

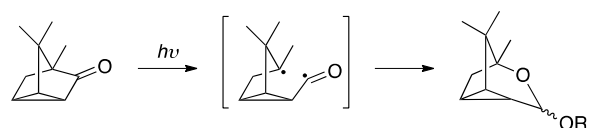
## A Vinylogous Norrish Reaction as a Strategy for Light-Mediated Ring Expansion

Evgueni Gorobets,<sup>a</sup> James W. Papatzimas,<sup>a</sup> Jorge Dourado,<sup>b</sup> Goonay Yousefalizadeh,<sup>c</sup> JinGyu Lee,<sup>a</sup> Duncan K. Brownsey,<sup>a</sup> Kevin Stamplecoskie,<sup>\*c</sup> Rebecca Davis,<sup>\*b</sup> Darren J. Derksen<sup>\*a</sup>

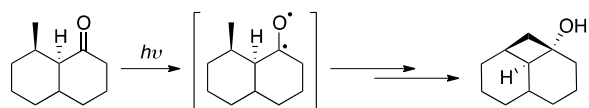
The reactions of bicyclic divinyl ketones display wavelength-dependent changes in product formation. UV irradiation results in the formation of competitive [6,3,5] and [7,3,5] tricyclic unsaturated ketones that subsequently undergo ring expansion and reaction with a range of nucleophiles. DFT calculations and transient absorption experiments were completed that are consistent with a vinylogous Type II Norrish pathway.

Photochemistry has become an important tool in organic synthesis for the preparation of complex molecules ranging from natural products to pharmaceuticals.<sup>1,2</sup> Polycyclic scaffolds are of particular interest synthetically based on the ability to rapidly form complex molecular architectures found in bioactive compounds and to utilize building blocks that are available from natural sources.<sup>3</sup> Notably, the natural product (-)-( $\alpha$ )-santonin contains a divinyl ketone moiety and is known to undergo a range of complex uncontrolled rearrangements when exposed to broad spectrum UV irradiation.<sup>4</sup> There is a need to better understand photomediated rearrangements of strained rings, such as vinylcyclopropanes or cyclopropane-fused heterocycles as strategic design can be used to rapidly form complex molecular scaffolds.<sup>5-7</sup> The ability to induce chemical reactivity without the need for activating groups such as geminal diesters, would be a major advancement for organic synthesis.<sup>8</sup> Photochemical cascade reactions based on Norrish-type chemistry (Scheme 1), are based on homolytic cleavage between a carbonyl and the  $\alpha$ -carbon (Scheme 1A)<sup>9</sup> or by formation of a biradical that subsequently undergo hydrogen abstraction/cyclization reactions (Scheme 1B,C).<sup>10-11</sup> In our

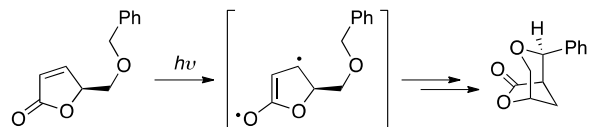
### A - Norrish Type I - Ring expansion/intramolecular cyclization



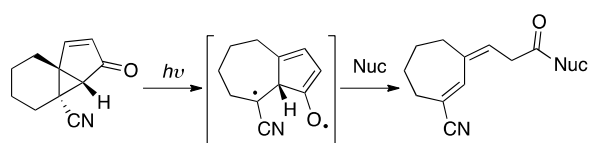
### B - Norrish-Yang cyclization



### C - Norrish Type II - Intramolecular cyclization



### D - This work - Photochemical ring expansion, addition



Scheme 1. Photomediated, cascade rearrangements

investigations exploring the irradiation of vinylcyclopropane-containing scaffolds, we identified a Norrish-type tandem photochemical ring expansion/nucleophilic addition method that leads to provides access to functionalized 7-membered rings in high yields (Scheme 1D).

