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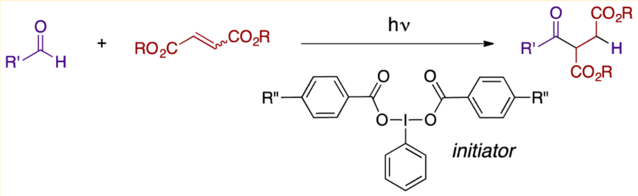
Mechanism of Metal-Free C−H Activation of Branched Aldehydes and Acylation of Alkenes Using Hypervalent Iodine Compound: A Theoretical Study

Julong Jiang,[†] Romain Ramozzi,[†] Shin Moteki,[‡] Asuka Usui,[‡] Keiji Maruoka,[‡] and Keiji Morokuma*,[†]

[†]Fukui Institute for Fundamental Chemistry, Kyoto University, Takano-Nishihiraki-cho 34-4, Kyoto 606-8103, Japan
[‡]Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan

Ⓢ *Supporting Information*

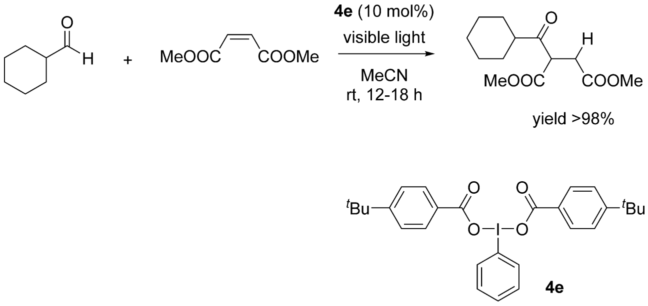


ABSTRACT: The mechanism of the C−H activation of aldehydes and the succeeding acylation of an alkene using a hypervalent iodine reagent is investigated by theoretical calculations. In contrast to the initial proposed mechanism, the present calculations show that the hypervalent iodine is the initiator of the radical reaction. The formation of acyl radical is rate-determining, and the resulting radical acts as the chain carrier. The kinetic isotope effect (KIE) of deuterated aldehyde, as well as other experimental observations, can now be rationalized from the newly proposed mechanism.

1. INTRODUCTION

The C−C bond formation reactions using carbon-centered radicals are particularly challenging and have attracted great interest during the past decades.[1,2] Among these reactions, various methods were developed for the acyl radical additions on alkenes:[3] the use of acyl derivatives,[4] the *in situ* formation of the acyl radical intermediate by using the carbon monoxide,[5] and a more straightforward way with aldehydes.[6] Recently, the Maruoka group reported the use of a hypervalent iodine(III) reagent **4e** (following the label of the original article) to perform the acylation of alkenes with branched aldehydes under mild conditions (see Scheme 1).[7] This reaction is performed under visible light irradiation, making this reaction possible at room temperature. Interestingly, no decarbonylated side-product was observed, which makes this reaction as a promising potential synthetic strategy in the future.[8−11]

Scheme 1. C−H Activation of Aldehydes Catalyzed by the Hypervalent Iodine(III) Reagent 4e



A variety of experimental studies have been carried out for clarification of the reaction mechanism,[7] and a mechanism was proposed as depicted in Scheme 2 (with labels from the original article). The reaction is initiated through the photon absorption by the hypervalent iodine molecule **4**. The absorption of a photon leads to the homolytic cleavage of an O−I bond of **4** and the subsequent formation of two radical species labeled **12** and **13**. The iodonyl radical **12** was proposed to be the active species that abstracts the hydrogen atom from aldehyde **5** to generate intermediate **16** (which bears an H−I bond), and acyl radical **11**. The acyl radical **11** then performs a nucleophilic attack to the electron-deficient alkene **6** to form the carbon-centered radical **15**. Finally, the carbon-centered radical **15** abstracts the H atom from the intermediate **16** to furnish the final product **7**. Meanwhile, the iodonyl radical **12** is regenerated for the next catalytic cycle.

To fully understand this reaction mechanism and to improve the reaction systematically in the near future, we decided to perform a theoretical investigation on this hydroacylation reaction. The first target is to identify the exact radical species responsible for the hydrogen transfer: i.e., is the H-abstraction of the aldehyde really performed by the iodonyl radical or another species? Furthermore, does the relative instability of the acyl radical, as originally claimed, explain the absence of decarbonylation? The present study will provide answers to these questions and rationalize all experimental observations as well.

