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Author/s:
Hirai, K;Takeda, R;Hutchison, JA;Uji-i, H

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Modulation of Prins Cyclization by Vibrational Strong Coupling

Kenji Hirai,*[a,b,c] Rie Takeda,[a, b] James A. Hutchison,[d] and Hiroshi Uji-i*[a,c,e]

Abstract: Light-molecule strong coupling has emerged within the last decade as an entirely new method to control chemical reactions. A few years ago it was discovered that the chemical reactivity could be altered by vibrational strong coupling (VSC). While the potential of VSC in organic chemistry appears enormous, only a limited number of reactions have been investigated under VSC to date, including solvolysis and deprotection reactions. Here we investigate the effect of VSC on a series of aldehydes and ketones undergoing Prins cyclization, an important synthetic step in pharmaceutical chemistry. We observe a decrease of the second-order rate constant with VSC of the reactant carbonyl stretching groups. We measure an increased activation energy due to VSC, but proportional changes in activation enthalpy and entropy suggest no substantive change in reaction pathway. The addition of common cycloaddition reactions to the stable of VSC-modified chemical reactions is another step towards establishing VSC as a genuine tool for synthetic chemistry.

In the last several decades, strong coupling between light and matter has been explored in a wide range of materials, from single atoms to proteins,[1–3] and over broad frequency ranges, from UV to terahertz. [4,5] In all these contexts, the criterion for strong coupling is the reversible exchange of energy between the material absorption and an optical resonance that is faster than any loss mechanisms. Vibrational strong coupling (VSC) of organic molecules is typically achieved using a Fabry-Pérot (FP) cavity with mirrors tuned with ~micron separation to be resonant with the molecular vibrational absorption bands. The resulting hybrid 'vibro-polariton' states exhibit a splitting of the normal mode vibration (the Rabi splitting, $\hbar\Omega$) proportional to $\sqrt{N}$, where N is the number of material oscillators present (Fig.1).[6–8] A few years ago it was discovered that, even in the absence of laser pumping of the optical cavity (the vacuum field regime), VSC influences the kinetics of organic reactions.[10–14] The kinetic changes are attributed to the vibro-polariton states, potentially reshaping the Morse potential of molecules and leading to the altered chemical reactivity.[9] To date, studies on VSC chemistry have been reported in deprotection[10,11], solvolysis,[12–14] and addition reactions.[12] Although recent work showed the utility of VSC in organic reactions, the field awaits comprehensive expansion to demonstrate its application for versatile reactions commonly used in organic chemistry.

Much of organic chemistry is focused on reactions that form carbon-carbon bonds to yield target products. For example, the Prins cyclization[15–17] is a common cycloaddition reaction that enables the synthesis of cyclic carbon compounds from two or more reactants. The reaction rate of the Prins cyclization is mainly determined by the ease of nucleophilic (e.g., carbon-carbon double bond) attack on the protonated carbonyl of an aldehyde or ketone.[18,19] This rate-limiting step is strongly dependent on the reactivity of the carbonyl group.

Herein we demonstrate that VSC of the aldehyde/ketone carbonyl stretching band can be used to control (slow) the rate of Prins cyclization. Temperature dependent studies point to an increased activation energy due to VSC, but no substantive change in mechanistic pathway, with relative changes in activation entropy and enthalpy being similar. This work further demonstrates the versatility of VSC as a tool to modulate organic reactions since the key mechanism, nucleophilic attack, is one of the most common in organic synthesis. This work may thus inspire the application of VSC to a much larger range of organic synthetic reactions.

