

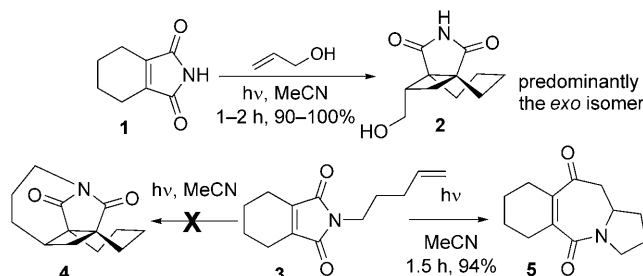
Reaction Control in Synthetic Organic Photochemistry: Switching between [5+2] and [2+2] Modes of Cycloaddition**

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Modern synthetic chemistry has evolved to such an extent that exquisite levels of chemo-, regio-, and stereocontrol can be readily achieved within complex, multifunctional molecules. Reaction control in synthetic photochemistry is a much more difficult prospect where the basic bond-forming step is generally controlled by the lifetime of a key excited state, the formation of which is often dominated by complex structural and photophysical issues. Different reaction pathways of a single chromophore (e.g. C=C bond) can be observed by populating either singlet or triplet states.^[1] Further limited modes of selection can be achieved by irradiation at user-selected wavelengths,^[2] through higher excited states from multiphoton absorption,^[3] and by feedback-based optical control using evolutionary algorithms and pulse shapers.^[4] More recently our research group has demonstrated that photon flux can be a useful parameter in controlling reaction pathways, albeit within the scale limitations imposed by tunable dye lasers.^[5]

Herein we demonstrate how sensitized and nonsensitized reactions of *N*-alkenyl maleimides lead to a selective reaction from different bonds (C–N vs. C=C) within the same molecule. This selection enables either a [5+2] or [2+2] cycloaddition pathway to be chosen, thus providing selective synthesis of complex 7,5-fused azepines or cyclobutanes, respectively.

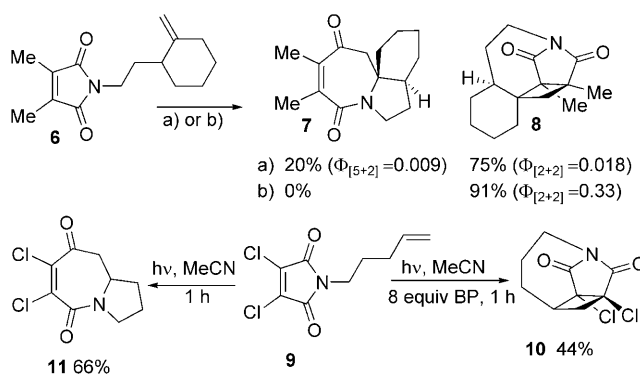
We previously described the intermolecular [2+2] photocycloaddition reactions of tetrahydrophthalimide anhydride **1** (Scheme 1) with alkenol and alkynol partners.^[6] We found these reactions to be remarkably efficient, with the [2+2] cycloadducts (e.g. **2**) being formed in high yields and with excellent stereoselectivity. In contrast, the attempted intramolecular [2+2] photocycloaddition of the pentenyl-substituted imide **3** yielded the tricyclic azepine **5** exclusively in excellent yield by a [5+2] pathway (attributed to cleavage



Scheme 1. Contrasting intermolecular [2+2] and intramolecular [5+2] photocycloaddition behavior of imide compounds.

of the C–N bond).^[7] This observation has since proved to be a general trend with maleimide derivatives: [2+2] photocycloaddition is observed with intermolecular reactions and [5+2] photocycloaddition with intramolecular variants.