2. COMPUTATIONAL DETAILS

All of the calculations were carried out at the DFT level of theory with the B3LYP[12,13] hybrid functional, corrected with the empirical dispersion term (known as Grimme-D3[14]), as implemented in Gaussian09.[15] The 6-311G(d,p) basis set[16] was employed for the C,

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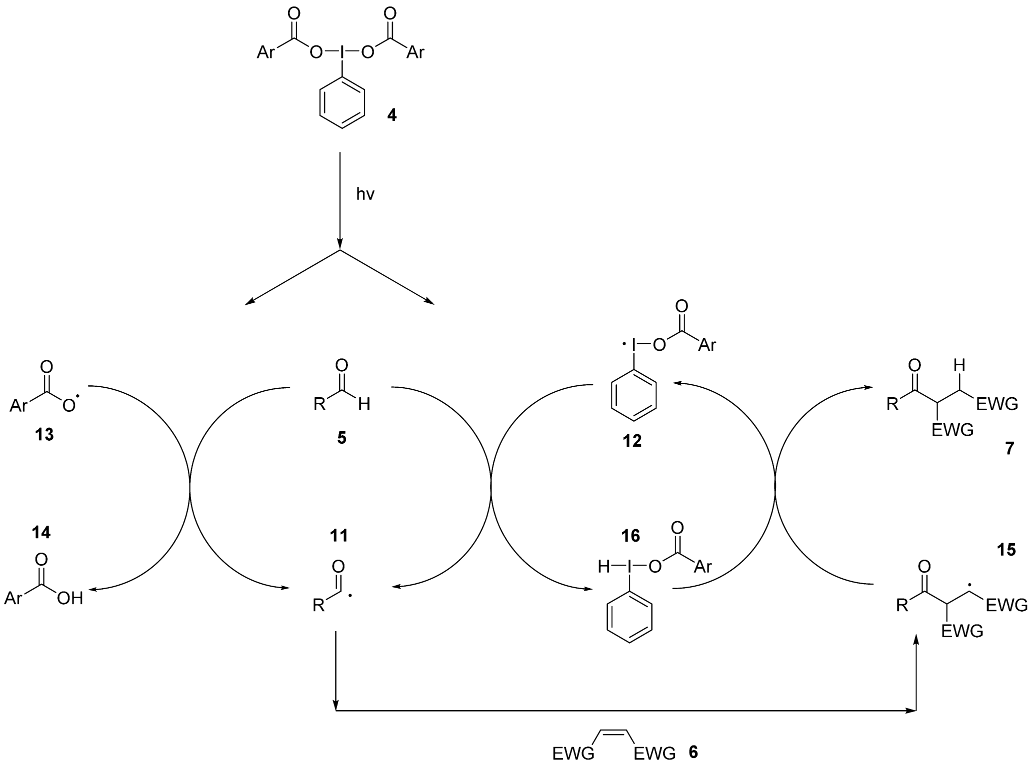
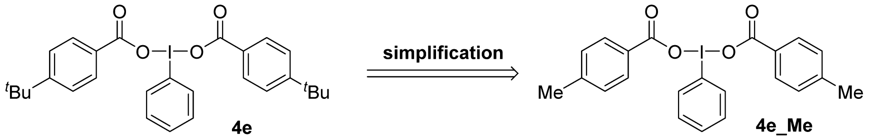
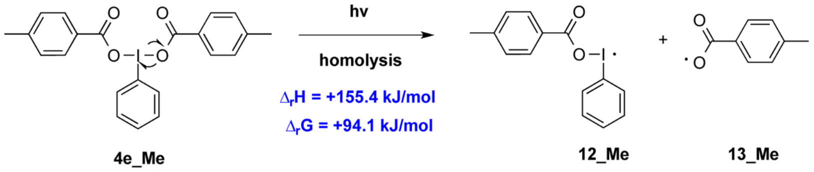
Scheme 2. Proposed Mechanism in Which an Iodonyl Radical Acts as a Catalyst (the So-Called Iodonyl Mechanism)



Scheme 3. Model Compound (4e_Me) Used in the Calculation



Scheme 4. Homolytic Cleavage of the O−I Bond in the Hypervalent Iodine(III) Reagent 4e_Me



H, and O atoms. The SDD basis set,[17] as an effective core potential basis set, was used for I atom with an additional d-polarization function ($\zeta_d = 0.289$).[18] The transition states were located by means of the QST3 method[19,20] and the Berny algorithm.[21] All of the reactant, intermediate, transition state, and product structures were fully optimized without any symmetric restrictions. The solvent effect was introduced through IEF-PCM model[22−24] with acetonitrile as the solvent ($\varepsilon = 35.688$) for both optimization and frequency calculations.

