an α-amino radical and molecular oxygen dissolved in the solvent would quench the cyanoarene anion radical to its original ground state, possibly making it available for a second oxidation step from α-amino radical similar to the electrolytic oxidation[17] of amines as shown in Fig. 1.

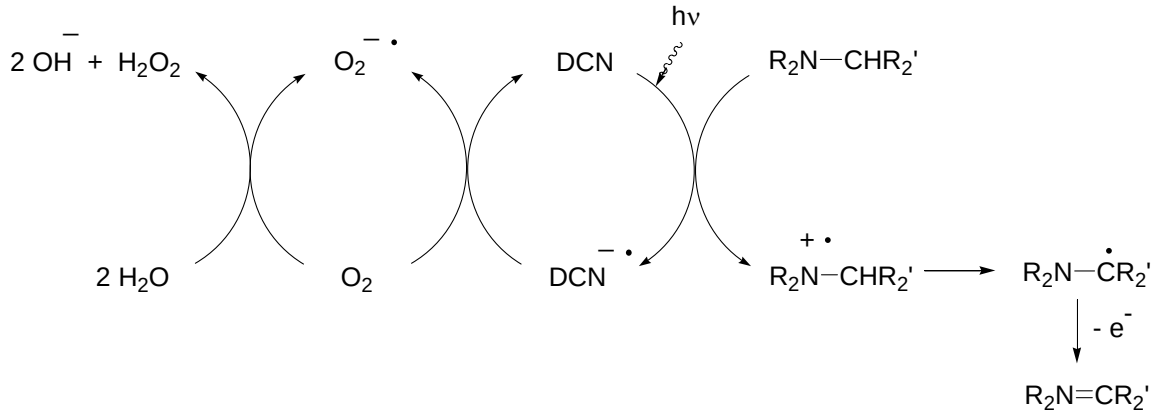


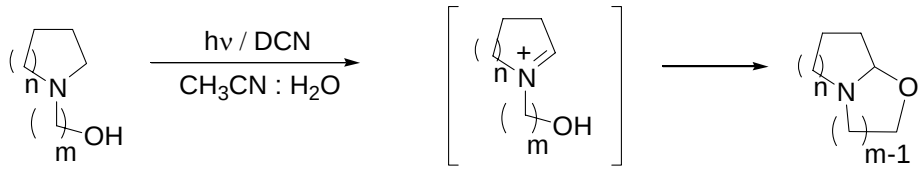
Figure 1

We have explored this concept extensively and chronicle in this account the progress we made in exploring the synthetic potentials of generating iminium cation through the PET concept.

Generation of regiospecific iminium cation: Synthesis of oxaazabicyclo[m.n.0]alkanes

Iminium cations are important electrophiles and are frequently utilized in preparing biologically active nitrogen heterocycles. Although, there are some synthetic approaches for generating iminium cation, they lack convenience and regioselecitivity.[18] As shown in Fig. 1, in our PET oxidation strategy, iminium cation would be formed from the further oxidation of an α-amino radical, generated by α- deprotonation of a planar amine cation radical owing to their low ionization potentials,[19] it was expected that the iminium cation, thus formed from unsymmetrical *t*-amines would be highly regiospecific and would depend upon the factors that influence the orientation of α-deprotonation from the initially formed amine radical cation. Kinetic acidity which is subject to stereoelectronic factors,[14] solvent polarity, basicity of the oxidizing agents and oxidation potential of amines are some of the important parameters that may influence the site of deprotonation of unsymmetrical amine radical cation.