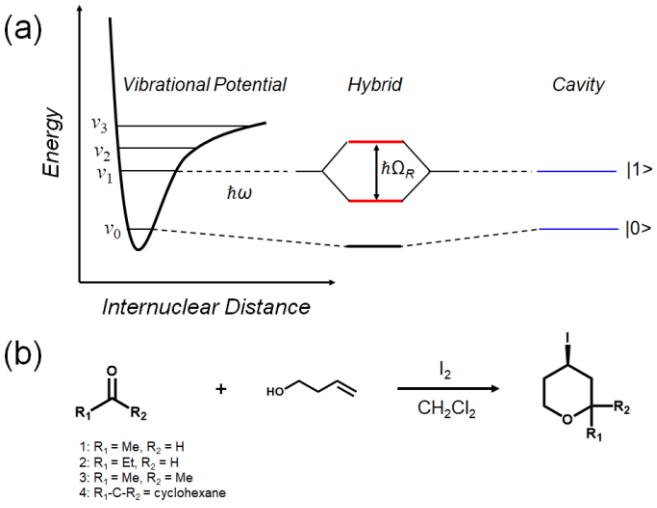


Figure 1. (a) Schematic energy levels of vibro-polaritonic states formed from the coupling of a molecular vibrational transition and a FP cavity mode, (the Rabi splitting, $\hbar\Omega$ indicated). (b) Prins cyclization in the presence of I_2.

[a] Prof. Dr. K. Hirai, R. Takeda, Prof. Dr. H. Uji-i
Division of Photonics and Optical Science, Research Institute for Electronic Science (RIES)
Hokkaido University
North 20 West 10, Kita ward, Sapporo, Hokkaido, Japan
E-mail: hirai@es.hokudai.ac.jp
[b] Prof. K. Hirai, R. Takeda
Precursory Research for Embryonic Science and Technology (PRESTO)
Japan Science and Technology Agency (JST)
4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan.
[c] Prof. Dr. K. Hirai, Prof. Dr. H. Uji-i
Division of Information Science and Technology, Graduate School of Information Science and Technology
Hokkaido University
North 14 West 9, Kita ward, Sapporo, Hokkaido, Japan
[d] Dr. James A. Hutchison
School of Chemistry
The University of Melbourne
Masson Rd, Parkville VIC 3052, Australia.
[e] Prof. Dr. H. Uji-i
Department of Chemistry
Katholieke Universiteit Leuven
200F, 3001 Heverlee, Leuven, Belgium.
E-mail: hiroshi.ujii@kuleuven.be

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We prepared a FP cavity consisting of two parallel mirrors separated by Kapton film. The mirrors were fabricated by sputtering Au onto ZnSe windows. The Au-sputtered mirrors were further protected by applying a spin-coated film of silicon resin (Fig. S1). Acetaldehyde mixed in dichloromethane was placed in the prepared FP cavity. The spacing between the mirrors was precisely tuned by fine-pitched microscrews to couple an optical cavity mode with the carbonyl stretching vibration of acetaldehyde. The 6th order cavity mode was coupled to the carbonyl stretching vibration of acetaldehyde to form two new vibro-polaritonic states, denoted as P+ and P- (Fig. 2a). The Rabi splitting energy between P+ and P- (105 cm^{-1}) was larger than both the carbonyl stretching vibration (FWHM = 27 cm^{-1}) and the optical cavity mode (FWHM = 54 cm^{-1}). This result suggests that VSC of the carbonyl stretching with the vacuum field (zero-point energy of the cavity) has been realized; this is also known as vacuum Rabi splitting.[7]

The magnitude of vacuum Rabi splitting is proportional to the square root of the concentration of acetaldehyde (Fig. S2), as predicted in light-matter strong coupling theory.[20,21] Furthermore, the angle-dependent transmission spectra show a typical signature of strong coupling: dispersion of both the upper and lower polariton branches with an anti-crossing at the bare absorption energy[22] (Fig. S3). These results strongly indicate that the carbonyl stretching vibration of acetaldehyde in the FP cavity is exhibiting vacuum Rabi splitting. Strong coupling of the carbonyls of propionaldehyde, acetone and cyclohexanone were also confirmed by the square root dependence of their concentration on the observed Rabi splitting[7] (Figs. S4-6).