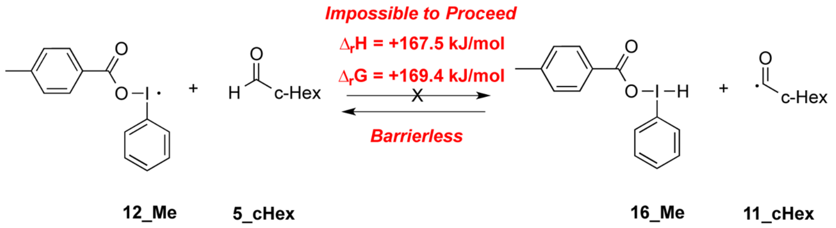
Frequency calculations were made to ensure the structure obtained is a real minimum or a transition state. Intrinsic reaction coordinate (IRC) calculations[25] were conducted to confirm that the transition state is connected to the correct reactant and product. All of the enthalpies and Gibbs energies shown in this Article were calculated at 1 atm and 298.15K.

In the Supporting Information (SI), we showed the potential energy profiles calculated by the meta-hybrid M06-2X[26] functional. To ensure consistency, both optimization and single point calculation were conducted at the same level of theory (M06-2X) with the same basis set. The results confirmed that the conclusions derived from the present calculations are valid with a different functional.

In order to thoroughly explore many possible reaction pathways without too expensive computational cost, a model compound called **4e_Me** (see Scheme 3), in which methyl groups are employed to replace the *tert*-butyl groups in the real substrate, was adopted throughout the paper.

How to handle the entropy of solvated molecules has been raised as a question for a long time.[27−30] Being different from those in the gas phase, molecules in solution are surrounded by solvent molecules and therefore cannot freely have translational and rotational motions. Thus, it is always a problem to calculate the contribution of translational and rotational motions to the entropy in solution. We have noticed that if the number of molecules changes during the reaction (like what can be seen from dissociation and addition reactions), the entropy contribution to the Gibbs energy change is largely overestimated. A very recent paper from the Singleton group carefully evaluated the entropy problem by conducting a comprehensive study of both experimental data and calculations results.[31] The overestimation even leads to the qualitatively incorrect conclusions. Thus, we decided to use mainly the enthalpy to describe reactions in the present article.[32,33]

Scheme 5. Energy Change for the H-Abstraction by the Iodonyl Radical 12_Me



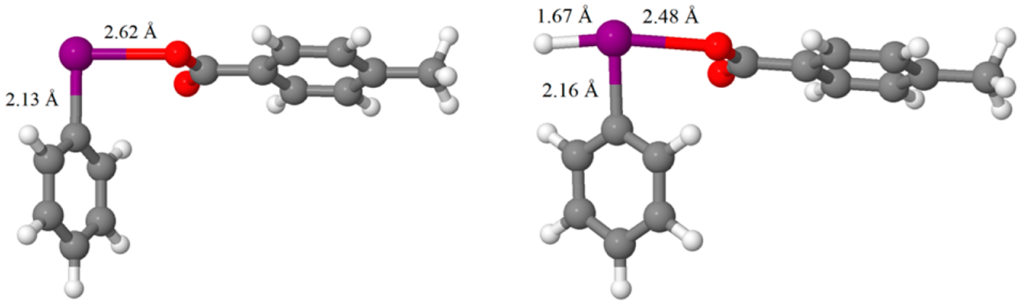


Figure 1. Optimized structures of **12_Me** and **16_Me**.

3. RESULTS AND DISCUSSION

The first calculation was carried out to confirm the energy required for homolytically breaking the O−I bond in the hypervalent iodine(III) reagent **4_Me**. The enthalpy for the homolytic cleavage was calculated to be 155.4 kJ/mol (see Scheme 4, calculated bond enthalpies of various species are also summarized in Table S1 in Supporting Information). By considering that the initiation step is driven by the absorption of a photon, the calculated energy required for breaking the O−I bond is reasonable. This relatively low bond enthalpy of the O−I bond can also rationalize why the reaction is performed under visible light irradiation rather than UV, as usually used in the photochemical reactions.

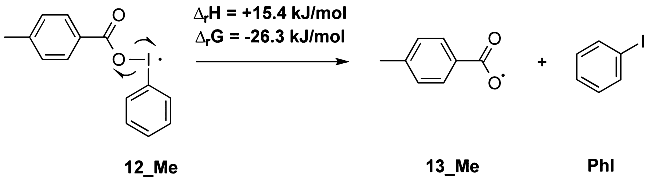
From these two radical species, the H abstraction can then occur from the iodonyl radical **12_Me** (the so-called iodonyl radical mechanism) or from **13_Me** (pathways A and B).