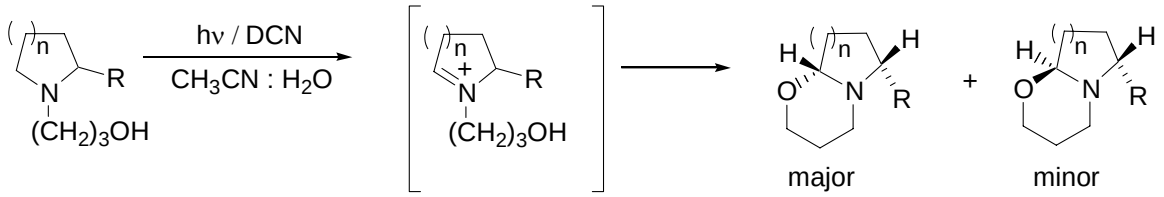
To illustrate this fact, PET reaction of amines of type **1,** due to the availability of two α-deprotonation sites, were studied[20] in aqueous acetonitrile utilizing 1,4-dicyanonaphthalene as light harvesting electron acceptor. PET reaction of **1** indicated complete regioselectivity for ring closure by producing oxaazabicyclo[m.n.0] alkanes (**3**) as the only product. The formation of **3** is explained by the intramolecular cyclization of –OH moiety to the iminium cation intermediate **2**. The regiospecificity of iminium cation **2** is rationalized by considering the faster rate of proton loss from the ring α -CH than the *exo*-cyclic α -CH from the corresponding amine cation radical owing to the stereoelectronic factors.



1 **2** **3**

a : m = 2, n = 1 70 %
b : m = 3, n = 2 72 %

To probe further, the regioselectivity aspect of iminium cation generation, we studied the reaction from the substrates **4** where two ring α-deprotonation site is available.[21] PET reaction of these substrates produced tetrahydro-1,3-oxazines (**6**) in complete regio and stereoselective manner.



4 **5** **6**

		a : b	
i	n = 2, R = Me	96 : 4	92%
ii	n = 2, R = n-Bu	90 : 5	90%
iii	n = 1, R = n-Bu	93 : 7	88%

The formation of **6** indicated that there is complete regioselectivity in the iminium cation generation towards the less substituted α -CH moiety of cyclic amines. Since the deprotonation step from amine cation radical requires the overlap of the half vacant nitrogen *p*-orbital with the incipient carbon radical *p*-orbital,[14] the stereoelectronic effect forces the generation of the least substituted α - amino radical and thus, the formation of the regioselective iminium cation **5**. The formation of major diastereomer **6a** in these cyclizations is explained[21] on the basis of the preferential front side attack of the hydroxy group on the iminium cation possible for steric reasons. Chlorine dioxide (ClO_2) mediated cyclization of **4i**, also known to proceed *via* an electron abstraction route, is reported[22] to show greater but not complete preference for ring closure towards the less substituted (ratio 6:1) carbon atom. Although, the exact reason for this difference could not be ascertained, reasonable efforts have been made to implicate the solvent polarity or basicity of $DCN^{-\cdot}$ for this observation.[21]

The rate of reaction is significantly accelerated by using methyl viologen (MV^{++}) as an electron relay. [23]

The lower reduction potential of MV^{2+} (MV^{2+} / $MV^{+\cdot}$ = 0.45 ev)[2524] than oxygen (O_2 / $O_2^{-\cdot}$ = -78 ev)[5a] facilitated the reaction and with the recovery of DCN as shown in Fig. 2.

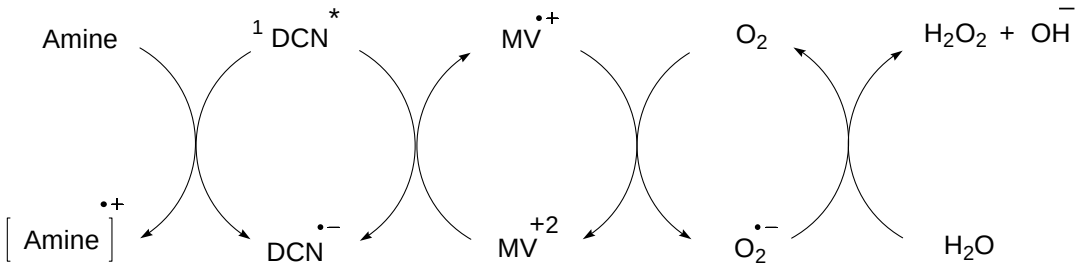
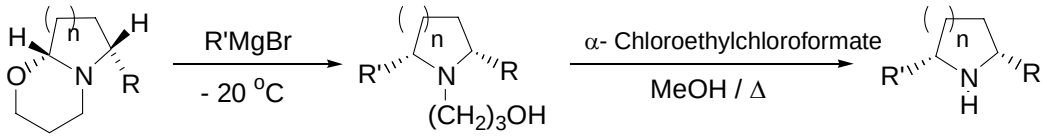