We carried out the Prins cyclization of acetaldehyde propionaldehyde, acetone, or cyclohexanone with 3-butene-1-ol in FP cavites under two conditions for each reaction, namely, with the cavity mode strongly coupled to (ON-resonance), or detuned from (OFF-resonance), the carbonyl groups. The reaction conditions (see Experimental section) were determined based on those typical for a bulk reaction in the presence of iodine (Fig. S7). This reaction mechanism is described in the Supporting Information (Fig. S8). As the reaction proceeds, the refractive index of the solution in FP cavity slightly increased in both ON- and OFF-resonance cases. The increase of the refractive index of the solution as the reaction progressed induced a shift of the resonant peak wavenumber (ν) of the progression of higher order, non-resonant FP cavity modes from $\nu_{initial}$ to ν_t. These shifts allowed the kinetics of the Prins cyclization to be monitored by transmission spectroscopy[11] (Figs. 2b-c). The plot of $(1 - c_\infty(\nu_0 - \nu_t)/(\nu_0 - \nu_\infty))$ against time gave a straight line, indicating the Prins cyclization was a second-order reaction (Fig. 2d and Figs. S9). The observed second-order kinetics of the Prins cyclization agrees with the reaction mechanism described in the literature,[19] namely second-order reaction (Fig. S10). In all the cases (acetaldehyde, propionaldehyde, acetone, and cyclohexanone), the change of the refractive indices under on-resonance conditions was slower than under off-resonance conditions (Fig. 2d). This suggests that VSC of the carbonyl stretching vibration of the aldehyde and ketone decreased the reactivity of the substrate in a Prins cyclization.

The reaction rate was quantitatively determined by gas chromatography-mass spectrometry (GC-MS) to monitor the decrease of the 3-butene-1-ol starting material. To confirm the effect of VSC on the reaction kinetics, the wavelength of the cavity mode was scanned around the carbonyl stretching vibration energy and the reaction repeated. The effect of VSC clearly depends on the degree of resonance, with the rate of reaction as a function of cavity mode energy (red dots) being well-superimposable on the shape of carbonyl stretching vibration band (black line) in Fig. 3. When the cavity mode was adjusted to match the maximum of the carbonyl stretch, the reaction rate was decreased by 70% compared to the completely detuned case.