3.1. Theoretical investigation on the proposed iodonyl radical mechanism. The H-abstraction from the aldehyde by the iodonyl radical is not favored thermodynamically as shown in Scheme 5. The high endothermicity (167.5 kJ/mol) is derived from the bond enthalpy of the C−H bond in the aldehyde **5_cHex** as 368.1 kJ/mol, which is much larger than that of the H−I bond (200.6 kJ/mol) in the intermediate **16_Me** (see Table S1 in Supporting Information). Moreover, a systematic search showed that there is no transition state for this step, and the reverse step takes place without a barrier. Therefore, this reaction cannot take place.

The optimized structures of the iodonyl radical (**12_Me**) and the initially proposed intermediate **16_Me** are presented in Figure 1. The I−O bond length in the iodonyl radical **12_Me** in Figure 1 is much longer (2.62 Å) than the normal I−O bond (around 2.10 Å), suggesting a very weak bond. Further calculations showed that the O−I bond enthalpy in **12_Me** is only 15.4 kJ/mol, and the dissociation free energy (if the full entropy is considered) is slightly exergonic (see Scheme 6). Either way, the dissociation of the iodonyl radical to form the carboxyl radical **13_Me** and an iodobenzene is more favorable.

This finding disagrees completely with the initially proposed iodonyl mechanism, and forces us to re-examine the mechanism of this reaction. Two other pathways are possible for the reaction: the first one, called pathway A, involves a direct H-abstraction by the carboxyl radical **13_Me**; the second one, called pathway B, is the H-abstraction by the aryl radical **17_Me**, resulting from the decarboxylation of **13_Me**. Both mechanisms are discussed in detail in the following sections.