Figure 2

The easy accessibility of **6** and its reactive N-O acetal functionality prompted us to utilize them for C-C bond formation reaction α- to nitrogen atom by nucleophilic ring opening reaction.[25] Reaction of **6** with alkyl Grignard reagent produced[20, 23] cis- α, α'- dialkylpiperidines and pyrrolidines (**7**), respectively. Both *cis*- and *trans*-α, α' - dialkylpiperidines and pyrrolidines

(**8**) are widely distributed alkaloids with significant biological activity.[26] Although, there are number of synthetic routes known[27] for the synthesis of these alkaloids, they lack selectivity as these methodologies end up giving mixtures of both *cis* and *trans* isomers. Therefore, our approach represents one of the most stereoselective routes for the synthesis of α, α'-dialkylpiperidine and pyrrolidines (**8**). The N-dealkylation of **7** was achieved by stirring with α-chloroethylchloroformate in dichloromethane followed by heating the resultant salt with methanol.[28]



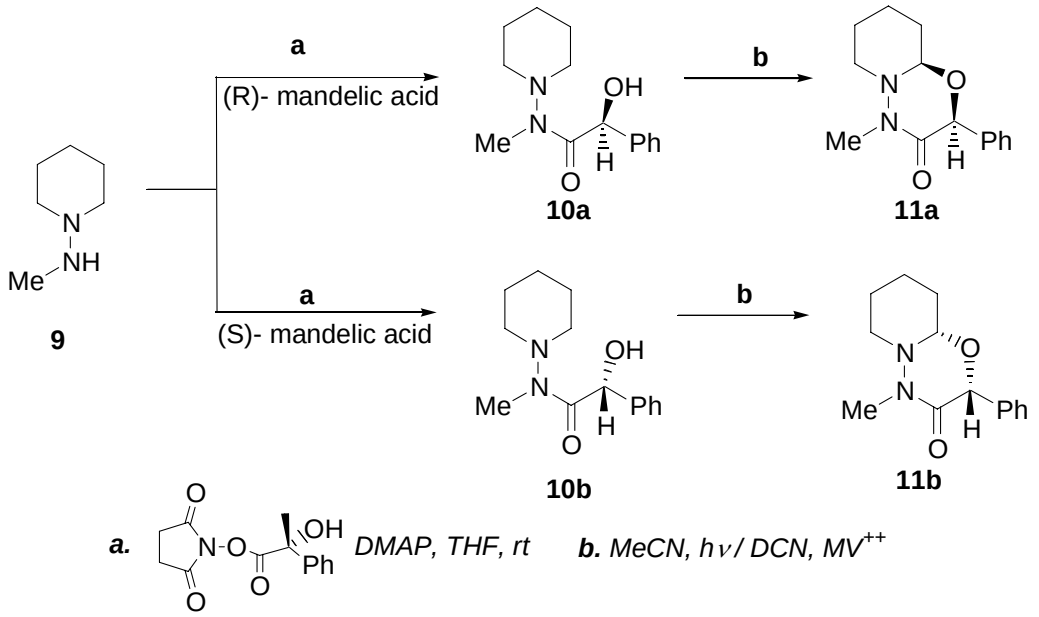
6 **7** **8**

n = 2, R = Me, R' = Bu	90%
n = 2, R = R' = n-Bu	95%
n = 1, R = R' = n-Bu	92%

Synthesis and utilization of chiral perhydropyrido[2,1-b] [1,3,4]-oxadiazinone for the preparation of conine