Our synthetic interests have led us to explore the use of UV light, particularly UV-A (315-400 nm), to mediate chemical reactions that are inaccessible by other methods. The commercial availability of UV-A sources compared to broad-spectrum UV sources make this high-energy light readily available with many practical synthetic advantages compared to broad spectrum UV light containing UV-C (200 nm-280 nm). In

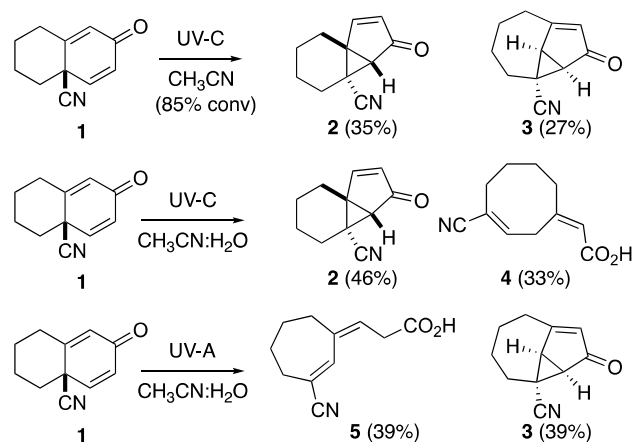
<sup>a</sup> Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary, AB, Canada, T2N1N4

<sup>b</sup> Department of Chemistry, University of Manitoba, 144 Dysart Road, Winnipeg, MB, Canada, R3T2N2

Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, ON, Canada, K7L3N6

Electronic Supplementary Information (ESI) available: [Synthetic details, spectra, computational results, and transient absorption spectra are provided. Crystal structures of **4** and **26** are available: CCDC 2114282, 2114283. See DOI: 10.1039/x0xx00000x

**Scheme 2.** Wavelength-dependent product selectivity. 3:1 E/Z ratio for **5** (See SI: Table SI-1)

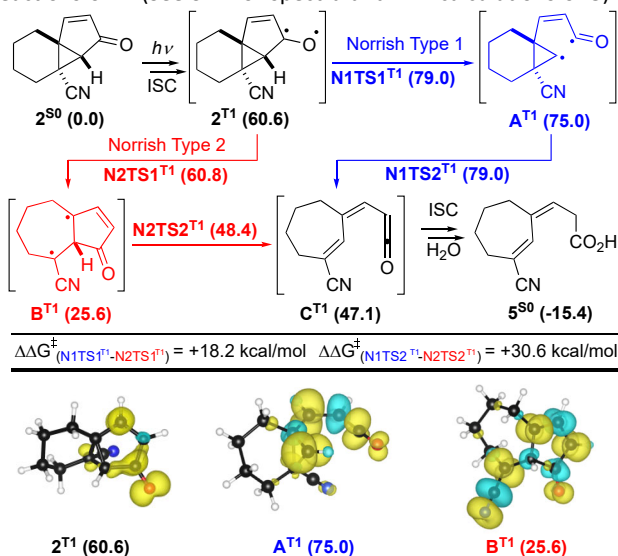


the course of exploring the reactivity of polycyclic divinyl ketones for the synthesis of natural products, we observed the appearance of reaction byproducts with an unusual dependence on the wavelength of light being used to irradiate the reaction (Scheme 2). Under rigorously anhydrous conditions, irradiation of divinyl ketone **1** using UV-C light produces approximately equal amounts of **2** and **3** (1.25:1 after 85% conversion). In the presence of water (10:1  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ ), irradiation of **1** forms the crystalline cyclooctene compound **4** while compound **3** is no longer detected. By comparison, UV-A irradiation of **1** in the presence of water (10:1  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ ), forms the unsaturated 7-membered ring **5**, while compound **2** is no longer detected. These results are consistent with a UV-A selective conversion of **2** to **5**, and a UV-C selective conversion of **3** to **4** that only occurs in the presence of water. Extended irradiation times led to an erosion of E/Z selectivity (See Table SI-1 for details).

Intrigued by the wavelength dependence of the product outcomes, we investigated these processes by transient absorption spectroscopy. Transient absorbance of both **2** and **3** were studied following 340 nm laser pulse (250 fs FWHM) excitation. In each case, light excitation results in the immediate formation of a species with induced absorbance with a maximum around 575 nm and having a lifetime of less than 5 ps. The absorbance spectra evolve to form a longer-lived transient species absorbing broadly from ~600 – 900 nm. In each case the transient absorption experiment shows behaviour that indicates the photochemical formation of new transient species resulting in different excited state absorbance features upon extended irradiation. Interestingly, compounds **2** and **3** show little reactivity on their own, with only minor conversion of the starting material as evidenced by changes in steady state absorbance features before and after extended irradiation. The pump/probe experiments consistently exhibit features that can be attributed to at least two different transient species, with excited state absorbances at 575 nm, and with a broad absorbance at longer wavelengths (See S.I. for spectra). As **3** was found to only react with water in synthetically