More recently we have focused on exploring the scope of this [5+2] cycloaddition and its application in natural product synthesis.^[8] During model studies towards the synthesis of the *Stemona* alkaloids we observed that an *N*-alkenyl maleimide displayed atypical [5+2] behavior (Scheme 2). Irradiation of



Scheme 2. Selective [2+2] vs. [5+2] cycloaddition by sensitization.

a) hv (125 W medium-pressure mercury lamp, Pyrex), MeCN, 7 h;
b) hv (125 W medium-pressure mercury lamp, Pyrex), benzophenone (BP; 1 equiv), MeCN, 1 h.

the maleimide system **6** (containing an exocyclic alkene unit) led to a high yield of cycloaddition products, but for the first time the intramolecular [2+2] adduct dominated. Although chemically efficient, the low quantum yields ($\Phi_{[2+2]}=0.018$ and $\Phi_{[5+2]}=0.009$) illustrate photochemically inefficient bond-forming processes. This observation was initially disregarded as an anomaly; however, recent similar results have

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prompted us to reinvestigate this system. From a mechanistic point of view we proposed that the [5+2] reaction proceeds from cleavage of the singlet N–C bond and subsequent addition of the resultant diradical to the pendant alkene unit.^[9] We assumed that the unusual intramolecular [2+2] reaction was a result of intersystem crossing (ISC) from the initially formed singlet (C=O, $n \rightarrow \pi^*$) to form the triplet diradical of the maleimide C=C bond. We then embarked upon a study to find a triplet quencher that would shut down this unwanted pathway without perturbing the key [5+2] singlet reaction.

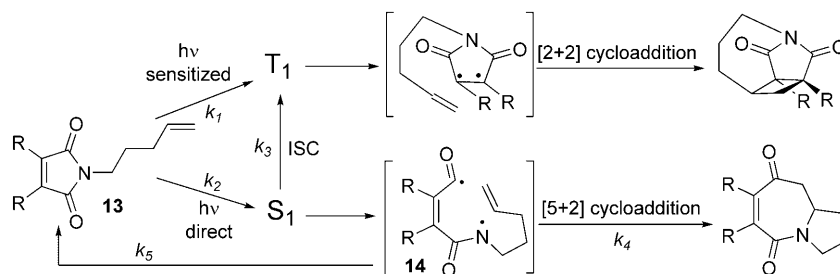
Previously, time-dependent density functional theory (TD-DFT) studies^[9] indicated that the T_1 energies for a variety of substituted maleimides were between 266–294 kJ mol⁻¹. After screening a large number of common triplet quenchers,^[10] with T_1 energies in the range of 148–311 kJ mol⁻¹, we were unable to shut down the [2+2] mode of cyclization. Surprisingly, however, when triphenylene (E_T = 280 kJ mol⁻¹), acetophenone (E_T = 310 kJ mol⁻¹), and benzophenone (E_T = 288 kJ mol⁻¹) were employed, the cyclobutane **8** was formed exclusively.

Clearly these three excited “quenchers” were instead acting as triplet sensitizers by transferring energy to populate the maleimide C=C triplet state and thus facilitating [2+2] cycloaddition only. Quantum yield measurements of the [2+2] cycloaddition with benzophenone ($\Phi_{[2+2]} = 0.33$) illustrated the efficiency of this sensitized process over direct irradiation ($\Phi_{[2+2]} = 0.018$). It was then demonstrated that this selective sensitization could be exploited in a preparative manner for the exclusive formation of **8** in 91% yield (Scheme 2). Even more importantly the application of these findings to dichloromaleimide **9** enabled, for the first time, the ability to choose exclusively between [5+2] or [2+2] modes of cycloaddition to give **11** or **10**, respectively.

Next, we explored the application of these observations to a variety of maleimide derivatives that had more recently reacted exclusively by a [5+2] pathway or had given mixed results (Table 1). Overall, sensitization afforded the [2+2] pathway exclusively, thus providing a route to hitherto unobtainable molecular architectures. When the maleimides were substituted α to the nitrogen center (entries 1–4) direct excitation gave efficient [5+2] cycloaddition only (except entry 4). Irradiation with two equivalents of benzophenone gave only [2+2] cycloaddition in good to excellent yields in all these cases. Similarly, entries 6–8, and 11 displayed complete switching of the mode of cycloaddition upon sensitized irradiation. Entries 4, 5, 9, and 10 (and compound **6**) were maleimides that we had recently studied in an attempted alkaloid synthesis, but had abandoned because of low yields of the [5+2] adduct, which resulted from competing [2+2] cycloaddition. On reinvestigation under sensitized conditions it was fascinating to observe the exclusive formation of their respective cyclobutane derivatives in good to excellent yields.