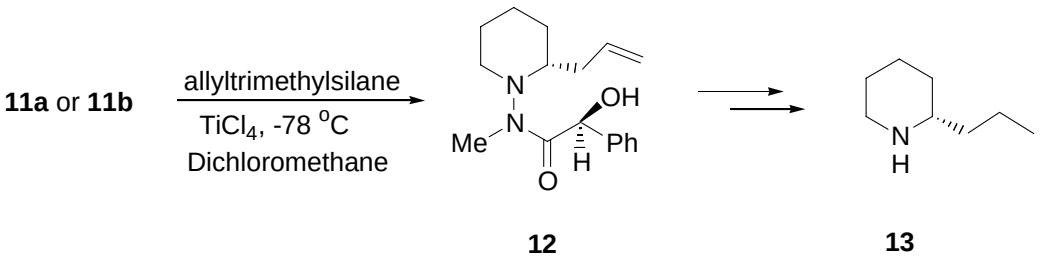
The easy access of cyclic N-O acetal functionality by the intramolecular cyclization of PET promoted *in situ* generated iminium cation by –OH moiety and its utilization for –C-C- bond formation reaction α to the nitrogen atom in a *t*-cyclic amine[20, 23] encouraged us further to envisage the chiral perhydropyrido[2,1-b] [1,3,4]- oxadiazinone (**11**) as a precursor for the enantioselective α-alkylation of cyclic amines.[29] 2-Alkylated piperidines and their synthetic analogues are endowed with a range of biological activities and have great pharmaceutical importance.[30] Most of the methodologies reported[31] in this area are indirect and none of them utilize piperidines as the precursor. Therefore, the alkylation strategy from **11**, derivable by the PET activation of **10**, would be of great significance as the chiral auxiliary would be recyclable.

Precursor **11,** in both enantiomeric forms (Scheme1) could be obtained in 80 % yield by the PET reaction of **10**, synthesized by the reaction with N-methylaminopiperidine (**9**) and either enantiomer of commercially available mandelic acid.



Scheme 1

The *cis* -stereochemistry between H_2 and H_9 of **11** emerged due to the front side attack of the nucleophile to the iminium cation intermediate.[29]



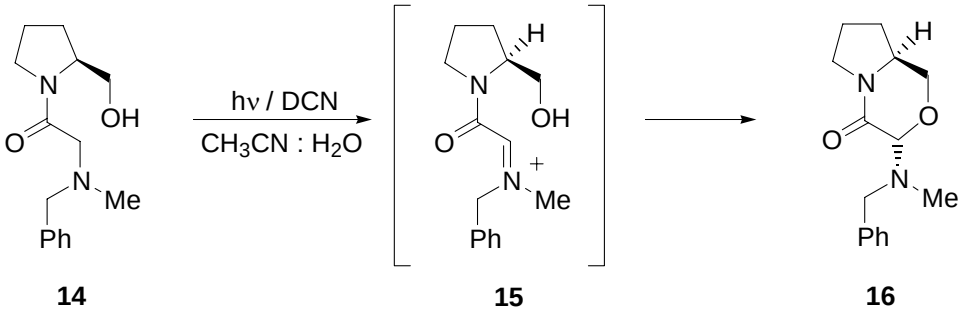
Nucleophilic alkylation of these oxadiazinones (**11**) by alkyltrimethylsilane in the presence of $TiCl_4$ in dry DCM at –78 °C afforded corresponding alkylated product **12** in >90% yields. Optically active hemlock alkaloid conine (**13**) is synthesized by the reductive elimination of hydrazide bond followed by olefinic reduction[29].