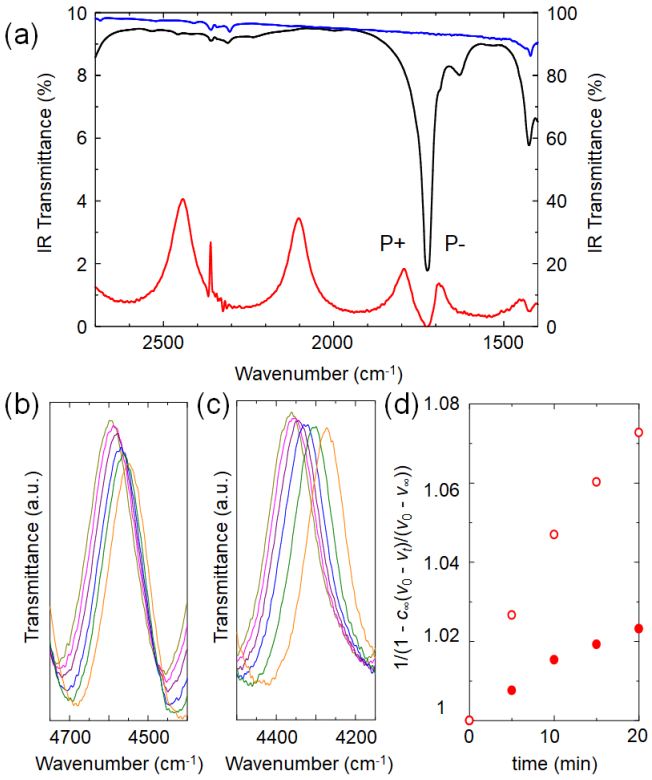


Figure 2. (a) IR transmission spectra of 50 vol% acetaldehyde in dichloromethane (black) and pure dichloromethane (blue). Vibro-polatironic states P+ and P- formed by coupling of the 6th order cavity mode with carbonyl stretching vibration (red). The vertical axis on the left is for the cavity peaks (red); the vertical axis on the right is for 50 vol% acetaldehyde in dichloromethane (black) and pure dichloromethane (blue). (b-c) The temporal shift of the higher-order cavity modes: (b) on-resonance and (c) off-resonance. Each color indicate the cavity peak at a certain reaction time: orange (0 min), green (5 min), blue (10 min), purple (15 min), magenda (20 min) and yellow (25 min). (d) Kinetics of the reactions in the FP cavities tuned to be on-resonance (red filled circle) and off-resonance (red open circles), as extracted from the temporal shifts in the higher-order cavity modes.

The reaction rates under On-resonance and Off-resonance conditions were also measured at different temperatures (22 °C, 30 °C and 40 °C, Fig. S11 and Table S2). At all the temperatures, the reaction rates of Prins cyclization was decreased by VSC of the carbonyl stretching vibration. The enthalpy and entropy of activation of the Prins cyclization under on- and off-resonance were estimated by Eyring plots (Fig. S12 and Table 1. Although aldehydes are more reactive than ketones in Prins cyclization because of the increased polarity of the carbonyl groups of the former, the activation enthalpy ($\Delta H^{\ddagger}$) of the Prins cyclization of all reactants increased by approximately 10 kJ/mol under VSC (*ca.* 1.5-fold increase); however, the activation entropy ($\Delta S^{\ddagger}$) was not altered as much (*ca.* 10% less negative). The activation enthalpy of all the reactions under ON- and OFF-resonance conditions was plotted against activation entropy (Fig. S13). The linear correlation

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between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ implies that all the aldehydes and ketones react by the same mechanistic pathway when subjected to carbonyl VSC, but with the energy barrier to reaction increased. The rate-limiting step in the Prins cyclization is the attack by the alcohol group of 3-butene-1-ol at the carbonyl group and protonation of the carbonyl group, which is facilitated by the latter's polarity. The increase of the activation energy by VSC observed here might suggest that the effect of VSC on the carbonyl stretching vibration is akin to decreasing the polarity of the carbonyl group.

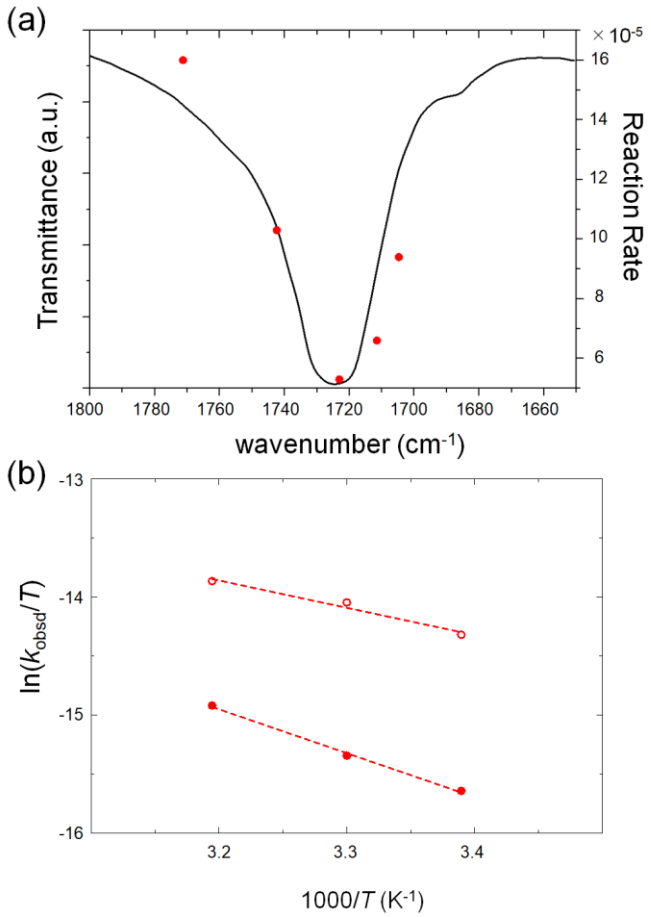


Figure 3. (a) The reaction rate as a function of the FP cavity tuning for reactions occurring within (red dots). The solid black line shows the IR transmission spectrum of the carbonyl stretching vibration of acetaldehyde. (b) Eyring plot of the Prins cyclization of acetaldehyde. The circles and dots indicate off-resonance, and on-resonance, respectively.

