A General Strategy for Absolute Stereochemical Control in Enone−Olefin [2 + 2] Photocycloaddition Reactions

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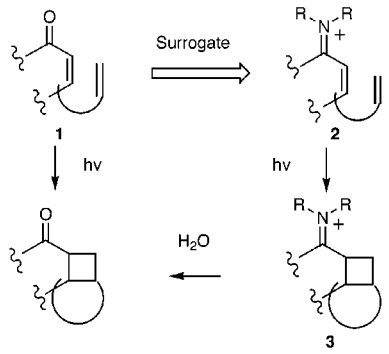
Intramolecular enone−olefin [2 + 2] photocycloaddition reactions have been widely used in organic synthesis as principle steps in routes for the preparation of structurally complex targets.[1] Among the advantageous features of these processes is that (1) elaborate polycyclic structures can be constructed under mild conditions, and (2) ring strain in the cyclobutyl-ketone photoproducts can be used to drive desired secondary fragmentation and rearrangement reactions. Despite extensive employment of this excited-state reaction in synthesis, wider applications are limited by two important factors. First, since the [2 + 2] photocycloadditions proceed via the intermediacy of triplet 1,4-biradicals[2] they occur with randomization of stereochemistry.[3] Second, universally applicable methods to control facial selectivities in these processes have not been developed. Although some highly creative approaches to solve the latter problem have been described[4] (e.g., the masterful use of solid-state photochemistry by Schultz and co-workers),[5] low levels of enantioselectivity are typically observed.

Observations made in our early studies of iminium salt photochemistry[6] have led us to formulate a potentially general strategy to solve both of these stereochemical problems. The concept is based on the use of eniminium salts **2** as surrogates for enones **1** (Scheme 1). Since the eniminium salts possess only $\pi-\pi^*$ excited states, intersystem crossing from singlet to triplet excited states is expected to be slow. As a result, [2 + 2] photocycloaddition reactions of these substrates (**2**→**3**) should occur from singlet excited states[6a] and, as a result, they could follow concerted mechanistic pathways. Results from our preliminary studies[7] of eniminium salt photochemistry validate this proposal. Specifically, intramolecular [2 + 2] photocycloadditions of the alkene-tethered salts **4** (Scheme 2) are efficient singlet excited-state processes that deliver tricyclic products **5** with a preference for retention of alkene stereochemistry.

Another key feature of this strategy is the control of [2 + 2] photocycloaddition facial selectivity by amine based, chiral auxiliaries. In transition states for concerted cycloadditions of the eniminium salts, properly designed N-linked chiral auxiliaries (e.g. those derived from C_2-chiral amines) could reside close to the sites of C−C bond formation. Consequently, face selectivities in [2 + 2] photocycloadditions of these substrates could be large. This proposal gains qualitative support from the results of molecular mechanics calculations (Macromodel, MM3, global energy minimization) performed on transition states for intramolecular [2 + 2] cycloadditions of C_2-chiral pyrrolidine-derived, β-substituted cyclic eniminium cations (Table 1). The calculations indicate that the 2,5-substituents in the N-heterocyclic moieties of these salts can induce large energy differences between the transition states for addition anti and syn to the near R-groups (R_N).

A demonstration of the feasibility of this eniminium salt-based strategy to control the absolute stereochemistry of enone−olefin photocycloadditions has come from investigations with the alkene-tethered, C_2-chiral pyrrolidino-cyclohexeniminium perchlorates **8**−**10** (Scheme 3). These substrates are prepared by $AgClO_4$-promoted O-alkylations of the enamino-ketones **7** with l-pentenyl bromide. The enaminones originate by condensation of 1,3-cyclohexandione with the known, enantiomerically pure *trans*-

Scheme 1



Scheme 2

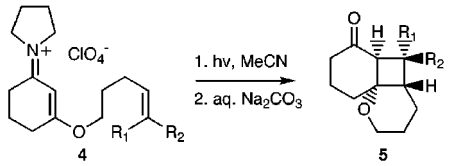
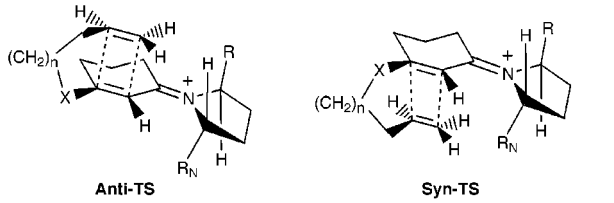


Table 1. Calculated (Macromodel) Energies of Globally Minimized Transition States for Intramolecular [2 + 2] Photocycloadditions of C_2-Chiral Eniminium Salt



variables			energy (kJ/mol)[a]		
R	X	n	anti-TS	syn-TS	difference
Me	O	2	169	180	11
CH_2OMe	O	2	94	107	13
Ph	O	2	163	180	17
Ph	CH_2	1	138	154	16

[a] Molecular mechanics calculations using Macromodel (MM3), parametrized [2 + 2] cycloaddition transition-state distances and angles, and the Monte Carlo method with 500 conformers sampled in each case.