Synthesis and utilization of 3-[benzyl(methyl)amino]-perhydro- pyrrolo[2.1-c] [1,4]oxazin-4-one in the preparation of optically active α-amino acids

To broaden further the synthetic scope of PET initiated *in situ* generation of iminium cation and its cyclization with tethered –OH group, substrate **17** was designed[32] as a precursor for the synthesis of optically active α -amino acids.

The design of **16** was conceived by considering its unique structural feature, a reactive α-amino ether functionality; highly suitable for stereoselective nucleophilic alkylation reactions,

ease of hydrolysis of the resultant amides to produce α-amino acids and their N-methyl derivatives.



PET activation of **14** gave **16** (73% yield) in 13.3:1 diastereomeric ratio, obviously involving iminium cation intermediate **15**. The preference for

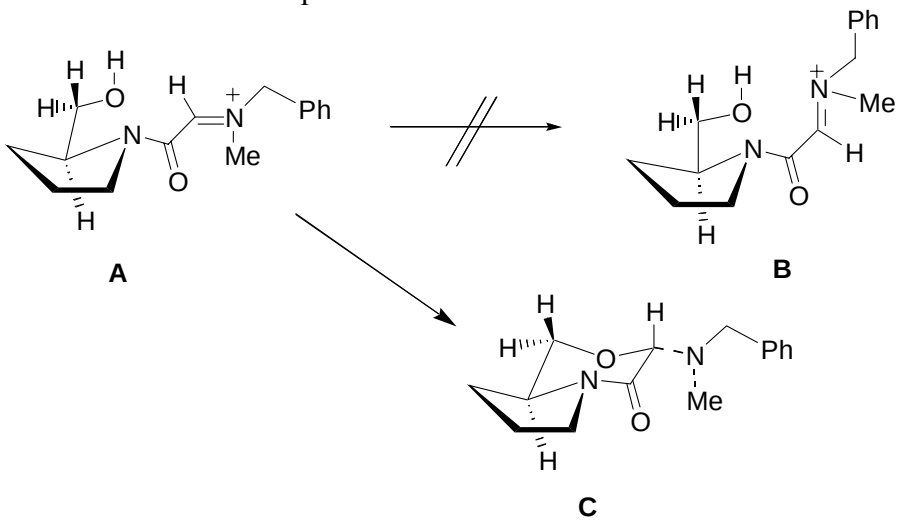
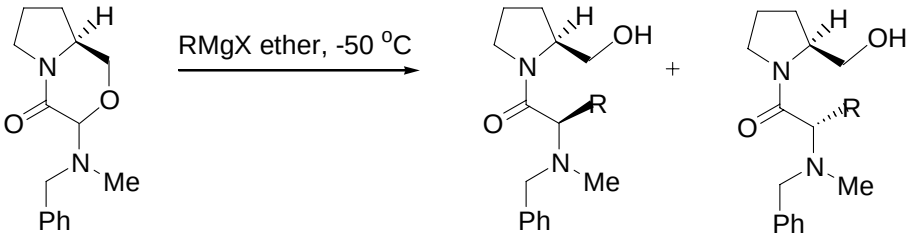


Figure 3

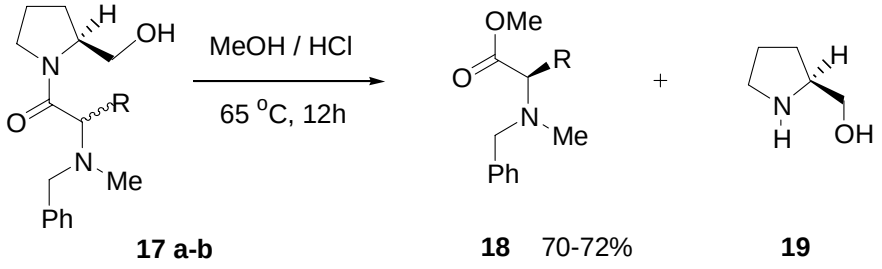
the formation of the major diastereoisomer (**17**) is explained[33] by assuming back side attack of the –OH moiety of prolinol on the iminium cation, leading to preferred energy minimized transition state in an equatorial position (C) so as to produce the energetically favorable *trans*-bicyclic system as shown in Fig. 3

Nucleophilic ring opening of **16** either by alkyl Grignard reagent or alkyl trimethylsilane in the presence of $TiCl_4$ gives corresponding amides **17** with the diastereomeric ratio as indicated in the parentheses[33].