Scheme 6. Decomposition of the Iodonyl Radical

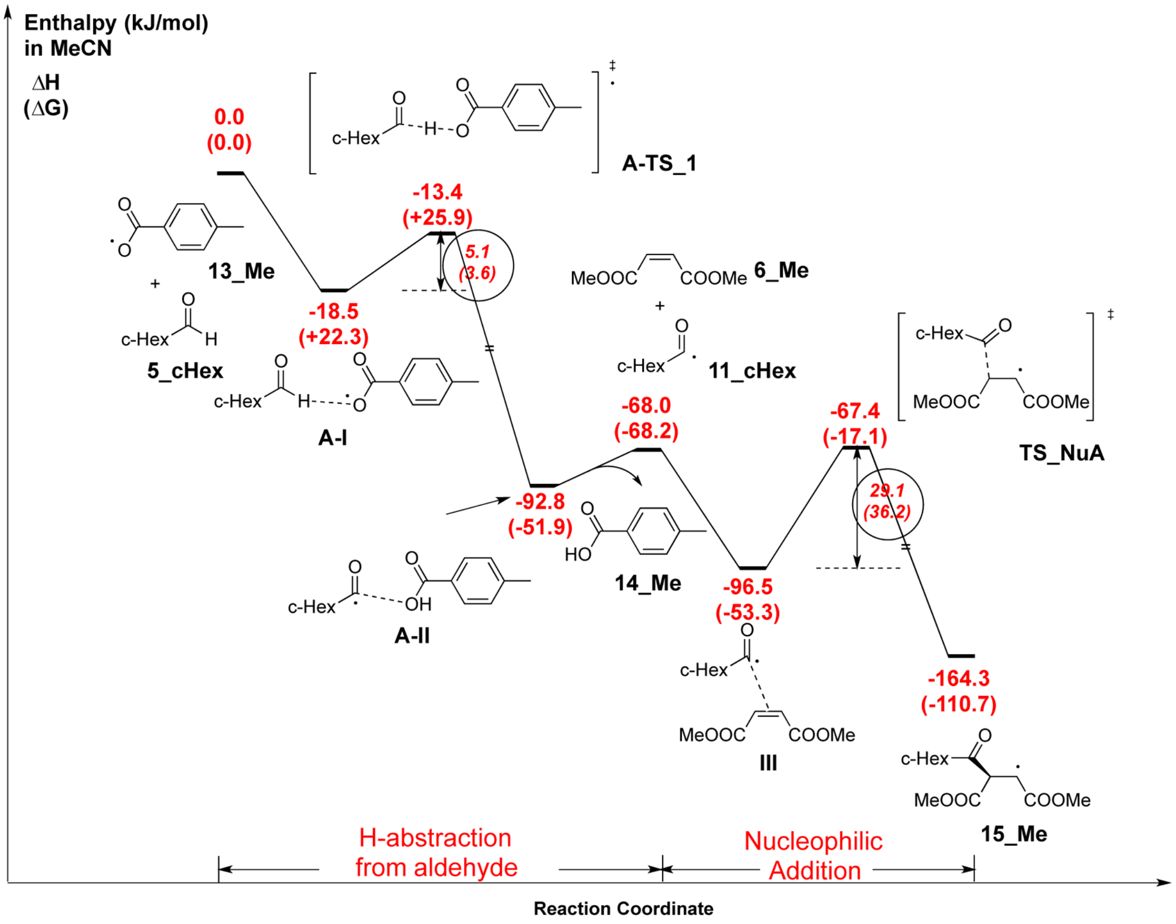


3.2. Pathway A: Direct H-Abstraction by the Carboxyl Radical (the Carboxyl Mechanism). The carboxyl radical **13_Me** is a good candidate for promoting the formation of acyl radical at the initiation stage.[34] Following the reaction pathway, the enthalpy profile for the entire hydroacylation reaction was calculated as shown in Scheme 7.

In the acetonitrile solvent, cyclohexanecarboxaldehyde **5_cHex** and the carboxyl radical **13_Me** can form a prereaction van der Waals complex **A-I** through a relatively weak C−H···O hydrogen bond interaction. The prereaction complex **A-I** then undergoes a H-transfer reaction to transfer the hydrogen atom from the aldehyde to the carboxyl radical, through transition state **A-TS_1** with a small enthalpy barrier of 5.1 kJ/mol. The very exothermic reaction gives a postreaction complex **A-II**, which dissociates formally to give the acyl radical **11_cHex** and the carboxylic acid **14_Me**.

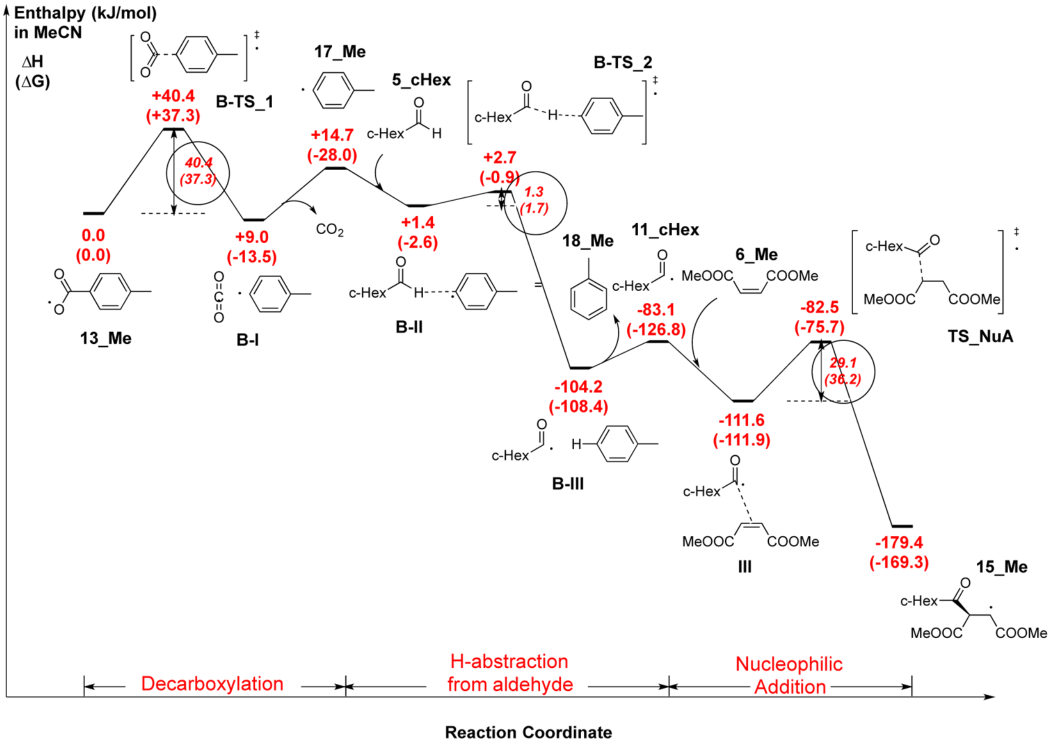
The free acyl radical **11_cHex** then approaches the model electron-deficient alkene, dimethyl maleate **6_Me**, to form another van der Waals complex **III**. The nucleophilic addition reaction of the acyl radical to **6_Me** proceeds with an enthalpy barrier of 29.1 kJ/mol via the transition state **TS_NuA**. A carbon-centered radical **15_Me** is therefore formed. The reaction is exothermic with an enthalpy change of −67.8 kJ/mol. Overall, the reaction proceeds with small barriers and large exothermicity, which are typical for a radical chain reaction.