The study also highlighted some interesting stereoselectivity differences between the [5+2] and [2+2] pathways. In entries 1–4 the [5+2] azepine products were always formed as two, often separable diastereomers (see the Supporting Information for ratios). In contrast, their corresponding [2+2] cyclobutanes were always isolated as a single diastereomer (see the Supporting Information for the X-ray structure of **12**).^[11] This result, we believe, is a clear reflection of the relative rates of reaction between a singlet and triplet process, where in the latter the lifetime of the excited state is much longer, thus allowing time for the substituted alkenyl side chain to adopt the lowest energy conformation for [2+2] cycloaddition (see below).

From the results in Table 1 two key mechanistic pathways can be proposed (Scheme 3). Direct irradiation leads to S_1 which can undergo subsequent α cleavage to diradical **14** followed by [5+2] cycloaddition forming the azepine product (k_4). Recombination of **14** could, however, also occur to



Scheme 3. Reactive pathways of the [5+2] and [2+2] photocycloadditions.

regenerate starting maleimide **13** (k_5). It is postulated that for entries 5, 9, and 10, where [2+2] products are observed under nonsensitized conditions the rate of cycloaddition is hindered by steric bulk in the alkenyl chain. In these examples recombination to give **13** is either favored or competitive (k_5 vs. k_4). The consequence is a continuous recycling of S_1 , thus allowing ISC (k_3) to T_1 and resulting in the observed [2+2] cycloaddition for these examples. If $k_3 > k_4$ then reaction will favor the triplet pathway and a larger ratio of cyclobutane to azepine will be observed (compare with entries 5, 9, and 10). The reverse scenario, where $k_4 > k_3$, results in more [5+2] product (entry 4). Where irradiation under nonsensitized conditions only yields the [5+2] azepines the rate of k_4 is considered to be sufficiently fast that diradical recombination, and hence the T_1 pathway is not observed.

In all these examples, sensitization with benzophenone clearly allows for very efficient population of the maleimide T_1 state ($k_1 \gg k_2$). From this point on only the [2+2] pathway is possible.

In addition to the quantum yield studies (Scheme 2), we compared the relative rates of the sensitized vs. nonsensitized reactions. Maleimide **6** was chosen as a model substrate as it displays dual cycloaddition behavior under direct irradiation. The rates of formation of **7** and **8** were monitored by ¹H NMR spectroscopy under the two different reaction conditions

Table 1: Pathway switching in photocycloaddition of *N*-alkenyl maleimides.

Entry	Substrate	Products		Direct irradiation ^[a] (yield in %) ^[c]	Sensitized irradiation ^[b] (yield in %) ^[c]
		[5+2] cycloaddition	[2+2] cycloaddition		
1				[5+2] only (69)	[2+2] only (84)
2				[5+2] only (81)	[2+2] only (67)
3				[5+2] only (70)	[2+2] only (87)
4				[5+2] + [2+2] (40) (19)	[2+2] only (100) ^[d]
5				[5+2] + [2+2] (20) (42)	[2+2] only (67)
6				[5+2] only (79)	[2+2] only (42)
7				[5+2] only (88)	[2+2] only (34)
8				[5+2] only (99)	[2+2] only (32)
9				[5+2] + [2+2] (8) (45)	[2+2] only (77)
10				[5+2] + [2+2] (3) (30)	[2+2] only (80)
11				[5+2] only (41)	[2+2] only (20)