	17a	17b	Yield (%) (isolated)
a R = CH_2Ph	5.3	1	76
b R = Me	3.6	1	72
c R = Ph	2.8	1	70
d R = $CH(Me)_2$	2.2	1	68

Hydrolysis of **17** followed by N-debenzylation gave the corresponding α-amino acid derivatives in good optical purity[32, 33] (Scheme2).



	$[\alpha]_D^{25}$	Optical Purity (%)
a R = CH_2Ph	-51.2 (c=1, $CHCl_3$)	70
b R = Me	-59.3(c=1, $CHCl_3$)	60
c R = Ph	+5.8(c=1, $CHCl_3$)	49
d R = $CH(Me)_2$	-26.1(c=1.2, $CHCl_3$)	38

Scheme 2

Conclusions

The results presented in this account demonstrate the development of a new concept of *in situ* generation of iminium cations directly from unsubstituted cyclic amines by PET oxidation. The most significant aspect of this invention lies in the generation of regioselective iminium cations from unsymmetrical *t*-amines in "true sensitized" manner (atom economy). The application of this concept in designing precursors for enantioselective α-alkylation to a cyclic amine and for the synthesis of optically active α-amino acid derivatives is very significant as chiral auxiliaries

are recoverable. It is expected that this concept will attract considerable application in the newer synthetic designs of alkaloids and other heterocycles.

Acknowledgements

I am indebted to all my colleagues whose names appear in the references for their intellectual and experimental contributions to this field.

References

1. Kochi, J. K.; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1227.
2. (a) Pross, A.; *Adv. Phys. Org. Chem*. **1985**, *21*, 99. (b) Pross, A., Shaik, S. S. *Acc. Chem. Res*. **1983**, *16*, 363.
3. Fox, M. A.; Chanon, M. D. *Photoinduced Electron Transfer Reactions*, Elsevier, Amsterdam, 1988, Parts A-D.
4. Fox, M. A. *Adv. Photochem*. **1986**, *13*, 295.
5. (a) Mattes, S.L.; Farid, S. *Organic Photochemistry*, Padwa, A. (Ed), Marcel-Dekker, Inc.; New York, 1986, *6*, 237. (b) Davidson, R. S.; *Adv. Phys. Org. Chem.* **1983**, *19*, 1.
6. Pandey, G. *Top. Curr. Chem*. **1993**, *168*, 175.
7. Pandey, G. *Molecular and Supramolecular Photochemistry*, Ramamurthy, V. (Ed), Marcel-Dekker Inc., New York, 1997, chapter 7, 245.
8. (a) Mattay, J. *Synthesis*, **1989**, 233. (b) Mattay, J. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 825.
9. Mataga, N.; Otolenghi, M. *Molecular Association*, Foster, R. (Ed), Academic Press, London**,** 1975, 2, chapter 1.
10. Gould, I. R.; Ege, D.; Moser, J. E.; Farid, S. *J. Am. Chem. Soc*. **1990**, *112*, 4290.
11. Kellett, M. A.; Whitten, D. G.; Gould, I. R.; Bergmark, W. R. *J. Am. Chem. Soc.* **1991**, *113*, 358.
12. Gan, H.; Zhao, X.; Whitten, D. G. *J. Am. Chem. Soc*. **1991**, *113*, 9409 and references cited therein.
13. Barltrop, J. A. *Pure Appl. Chem*. **1973**, *33*, 179.
14. (a) Lewis, F. D. *Acc. Chem. Res*. **1986**, *19*, 401. (b) Lewis, F. D.; Ho, T-I.; Simpson, T. *J. Am. Chem. Soc*. **1982**, *104*, 1924; *idem. J. Org. Chem*. **1981**, *46*, 1077.
15. Hub, W.; Schneider, S.; Dorr, F.; Lewis, F. D. *J. Am. Chem. Soc*. **1982**, *104*, 2044; *idem. ibid.* **1984**, *106*, 708.
16. Ohashi, M.; Kudo, H.; Yamada, S. *J. Am. Chem. Soc*. **1979**, *101*, 2002.
17. Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev*. **1978**, *78*, 243.

