



A potentially general method to control relative stereochemistry in enone–olefin 2+2-photocycloaddition reactions by using eniminium salt surrogates[†]

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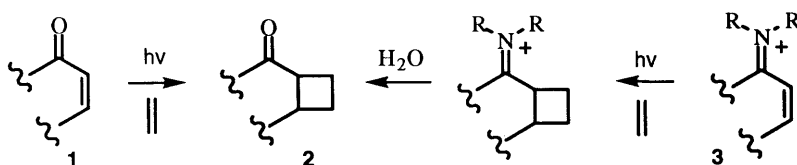
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Abstract

A new strategy to control the stereochemistry of enone–olefin 2+2-photocycloaddition reactions, based on the use of eniminium salt surrogates, is experimentally tested. In contrast to enone–olefin photocycloadditions, which emanate from enone triplet excited states and follow non-concerted pathways, analogous reactions of conjugated eniminium salts can occur by singlet, concerted routes and, as a result, would deliver cyclobutane ring containing products with complete control of relative stereochemistry. This proposal was tested by using a series of eniminium salts, which contain electron rich and electron poor olefin tethers. The results show that intramolecular 2+2-photocycloadditions of these substrates display moderate to high degrees of stereospecificity. © 2000 Elsevier Science Ltd. All rights reserved.

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Enone–olefin 2+2-photocycloadditions (**1**→**2**, Scheme 1) rank among the most general of all organic photochemical processes. The intramolecular version of this excited-state reaction, discovered nearly a century ago when photochemistry was in its infancy,¹ has blossomed into a



Scheme 1.

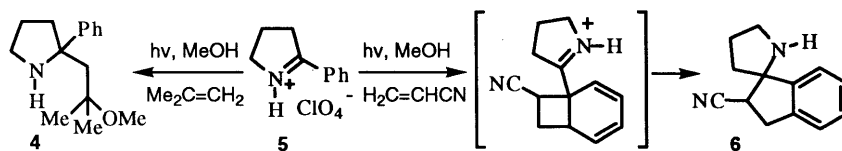
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[†] This paper is dedicated to Harry H. Wasserman, an outstanding scholar and teacher whose tireless work as editor of this journal contributed enormously to the science of organic chemistry.

synthetically potent methodology.² The numerous examples of natural product syntheses, which incorporate photoinduced polycyclic cyclobutylketone formation and fragmentation as a key design element, attest to the preparative power of these 2+2-cycloaddition reactions.³ Despite its wide use, several features of this process hinder its application in synthetic chemistry. Firstly, since most, if not all, of 2+2-photocycloadditions emanate from enone triplet excited states, cyclobutane ring formation follows a non-concerted route via the intermediary of a triplet 1,4-diradical.⁴ Consequently, relative stereochemistry in the olefin and, in some cases, the enone is lost. Secondly, a general method to control the absolute stereochemistry of enone-olefin photocycloadditions has not yet been developed.⁵

Results of our early studies of iminium salt photochemistry⁶ have led to the formulation of potentially general solutions to both of these problems. Conjugated ketones (**1**, Scheme 1) possess low lying $n-\pi^*$ singlets and, as a result, they have rapid and efficient routes for intersystem crossing (ISC) ($^1n-\pi^* \rightarrow ^3\pi-\pi^*$).⁷ In contrast, ISC in the analogous iminium salts **3** is less rapid owing to the forbidden nature of $^1\pi-\pi^* \rightarrow ^3\pi-\pi^*$ processes.⁷

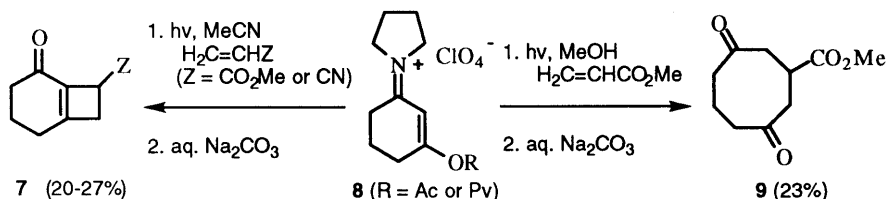
Owing to this feature, iminium salts have contrastingly longer lived, efficiently fluorescing and chemically reactive singlet excited states. 2-Phenyl-1-pyrrolinium perchlorate (**5**) is exemplary in this regard in that its $\pi-\pi^*$ singlet ($\tau_{S1}=20$ ns, $\phi_f=0.16$) participates in both SET (\rightarrow **4**) and 2+2-cycloaddition (\rightarrow **6**) reactions with olefins (Scheme 2).^{6b}



Scheme 2.