[a] $h\nu$ (125 W medium-pressure mercury lamp), 150 mL Pyrex immersion well, MeCN (1 mmol), 1–9 h. [b] $h\nu$ (125 W medium-pressure mercury lamp) 150 mL Pyrex immersion well, MeCN (1 mmol), benzophenone (2 equiv), 1 h. [c] Yield of isolated product after column chromatography. [d] Reaction performed in MeCN (3 mL) in a quartz cuvette taped to a water-cooled Pyrex jacket containing a 125 W medium-pressure mercury lamp (30 min irradiation); yield was determined from the ^1H NMR spectrum of the evaporated photolysate.

and the results are plotted in Figure 1. The chemical efficiency of the sensitized [2+2] cycloaddition to **8** is striking; 79 times faster than the unsensitized reaction. This result clearly illustrates the exceptionally efficient energy transfer

(k_1) from the excited benzophenone to the maleimide chromophore.

In summary, appropriate choice of irradiation conditions has enabled synthetically useful reaction control in maleimide

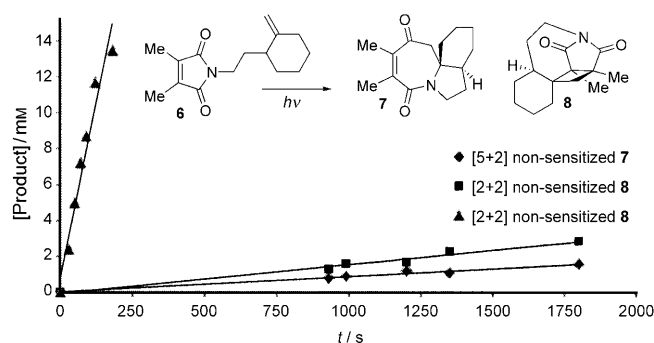


Figure 1. Rate of product formation of **7** and **8** for direct and sensitized irradiations of maleimide **6**.

photochemistry to be demonstrated for the first time. Significantly we have shown that for a molecule containing a complex chromophore, two different modes of cycloaddition can be selected by judicious choice of reaction conditions. The sensitized conditions have enabled routine synthesis of cyclobutane adducts that were previously inaccessible because of the unimodal [5+2] behavior typically observed for *N*-alkenyl maleimides. These observations will greatly extend the scope of maleimide photochemistry in the synthesis of complex polycyclic molecules.

Experimental Section

Reaction conditions for [5+2] cycloaddition (Table 1, entry 1): A solution of **S11** (see the Supporting Information) (207 mg, 1.0 mmol) in degassed MeCN (150 mL) was irradiated using a 125 W medium-pressure lamp in a Pyrex immersion well for 1 h. Purification by column chromatography (60% EtOAc in petroleum ether) yielded the azepine **S27** (see the Supporting Information) as two inseparable diastereomers (1:1.27, 142 mg, 69%); R_f = 0.09 (30% EtOAc in petroleum ether); ^1H NMR (400 MHz, CDCl_3): δ_{H} = 4.34–4.09 (4H, m, NCHCH_3 and NCHCH_2 , both isomers), 2.81–2.43 (4H, m, COCH_2 , both isomers), 2.31–1.52 (12H, m, $\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_2$, both isomers), 1.99 (3H, d, J = 1.1 Hz, $\text{C}=\text{CCH}_3$, minor isomer), 1.98 (3H, d, J = 1.1 Hz, $\text{C}=\text{CCH}_3$, major isomer), 1.86 (3H, d, J = 1.1 Hz, $\text{C}=\text{CCH}_3$, major isomer), 1.83 (3H, d, J = 1.1 Hz, minor isomer), 1.21 (3H, d, J = 6.4 Hz, CHCH_3 , major isomer), 1.15 ppm (3H, d, J = 6.4 Hz, CHCH_3 , minor isomer); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 202.4 (CO), 202.3 (C), 166.4 (CO), 166.2 (CO), 140.1 (C), 138.8 (C), 138.3 (C), 136.9 (C), 54.1 (CH), 54.1 (CH), 53.4 (CH₂), 53.2 (CH), 52.8 (CH), 51.5 (CH₂), 31.0 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 28.3 (CH₂), 20.3 (CH₃), 18.8 (CH₃), 17.9 (CH₃), 17.5 (CH₃), 16.1 (CH₃), 15.5 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2967 (w), 1671 (m), 1630 (s), 1602 (s), 1417 (s), 1284 (m), 937 (m), 755 cm^{-1} (s). All data is in accordance with literature values.^[7b]