18. (a) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc*. **1960**, *82*, 5148. (b) Lounasmaa, M.; Koskineu, A. *Heterocycles* **1984**, *22*, 1591 and references cited therein. (c) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (d) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem*. **1990**, *55*, 215.
19. Griller, D.; Lossing, F. P. *J. Am. Chem. Soc*. **1981**, *103*, 1586.
20. Pandey, G.; Kumaraswamy, G. *Tetrahedron Letters* **1988**, *29*, 4153.
21. Pandey, G.; Reddy, P. Y.; Bhalerao, U. T. *Tetrahedron Letters* **1991**, *32*, 5147.
22. Chien, C. K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc*. **1988**, *110*, 4829.
23. Pandey, G.; Kumaraswamy, G.; Reddy, P. Y. *Tetrahedron* **1992**, *48*, 8295.
24. Arnold, D. R.; Wong, P. C.; Maroulis, A. J.; Cameron, T. S. *Pure and Appl. Chem*. **1980**, *52*, 2609.
25. Huang, P. Q.; Arseniyadis, S.; Husson, H-P. *Tetrahedron Letters* **1987**, *28*, 547.
26. (a) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev*. **1983**, *83*, 379. (b) Adrouny, G. A.; Derbes, V. J.; Jung, R. C. *Science* **1959**, *130*, 449. (c) Blum, M. S.; Walker, J. R.; Callahan, P. S.; Novak, A. F. *Science* **1958**, 128, 306.
27. (a) Wasserman, H. H.; Rodriques, K.; Kucharczyk, R. *Tetrahedron Letters* **1989**, *30*, 6077. (b) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Letters* **1986**, *27*, 1489. (c) Takahashi, K.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem*. **1985**, *50*, 4368.
28. Olofson, R. A.; Martz, J. T. *J. Org. Chem*. **1984**, *49*, 2081.
29. Pandey, G.; Das, P. *Tetrahedron Letters* **1997**, *38*, 9073.
30. (a) Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem*. **1997**, *40*, 591. (b) Vecchietti, V; Giordani, A.; Giardina, G.; Colle, R.; Clarke, G. D. *J. Med. Chem*. **1991**, *34*, 397. (c) Adger, B.; Dyer, U.; Hutton, G.; Woods, M. *Tetrahedron Letters* **1996**, *37*, 6399.
31. (a) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Letters* **1994**, *35*, 6119. (b) Yamazaki, N.; Kibayashi, C. *Tetrahedron Letters* **1997**, *38*, 4623. (c) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetrahedron Letters* **1992**, *33*, 7635. (d) Marx, E.; Bouz, M. E.; Celerier, J. P.; Lhommet, G. *Tetrahedron Letters* **1992**, *33*, 4307. (e) Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Letters* **1994**, *35*, 7015. (f) Waldmann, H.; Braun, M. *J. Org. Chem*. **1992**, *57*, 4444.
32. Pandey, G.; Reddy, P. Y.; Das, P. *Tetrahedron Letters* **1996**, *37*, 3175.
33. Pandey, G.; Das, P.; Reddy, P. Y. *Eur. J. Org. Chem*. **2000**, 657.