Scheme 7. Enthalpy Profile for Pathway A (the Carboxyl Mechanism)[a]



[a]See Figure S1 in Supporting Information for 3D structures.

Scheme 8. Energy Profile for Pathway B (the Aryl Mechanism)



3.3. Pathway B: H-Abstraction by the Aryl Radical (the Aryl Mechanism). Slightly different from pathway A discussed above, it is also common to observe that the carboxyl radical generated through the radical initiation reaction undergoes a decarboxylation to give an aryl radical for the succeeding H-abstraction. This decarboxylation pathway (pathway B) is now discussed (see Scheme 8).

In general, the enthalpy profile has a contour similar to what is shown in Scheme 7. However, instead of a direct H-abstraction by the carboxyl radical, the first step in pathway B is the decarboxylation of the carboxyl radical. The transition state labeled as **B-TS_1** for the decarboxylation has been found with an enthalpy barrier of 40.4 kJ/mol. Although the release of CO_2 seems to be an entropy-driven reaction in the gas phase, it does not give too much driving force in solution. The enthalpy change of the decarboxylation reaction is even slightly positive (+9.0 kJ/mol), while the full free energy change is only −13.5 kJ/mol. A *p*-tolyl radical is thus generated and then joins the subsequent H-abstraction reaction, leading to the formation of the toluene molecule and the corresponding acyl radical. The *p*-tolyl radical (**17_Me**) is more reactive than the carboxyl radical (**13_Me**) for the H-abstraction since the enthalpy barrier for the abstraction is as low as +1.3 kJ/mol. Once the acyl radical is formed, it quickly reacts with the electron-deficient alkene **6_Me** via a nucleophilic addition to give out a carbon-centered radical, which is the same species described in pathway A.

Despite reasonable activation energies, the decarboxylation step in pathway B is thermodynamically and kinetically less favorable than pathway A. Therefore, pathway A is likely to be the most competitive pathway for the initiation step.

3.4. H-Transfer to the Carbon-Centered Radical: Rate-Determining Step. As shown above, the carbon-centered radical **15_Me** is generated through a nucleophilic addition of the acyl radical to the alkene **6_Me**. To keep propagating the reaction, **15_Me** needs to take a hydrogen atom from any potential H-source in the system to form the final product. Only three species have the possibility of being a H atom donor: the *p*-methylbenzoic acid (**14_Me**, from pathway A), the toluene (from pathway B), and, a more straightforward way, the aldehyde itself. However, the hydrogen abstractions from **14_Me** or toluene are thermodynamically and kinetically unfavored (see Table S1 and Scheme S2 in Supporting Information). Therefore, these two molecules can be excluded as the potential H-source. This result is consistent with the absence of deuterated product when *p*-$^tBuC_6H_4COOD$ is employed as an additive (see Scheme S1 in Supporting Information).

The enthalpy barrier of the hydrogen abstraction from the aldehyde is +34.1 kJ/mol, and therefore the only H-source of the present system is the aldehyde (see Scheme S2 in Supporting Information). The optimized structure of the transition state (**C-TS**) is illustrated in Figure 2.

Combined with the results obtained from Schemes 7 and 8, we conclude that the final H-abstraction step is the rate-determining step along the entire reaction pathway, which is consistent with the experiments. With application of the standard Eyring equation to the present results, a value of 4.8 is predicted theoretically as detailed in Supporting Information. This result is very close to the experimental data of 4.5. Moreover, the new mechanism indicates that the entire reaction is a radical chain reaction, as the last step generates the desired product and another acyl radical for next cycle. Thus, the hypervalent iodine(III) reagent is actually an initiator that starts the radical chain reaction, rather than a catalyst that is directly involved in the catalytic cycle as initially proposed (see Scheme 2). A supporting result has been found in the experimental work reported by Caddick and co-workers, in which an oxygen molecule in the ground state was used as the initiator of a radical chain reaction to facilitate the hydroacylation.[6k]