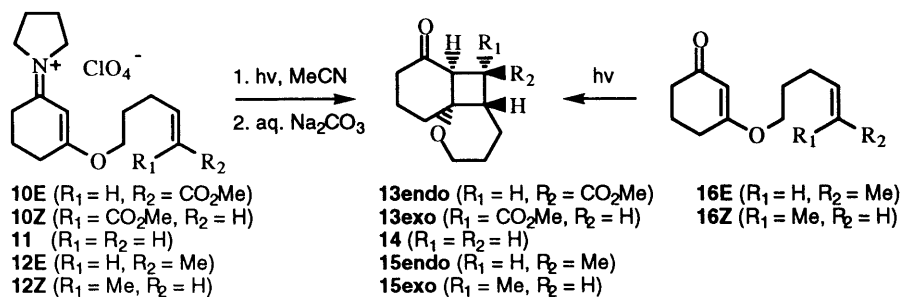
These observations suggest that 2+2-cycloaddition reactions of eniminium salts **3** (Scheme 1) are likely to be singlet processes and, consequently, that they could follow concerted pathways. In this event, cyclobutylketones, generated by hydrolysis of the corresponding cyclobutyliminium salts, would be produced with retention of double-bond stereochemistry. Since eniminium salts are easily prepared from 1,3-diketones, they would serve as simple surrogates in enone-olefin photocycloadditions when control of relative stereochemistry is an issue. In addition, the secondary amine moiety in these salts could serve as the site for chiral auxiliary placement when control of facial selectivity (i.e. enantioselectivity) is desired.⁸

Preliminary studies have been conducted to test several features of these proposals. The results presented below demonstrate that conjugated eniminium salts undergo both inter- and intramolecular 2+2-photocycloadditions with electron-poor and electron-rich olefins and that these reactions occur with modest to high degrees of stereospecificity. Initial investigations focused on intermolecular reactions of the 1,3-cyclohexandione derived perchlorate salts **8**⁹ in order to probe the feasibility of the cycloaddition process. Irradiation ($\lambda > 250$ nm) of MeCN solutions of these substances, containing methyl acrylate or acrylonitrile, followed by aq. Na_2CO_3 work-up and chromatographic separation leads to isolation of the corresponding bicyclic-ketones **7** (Scheme 3). In contrast, the cyclooctanedione **9** is produced in the photoreactions of methyl acrylate with **8** in MeOH. Although proceeding with low chemical efficiencies, these reactions demonstrate that conjugated eniminium salts do participate in 2+2-photocycloaddition reactions. In these cases, the initially formed cyclobutyliminium salts undergo secondary reactions involving elimination (\rightarrow **7**) or fragmentation (\rightarrow **9**).



Scheme 3.

To determine the stereochemical course and olefin dependence of these reactions, several tethered substrates **10**–**12** (Scheme 4) were prepared by silver ion promoted, *O*-alkylation reactions of 3-pyrrolidinocyclohex-2-en-1-one.⁹ Irradiation of MeCN solutions of these salts, followed by aq. Na₂CO₃ work-up and chromatographic separation, gave the corresponding tricyclic ketones shown in Scheme 4.¹⁰ The results (Table 1) indicate that eniminium salts tethered to electron-poor olefins undergo efficient intramolecular 2+2-photocycloadditions. Although dependent on the percent conversion/irradiation time, these processes appear to be highly stereospecific. Accordingly, photocyclization of the *E*-ester substrate **10E** yields **13endo** (ca. 100:1) while the epimer **13exo** is produced predominantly (ca. 7:1) from the *Z*-ester containing salt **10Z**.¹⁰



Scheme 4.

Concerns about the potential for competing SET between electron-rich olefins and the eniminium salt excited states mandated our study of the tethered substrates **11** and **12**. The results show that the vinyl analog **11** undergoes efficient intramolecular 2+2-photocycloaddition to produce tricyclic ketone **14**. The *E*- and *Z*-propenyl tethered salts react similarly and, in contrast to the corresponding enones **16E** and **16Z** (Scheme 4, Table 1), their photocyclization reactions display conversion dependent, fair to high degrees of stereospecificity.