Table 1. Reaction rates of the Prins Cyclization at 22 °C

Reactant	*state*	k_{obsd} *(mol/L•s)*
Acetaldehyde	OFF-resonance	1.8×10^{-4}
	ON-resonance	4.7×10^{-5}
propionaldehyde[j]	OFF-resonance	1.1×10^{-4}
	ON-resonance	2.5×10^{-5}
Acetone	OFF-resonance	1.1×10^{-4}
	ON-resonance	3.1×10^{-5}
cyclohexanone	OFF-resonance	7.4×10^{-5}
	ON-resonance	1.4×10^{-5}

Table 2. Activation enthalpy, entropy and energies of aldehydes and ketones under On- and OFF- resonance.

Reactant	*state*	$\Delta H^{\ddagger}$ [a] (kJ/mol)	$\Delta S^{\ddagger}$ [b] (J/mol•K)	*Ea* [c] *(kJ/mol)*
Acetaldehyde	OFF-resonance	19.2	-251.1	21.8
	ON-resonance	30.9	-222.7	33.5
propionaldehyde[j]	OFF-resonance	23.4	-240.7	26.0
	ON-resonance	37.6	-204.7	40.1
Acetone	OFF-resonance	25.0	-236.5	27.5
	ON-resonance	36.8	-209.9	39.4
cyclohexanone	OFF-resonance	27.1	-231.7	29.6
	ON-resonance	38.8	-205.6	41.3

[a] Activation enthalpy, [b] activation entropy and [c] activation energy estimated by Arrhenius plot

While broadly attributed to the re-shaping of the reaction potential energy landscape by hybrid light-matter states, a clear picture of the effect of VSC on organic chemistry is still lacking. Nevertheless the results presented here add new insights and hint at trends which may help interpret the four reports published so far in this field.[7-11] The deprotection of silyl groups slows down under VSC of the Si-C vibration, correlating with the slowing down of cyclization observed here. The rate-limiting step of silyl deprotection is the attack of an alcohol at the Si center, so one could again speculate that decreasing the polarity of Si-C bond would decrease the rate of the deprotection reaction.[10,11] However in that work VSC lead to a large increase in activation entropy indicating a change from an associative to a dissociative transition state, something not observed here for Prins cyclization. While we speculate that VSC of the reactants gives an effect similar to that of decreasing the polarity of functional groups coupled to the cavity mode, other works focusing on cooperative VSC of solvents and reactants reveal contrary trends.[12–14] For the solvolysis of *para*-nitrophenyl acetate for example, the reaction rate increases, the activation entropy decreases, and a more polar activated complex is invoked. Indeed while a global (and predictive) model for the effect of VSC on reactions rates would be intellectually pleasing, it may turn out that the minutiae of each specific reaction dominates.

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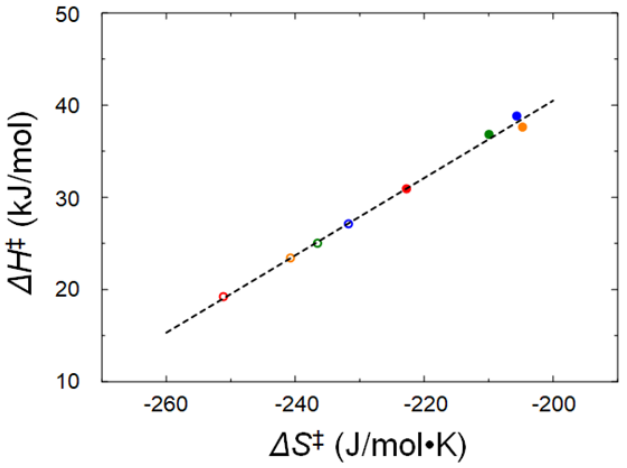