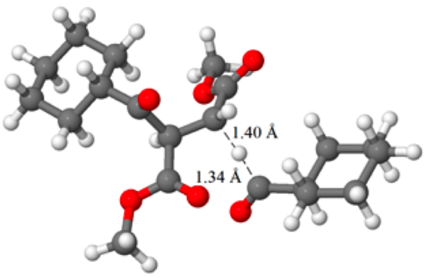
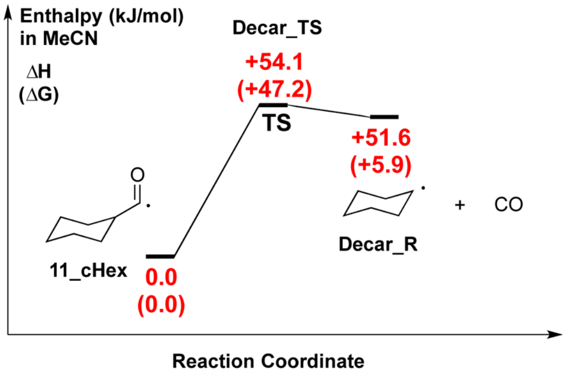


Figure 2. Optimized structure for the key transition state of H atoms transfer (**C-TS**).

3.5. Explanation for the Relative Stability of the Acyl Radical. While we have rationalized some important experimental observations, it should not be ignored that the acyl radical is a relatively unstable intermediate, which can decompose into alkyl radical and carbon monoxide easily. This process, called decarbonylation, is expected to proceed along with the nucleophilic addition reaction in a common situation. Therefore, a theoretical investigation was carried out for the decarbonylation reaction of the acyl radical **11_cHex**, as shown in Scheme 9.

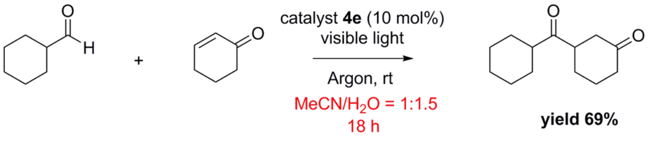
Scheme 9. Energy Profile for the Decarbonylation Reaction of the Acyl Radical 11_cHex



The calculation results suggest that the decarbonylation of the acyl radical **11_cHex** has an enthalpy barrier of only 54.1 kJ/mol (47.2 kJ/mol in the free energy). Kinetics experiments studying the decarbonylation of acyl radicals also confirmed this calculated barrier.[8,9] In the present reaction, however, the acyl radical **11_cHex** directly reacts with the alkene **6_Me** with a lower activation enthalpy (29.1 kJ/mol) to form the carbon-centered radical (see Scheme 7). Therefore, with a relatively smooth experimental condition (visible light irradiation at room temperature), it is not likely that the decarbonylation is a major pathway in the entire reaction cycle.

3.6. Factors That Control the Yield of Hydroacylation. So far, we came to the conclusion that the hypervalent iodine reagent is not relevant to the propagating reaction happening after initiation. We also found that the radical chain propagation cycle consists of an addition of the acyl radical to the alkene and an H-abstraction by the resultant carbon-centered radical from the aldehyde. Thus, the yield of the hydroacylation product should thus depend on the properties of alkenes. The Maruoka group found good performance of several different alkenes in this reaction. Interestingly, it has been found that 2-cyclohexen-1-one (**6_cHexen**) required harsher reaction conditions (18 h with addition of water) to achieve a moderate yield of 69% (see Scheme 10).

Scheme 10. Selective Hydroacylation of 2-Cyclohexen-1-one



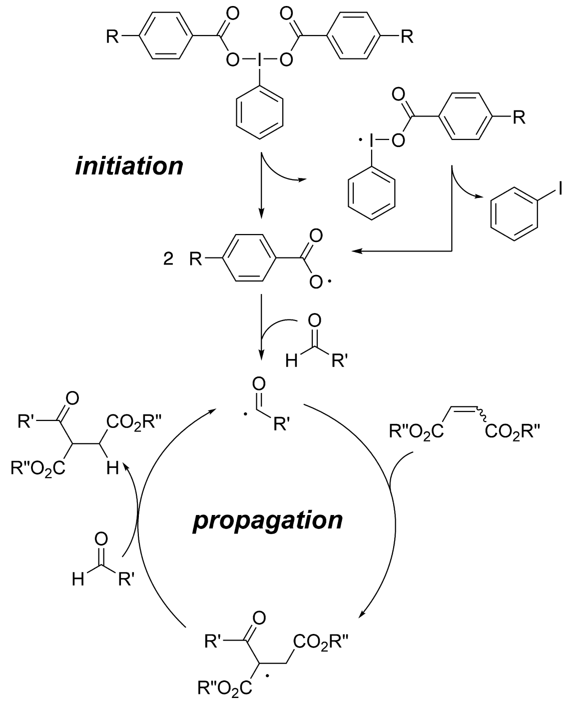
In order to gain insight into the selection criteria of alkene substrates, which is important for any future exploration of the radical process, the energy profile of the hydroacylation reaction is calculated using the 2-cyclohexen-1-one (**6_cHexen**) as the substrate and shown in Scheme 11. The rate-determining H-abstraction step is slightly endothermic and has a higher enthalpy barrier of 47.1 kJ/mol, compared to the exothermic reaction (with a much lower barrier), in which dimethyl maleate **6_Me** is involved (**C-TS** in Scheme S2). Qualitatively speaking, 2-cyclohexen-1-one **6_cHexen** is less electrophilic than dimethyl maleate **6_Me**, making it less reactive for a chain propagation process.