**Scheme 3.** Calculated Mechanisms - Norrish Type 1 vs 2 (relative free energies in kcal/mol)

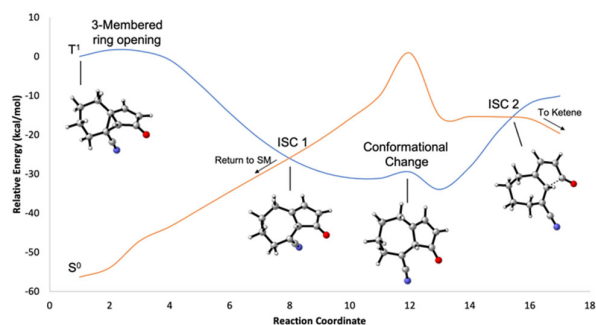
useful yields upon irradiation, we focused our attention on reactions of **2**. (See S. I. for spectra and DFT calculations of **3**).



These results are consistent with our proposed mechanism where intermediate **B** ( $B^{T_1}$ , Scheme 3) is formed immediately upon irradiation, and then forming **C** ( $C^{T_1}$ ) as the second, long-lived, red-shifted intermediate before reacting with a nucleophile.

Building upon the transient absorption spectroscopy results, we computationally explored the mechanism of this wavelength-dependent reaction (Scheme 3). Calculations<sup>12</sup> using uM062X<sup>13</sup>/def2-TZVP<sup>14,15</sup> are consistent with a lower energy pathway for the photochemical ring expansion-nucleophilic addition cascade reaction proceeding through a Norrish Type II pathway (Scheme 3). Our results show that after irradiation, compound **2** readily undergoes a ring expansion by cleavage of the cyclopropane moiety ( $N2TS1^{T_1} = 60.8$  kcal/mol) forming a low energy intermediate **B** ( $B^{T_1}$ , Scheme 3 – Norrish Type 2 Pathway). This intermediate then undergoes ring-opening of the cyclopentenone ring ( $N2TS2^{T_1} = 48.4$  kcal/mol) giving the ketene intermediate **C** ( $C^{T_1}$ ) that undergoes ISC and reacts with water to form **5**. A Norrish Type 1 mechanism via intermediate **A** ( $A^{T_1}$ ) and other pathways were also considered however, they were either very high in energy or did not lead to the observed product. (See S.I. for details).

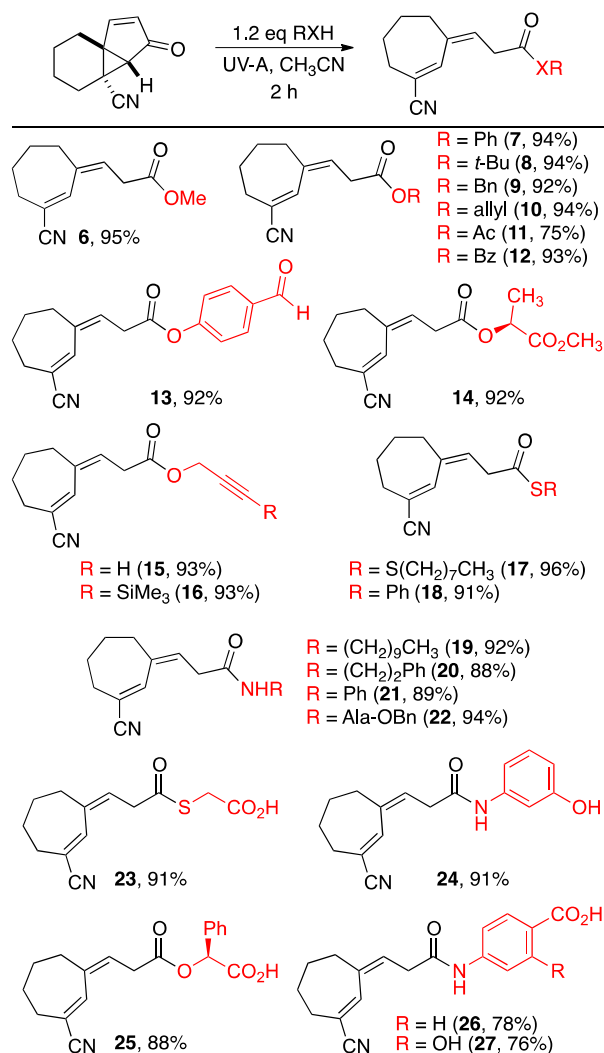
Scans of the  $T^1$  and  $S^0$  surfaces of the rearrangement of the [6,3,5] tricyclic unsaturated ketone **2** show that the  $T^1$  and  $S^0$  surfaces only cross two different points (Figure 1). The first crossing (ISC1) occurs upon opening of the cyclopropyl ring. At this point the substrate can reform the ground state reactant by proceeding along the  $S^0$  surface. Following the  $T^1$  surface, the molecule undergoes a slight conformational change in the newly formed 7-membered ring. This allows the subsequent ring opening of the cyclopentenone to produce a cis double bond in the ring. The second crossing of the  $S^0$  and  $T^1$  surfaces occurs as the cyclopentenone ring is being cleaved. This crossing leads to the production of the ground state ketene, which can then go on to react with a nucleophile and form the observed products.