Several additional observations provide information about the mechanism for the olefin–eniminium salt photocycloadditions and the dependence of product diastereomer ratios on the extent of starting material conversion. Firstly, ¹H NMR monitoring of the photolysates shows that olefin isomerization in the starting salts does not occur during the photoreactions. Thus, the mechanism for these processes does not involve the intermediacy of a 1,4-diradical, which is capable of undergoing stereomutation and fragmentation in competition with cyclobutane ring formation. Secondly, the lower degrees of stereospecificity observed at higher conversions are likely due to secondary photo-epimerization reactions of the tricyclic ketones, formed by in situ hydrolysis of the cyclobutyliminium salts. In accord with this suggestion is the observation that irradiation of MeCN solutions of the tricyclic ketone pairs **13endo**–**13exo** and **15endo**–**15exo** results in isomer interconversion.¹¹

Table 1
Photoreactions of the tethered eniminium perchlorates **10–12**

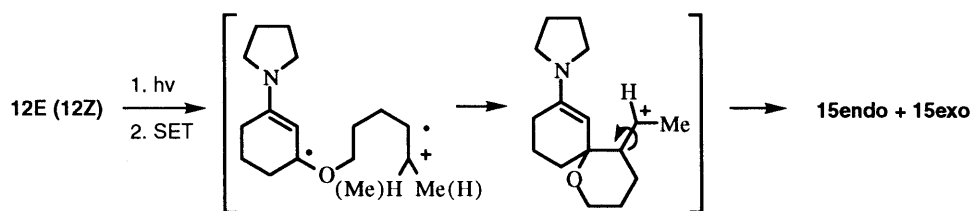
Eniminium perchlorates	Percent conversion ^a	Percent yield ^b	Products (ratios) ^c
10E	100	84	13endo + 13exo (100:1)
10E	20	80	13endo + 13exo (100:1)
10Z	100	39	13endo + 13exo (6:1)
10Z	90	54	13endo + 13exo (3:1)
10Z	40	55	13endo + 13exo (1:7)
11	100	75	14
12E	75	49	15endo + 15exo (2.3:1)
12E	30	56	15endo + 15exo (2.6:1)
12Z	75	48	15endo + 15exo (1:6)
12Z	30	42	15endo + 15exo (1:10)
16E	75	25	15endo + 15exo (1.4:1)
16E	35	62	15endo + 15exo (1.6:1)
16Z	50	66	15endo + 15exo (1.5:1)
16Z	35	54	15endo + 15exo (1.4:1)

^a Determined by UV-spectroscopic monitoring of the photolysate.

^b Based on reacted eniminium salt.

^c Determined by ¹H NMR integration of product mixtures.

Although additional studies are required to prove the mechanistic proposals offered above and to explore the scope of this strategy, the current effort has shown that conjugated eniminium salts participate in stereospecific intramolecular 2+2-photocycloaddition reactions. This is a likely result of the operation of a singlet excited state, concerted mechanism for these processes. However, photocyclizations of electron-rich olefin-tethered eniminium salts occur with reduced levels of stereochemical control compared to those of their electron-poor olefin counterparts. This might be due to competition between concerted and SET (Scheme 5) pathways for 2+2-cycloaddition of olefins, which have lower oxidation potentials (i.e. better electron donors).



Scheme 5.

Acknowledgements

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8. Molecular mechanics (Macromodel) calculations on globally minimized transition states for inter- and intramolecular 2+2-additions of olefins to cyclic eniminium salts, derived from C-2 chiral *trans*-2,5-disubstituted-pyrrolidines, suggest that photoreactions of these substrates will display high degrees of facial selectivity.
9. The perchlorate salts, used in this study, were prepared by treatment of 3-pyrrolidino-cyclohex-2-en-1-one with the requisite acid chloride or alkenyl bromide in the presence of silver perchlorate in MeCN followed by silica gel chromatographic purification. The salts have UV-absorption maxima at 283–284 nm ($\epsilon = 2\text{--}4 \times 10^4$).
10. (a) All previously unreported substances have spectroscopic data in accord with their assigned structures. The tricyclic ketone **14** was described previously (Ref. 10b). Stereochemical assignments to the ketones **13endo** and **13exo** were made by use of X-ray crystallography; (b) Tamura, Y.; Ishibashi, H.; Kita, Y.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1973**, 101; Mattay, J.; Banning, A.; Biscof, E. W.; Heidbreder, A.; Runsink, J. *Chem. Ber.* **1992**, *125*, 2119.
11. The photoisomerization processes most likely occur by an excited state α -cleavage, 1,4-diradical recombination pathway.