In addition, the difference in energy for the nucleophilic addition between the original reaction (with **6_Me**) and the present reaction (with **6_cHexen**) leads to some other dissimilarities in the reaction mechanism. For instance, the decarbonylation reaction of the acyl radical **11_cHex** having an enthalpy energy barrier of 54.1 kJ/mol becomes competitive with the H-abstraction reaction, which could also explain a lower yield.

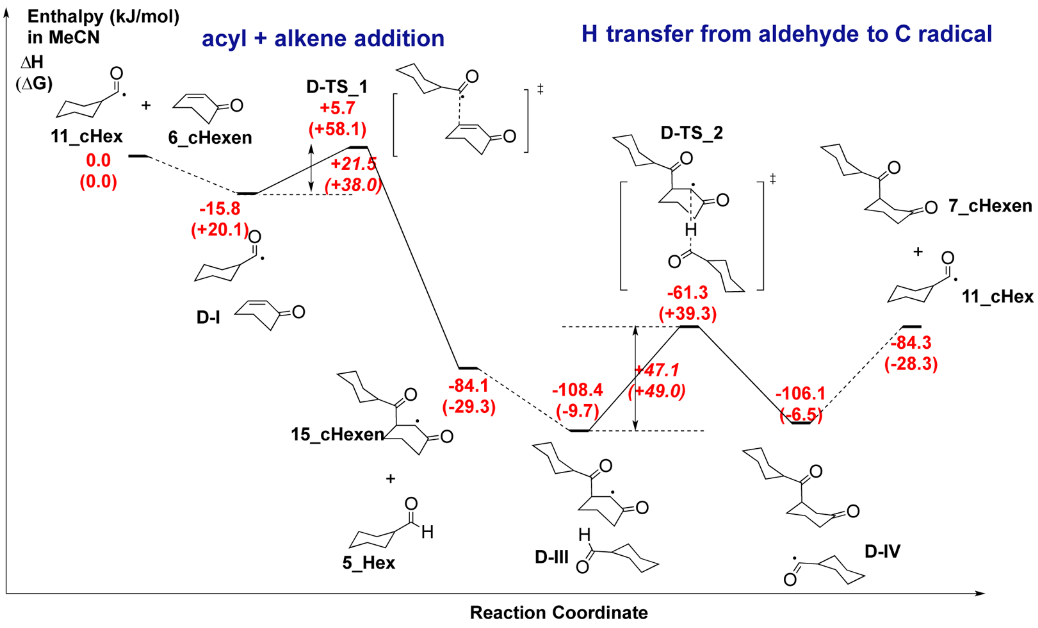
4. CONCLUSION

In the present study, theoretical investigations revealed the mechanism of hydroacylation of alkene by aldehyde in the presence of a hypervalent iodine reagent. The calculations have shown that the hypervalent iodine reagent is an initiator of the reaction. After initiation, the reaction proceeds via a chain propagation mechanism: addition of the acyl radical to the electron-deficient alkene, followed by a hydrogen abstraction from the aldehyde by the resultant carbon-centered radical

Scheme 12. Revised Mechanism of the C−H Activation and Acylation Reaction



Scheme 11. Energy Profile for the Radical Chain Reaction Involving 2-Cyclohexen-1-one (6_cHexen)



species, which is rate-determining for the process. The reaction mechanism is summarized in Scheme 12.

The calculations rationalized some critical experimental observations: the kinetic isotopic effect value obtained with a deuterated aldehyde (measured to be 4.5 and predicted to be 4.8), the absence of deuterated product when p-^{t}BuC$_6$H$_4$CO$_2$D is employed as an additive, the absence of decarbonylation of the acyl radical intermediate, and the lower yields obtained with enones. We do hope that the present results will help the organic community to extend the application of this type of reaction to other systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01695.

> Bond dissociation energies of various species, energy profiles at the M06-2X level, intermediates and transition state structures figures for pathway A, and Cartesian coordinates (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: morokuma@fukui.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

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