Reaction conditions for [2+2] cycloaddition (Table 1, entry 1): A solution of **S11** (see the Supporting Information) (207 mg, 1.0 mmol) and benzophenone (2 equiv, 364 mg, 2.0 mmol) dissolved in degassed acetonitrile (150 mL) was irradiated using a 125 W medium-pressure mercury lamp in a Pyrex immersion well for 1 h. Purification by column chromatography (0–15% EtOAc in petroleum ether) yielded the cyclobutane **S28** (see the Supporting Information) (174 mg, 84%) as a colorless oil; R_f = 0.36 (30% EtOAc in petroleum ether); ^1H NMR (300 MHz, CDCl_3): δ_{H} = 4.35 (1H, quint, J = 7.4 Hz, NCH), 2.42 (1H, dd, J = 12.3 Hz, J = 10.3 Hz, NCOCCHH), 2.29–2.20 (1H, m, NCOCCH), 2.20–2.05 (1H, m, NCHCHH), 2.01 (1H, dd, J = 12.3 Hz, J = 2.6 Hz, NCOCCHH), 1.86 (1H, tt, J = 14.9 Hz, J =

2.0 Hz, NCHCH_2CHH), 1.61–1.50 (1H, m, NCHCH_2CHH), 1.49 (3H, d, J = 7.4 Hz, CHCH_3), 1.38 (1H, qd, J = 14.9 Hz, J = 2.0 Hz, NCHCHH), 1.25 (3H, s, $\text{C}=\text{CCH}_3$), 1.13 ppm (3H, s, $\text{C}=\text{CCH}_3$); ^{13}C NMR (100 MHz, CDCl_3): δ_{C} = 189.2 (CO), 183.1 (CO), 53.5 (CH), 52.6 (C), 45.0 (C), 38.5 (CH), 32.8 (CH₂), 29.3 (CH₂), 23.9 (CH₂), 17.1 (CH₃), 14.9 (CH₃), 11.3 ppm (CH₃); IR (neat): $\tilde{\nu}$ = 2950 (w), 1774 (w), 1700 (s), 1447 (m), 1020 cm^{-1} (m); HRMS (CI) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ ($[\text{MH}^+]$): 208.1259; found: 208.1337.

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- [10] Sensitizers tested were: perylene ($E_T = 148\text{--}151\text{ kJ mol}^{-1}$); isoprene ($E_T = 251\text{ kJ mol}^{-1}$); naphthalene ($E_T = 253\text{--}255\text{ kJ mol}^{-1}$); quinoline ($E_T = 258\text{--}261\text{ kJ mol}^{-1}$); styrene ($E_T = 258\text{ kJ mol}^{-1}$); α -methyl styrene ($E_T = 260\text{ kJ mol}^{-1}$); indene ($E_T = 264\text{ kJ mol}^{-1}$); phenaxanthin ($E_T = 267\text{ kJ mol}^{-1}$); *m*-terphenyl ($E_T = 269\text{ kJ mol}^{-1}$); biphenyl ($E_T = 274\text{ kJ mol}^{-1}$); triphenylene ($E_T = 280\text{ kJ mol}^{-1}$); fluorene ($E_T = 282\text{--}289\text{ kJ mol}^{-1}$); indazole ($E_T = 284\text{ kJ mol}^{-1}$); benzotriazole ($E_T = 295\text{ kJ mol}^{-1}$); benzophenone ($E_T = 287\text{--}289\text{ kJ mol}^{-1}$); acetophenone ($E_T = 310\text{--}311\text{ kJ mol}^{-1}$); from S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, Marcel Dekker, New York, **1993**, pp. 56–97.
- [11] CCDC 739183 (**12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.