Figure 4. The activation enthalpy ($\Delta H^{\ddagger}$) is plotted against the activation entropy ($\Delta S^{\ddagger}$). Red, orange, green and blue indicate acetaldehyde, propionaldehyde, acetone, and cyclohexanone, respectively. The circles and dots indicate off-resonance, and on-resonance, respectively.

In summary, we investigated the effect of VSC on a series of carbonyl reactants undergoing a Prins cyclization. Under VSC the reaction rate was significantly decreased in all cases without evidence of a change in mechanistic pathway. This comprehensive work on a series of aldehydes and ketones suggests that VSC has an effect similar to that of weakening the polarity of carbonyl groups. This is the first example of VSC-induced control of a nucleophilic reaction and it suggests that VSC may have wide application because nucleophilic attack is a feature of a vast number of organic reactions.

Experimental Section

FP Cavity: The cavity cell, with fine-pitched microscrews, was purchased from TTC Inc., Japan. Kapton film of 5-micron thickness was purchased from Du Pont-Toray Co., Ltd. ZnSe windows were purchased from Specac Ltd., UK. Au of 10-nanometer thickness was coated onto ZnSe windows by sputtering. Silicon resin solution was spin-coated on top of the Au coat, followed by drying in an oven.

Reaction Conditions: I_2 (25.4 mg, 0.1 mmol) was dissolved in dichloromethane (0.5 mL). Aldehyde or ketone (4 mmol), and 3-butene-1-ol (688.4 µl, 8 mmol) were added to the resultant solution. The cavity was filled with the obtained solution and the temperature controlled.

Gas Chromatography-Mass Spectroscopy: The reaction solution was taken out from the cavity and diluted with diethyl ether. The resultant solution was analyzed by JMS-Q1500GC. A Zebron ZB-624 capillary GC column (Length: 60m, I.D.: 0.25mm, film thickness: 1.40µm) was installed on the instrument. The reaction kinetics was estimated from the decrease of 3-butane-1-ol.

Estimation of Reaction Rates: As shown in Fig.S11a, 3-butene-1-ol was detected in the chromatogram as peak 2. The decrease of 3-butene-1-ol was estimated from the peak area and the calibration curve (Fig.S11d). The concentration of aldehyde or ketone (denoted as [*A*]) at 5 min was estimated from the decrease of 3-butene-1-ol. The reaction rate (k_{obsd}) was calculated from Eq. S1 by using [*A*].

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Keywords: Rabi splitting • vibrational strong coupling • Prins cyclization• infrared spectroscopy•microcavity