**Figure 1.** T<sup>1</sup> energy profile (blue) and S<sup>0</sup> energy profile (orange) for Norrish Type 2 rearrangement of **2**.

The production of the ketene from ISC2 is also consistent with the observed isomer of the product. Calculations on the ground state ketene intermediate show that the *E*-isomer should be thermodynamically preferred over the *Z*-isomer by 1.2 kcal/mol. However experimental data shows the *Z*-isomer to be formed almost exclusively. Examination of the double bond configuration at ISC2 is consistent with formation of the *Z*-isomer.

Our initial attempts to expand the scope of nucleophiles in photomediated reactions from **1** were pursued, but produced modest over extended reaction times and challenges with purification (See S.I. for details, Table SI-1). With an improved understanding of the photomediated, cascade reaction mechanism, however, it was clear that reactions with **2** were amenable to the synthesis of unsaturated 7-membered rings and that the ketene intermediate could be intercepted by more complex nucleophiles. The scope of this ring expansion reaction was explored using a range of reactants (Scheme 4). Alkyl, benzyl, allyl alcohols and phenols all form ester products in greater than 92% yield (Scheme 4, **6-10,13**). Formation of anhydrides also occurred readily with acid nucleophiles (**11, 12**). (*S*)-methyl lactate formed the ester product (**14**, 92%). Propargylic alcohols react cleanly to produce the corresponding esters with or without protection of the acetylenic position (**15, 16**). Formation of thioesters proceed in high yields (**17, 18**). Reaction with alkyl amines, protected amino acids, and anilines all form the corresponding amides in high yields (**19-22**). The reactivity of the intermediate ketene was also explored in competition experiments using substrates with multiple sites of reactivity. Thioglycolate reacts under the reaction conditions to form thioester **23** while 3-aminophenol reacted selectively to provide the amide product **24**. (*S*)-Mandelic acid forms the ester product **25**. 4-aminosalicylic acid and 4-aminobenzoic acid both react to form the amide products (**26, 27**). The structure of **26** was confirmed using x-ray crystallography. These results are consistent with the proposed mechanism and the most nucleophilic position reacting with the intermediate ketene leading to product. This chemoselective reactivity provides a strategy for incorporation of orthogonal synthetic handles without the use of protecting groups.



**Scheme 4.** Reaction scope of **2** with nucleophiles under UV-A irradiation (See Table SI-2)

## Conclusions

We have demonstrated that a vinylogous Norrish Type II - cascade reaction can occur for unsaturated ketones substituted with cyclopropanes. Embedded within a tricyclic ring system, this reaction leads to a ring expansion with concomitant ring opening to generate a reactive ketene that can react with nucleophiles. These processes were investigated using DFT calculations and transient absorption spectroscopy providing experiment evidence consistent with our proposed mechanism. We anticipate that this strategy will find further application in organic synthesis by employing UV-A irradiation to induce skeletal rearrangements and synthetically useful ketene intermediates.

## Author Contributions

JD and RD completed all of the computational work and DFT studies. GY and KS completed the transient absorption spectroscopy studies. EG, JWP, JL, DKB, and DJD completed all

aspects of the organic synthesis in this project and related background studies. The manuscript was written with input from all authors.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

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