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Scheme 3

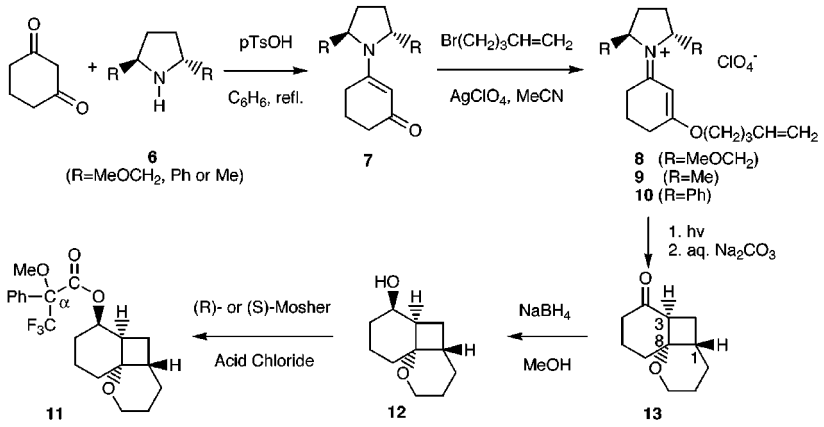

Table 2. Facial Selectivities (% ee) in Intramolecular [2 + 2] Photocycloadditions of the C_2-Chiral Eniminium Perchlorates **8** and **9**

	conditions[a]			
eniminium perchlorate	conversion (%)[c]	temperature (°C)	yield (%)	% ee[b] tricyclic ketone **13**
8	90	20	51	63
8	56	20	65	75
8	40	20	61	82
8	60	4	60	78
8	46	4	56	80
9	53	20	20	37
9	51	20	25	31
9	48	20	31	37

[a] All photoreactions were run in MeCN by using Corex glass-filtered light. [b] From the % de of the ester derivative, formed by reaction of alcohol **12** with (*R*)(−)-Mosher acid chloride, by using HPLC on a Chiralcel-OJ column with 9:1 hexane−^{i}PrOH as eluant. [c] Determined by UV-spectroscopic monitoring of the photolyzate.

2,5-disubstituted-pyrrolidines.[8] Like the parent eniminium salt **4**,[7] **8** is transformed to the tricyclic ketone **13** by irradiation ($\lambda >$ 250 nm) in MeCN followed by aqueous Na_2CO_3 workup. The degree of facial selectivity attending this process is assessed by determining the % de of the Mosher ester derivatives **11** of the alcohol **12,** produced by $NaBH_4$ reduction of **13**. The four stereoisomers of **11**, obtained by treatment of racemic **12** with (*R*)- and (*S*)-Mosher acid chlorides, can be separated by HPLC on a Chiralcel-OJ column using 9:1 hexane−^{i}PrOH as eluant. The enantiomer ratio in photoproduct **13** is best determined by using HPLC analysis of the ester derived by treatment of **12** with (*R*)(−)-Mosher acid chloride. The data (Table 2) show that intramolecular photocycloaddition of the bis-methoxymethyl-substituted pyrrolidino-eniminium salt **8** proceeds with moderately high facial selectivity especially for reactions in which conversion of **8** is maintained in the 40−60% range.

Preparative HPLC provides a crystalline sample of the minor ester **11a**, formed by a sequence of reactions involving irradiation of eniminium salt **8**, reduction of ketone **13**, and reaction of alcohol **12** with (*R*)(−)-Mosher acid chloride. X-ray crystallographic analysis (Figure 1) of this substance shows that it has the (1*R*,3*S*,4*S*,8*R*,α-*S*)-absolute stereochemistry. Thus, the major enantiomer of **13** formed by irradiation of **8** has the (1*S*,3*S*,8*S*)-stereochemistry.

The direction but not magnitude of facial selectivity in the intramolecular photocycloaddition reaction of 2,5-dimethylpyrrolidino-eniminium perchlorate **9** matches that observed for **8** (Table 2). The lower % ee observed in this case parallels the transition-state modeling results (Table 1) and indicates the need for sterically bulky pyrrolidine 2,5-substituents to maximize facial selectivity. Unfortunately, the diphenyl derivative **10**, although predicted (Table 1) to display the highest % ee in the intramolecular cycloaddition process, is not transformed to the tricyclic ketone **13** by irradiation in MeCN. The photostability of this substance might be due to internal quenching of the eniminium singlet excited state by SET from the pendant phenyl donor groups.[9]

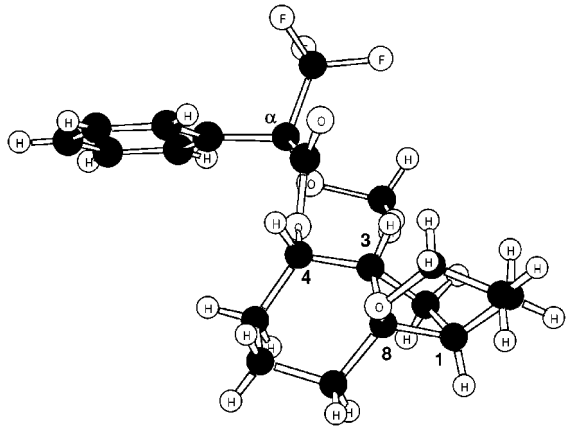

Figure 1. Chem-3D plot of the X-ray crystallographic data obtained for **11a**.

Although not yet extensive, the investigation chronicled above demonstrates the efficacy of a C_2-chiral eniminium salt-based strategy for controlling absolute stereochemistry in intramolecular enone−olefin [2 + 2] photocycloaddition reactions. Studies probing applications of this methodology to photoreactions of eniminium salts bearing various types and positioned alkene-tethers as well as those of alkene linked β-enaminoketones are continuing.

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Supporting Information Available: (1) ^{1}H- and ^{13}C NMR spectra for all previously unreported compounds including enamino-ketones **7** (R = CH_2OMe, Me, Ph), eniminium salts **8**−**10**, the Mosher ester derivatives **11a** and **11b**, and alcohol **12**, and (2) X-ray crystallographic data for **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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