[1] R. Houdré, R. P. Stanley, M. Ilegems, *Phys. Rev. A - At. Mol. Opt. Phys.* **1996**, *53*, 2711–2715.
[2] J. Casanova, G. Romero, I. Lizuain, J. J. García-Ripoll, E. Solano, *Phys. Rev. Lett.* **2010**, *105*, 263603.
[3] R. M. A. Vergauwe, J. George, T. Chervy, J. A. Hutchison, A. Shalabney, V. Y. Torbeev, T. W. Ebbesen, *J. Phys. Chem. Lett.* **2016**, *7*, 4159
[4] M. Hertzog, M. Wang, J. Mony, K. Börjesson, *Chem. Soc. Rev.* **2019**, *48*, 937
[5] R. Damari, O. Weinberg, D. Krotkov, N. Demina, K. Akulov, A. Golombek, T. Schwartz, S. Fleischer, *Nat. Commun.* **2019**, *10*, 3248.
[6] J. P. Long, B. S. Simpkins, *ACS Photonics* **2015**, *2*, 130–136.
[7] T. W. Ebbesen, *Acc. Chem. Res.* **2016**, *49*, 2403–2412.
[8] F. Herrera, F. C. Spano, *Phys. Rev. Lett.* **2016**, *116*, 1–6.
[9] J. Flick, M. Ruggenthaler, H. Appel, A. Rubio, *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 3026–3034.
[10] A. Thomas, J. George, A. Shalabney, M. Dryzhakov, S. J. Varma, J. Moran, T. Chervy, X. Zhong, E. Devaux, C. Genet, et al., *Angew. Chemie - Int. Ed.* **2016**, *55*, 11462–11466.
[11] A. Thomas, L. Lethuillier-Karl, K. Nagarajan, R. M. A. Vergauwe, J. George, T. Chervy, A. Shalabney, E. Devaux, C. Genet, J. Moran, et al., *Science* **2019**, *363*, 615–619.
[12] H. Hiura, A. Shalabney, J. George, *Chemrxiv.Org* **2018**.
[13] J. Lather, P. Bhatt, A. Thomas, T. W. Ebbesen, J. George, *Angew. Chemie Int. Ed.* **2019**, *58*, 10635–10638.
[14] R. Vergauwe, A. Thomas, K. Nagarajan, J. George, T. Chervy, M. Seidel, E. Devaux, V. Torbeev, T. W. Ebbesen, *Angew. Chemie Int. Ed.* **2019**, *58*, 15324–15328.
[15] J. S. Yadav, B. V Subba Reddy, V. H. Krishna, T. Swamy, G. K. Narayana Kumar, *Can. J. Chem.* **2007**, *85*, 412–415.
[16] X. Gang, Y. Zhu, H. Birch, H. A. Hjuler, N. J. Bjerrum, *Appl. Catal. A Gen.* **2004**, *261*, 91–98.
[17] G. Sabitha, K. B. Reddy, M. Bhikshapathi, J. S. Yadav, *Tetrahedron Lett.* **2006**, *47*, 2807–2810.
[18] L. J. Dolby, C. L. Wilkins, R. M. Rodia, *J. Org. Chem.* **1968**, *33*, 4155–4158.
[19] K. B. Schowen, E. E. Smissman, R. L. Schowen, *J. Org. Chem.* **1968**, *33*, 1873–1876.
[20] R. M. A. Vergauwe, J. George, T. Chervy, J. A. Hutchison, A. Shalabney, V. Y. Torbeev, T. W. Ebbesen, *J. Phys. Chem. Lett.* **2016**, *7*, 4159–4164.
[21] B. S. Simpkins, K. P. Fears, W. J. Dressick, B. T. Spann, A. D. Dunkelberger, J. C. Owrutsky, *ACS Photonics* **2015**, *2*, 1460–1467.
[22] J. George, T. Chervy, A. Shalabney, E. Devaux, H. Hiura, C. Genet, T. W. Ebbesen, *Phys. Rev. Lett.* **2016**, *117*, 153601.

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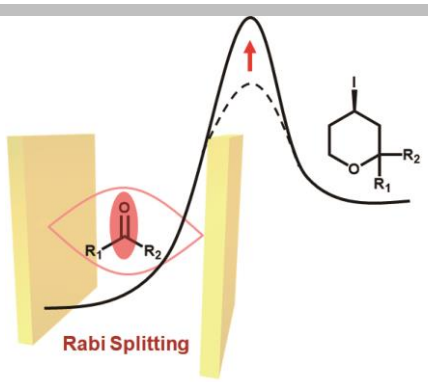
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Entry for the Table of Contents

Layout 1:

COMMUNICATION

Vibrational strong coupling (VSC) of a series of aldehyde and ketone reactants in Prins cyclization is investigated. The second-order rate constant is decreased by VSC of the carbonyl stretching band. The extension of VSC chemistry to common cycloadditions further establishes a link between quantum electrodynamics and synthetic chemistry.



Kenji Hirai, Rie Takeda, James A. Hutchison, and Hiroshi Uji-i**

Page No. – Page No.

Modulation of Prins Cyclization by Vibrational Strong Coupling

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