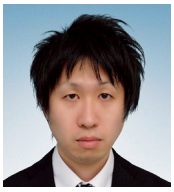
Drug development, Carbon neutral society, Air recycling

Photo/electrochemical CO_2 insertion into unreactive organic molecules



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Researchmap https://researchmap.jp/ysagagerrard?lang=en

Abstract

There has been a significant demand for novel 'green' synthetic technologies that enable the synthesis of high value-added molecules, such as fine chemicals and pharmaceuticals, starting from inexpensive and abundant resources, using renewable energy. In this work, we achieve the first single-step synthesis of γ-keto acids, important structural motifs found in many pharmaceuticals, using inexpensive CO_2 and alkenes under visible light-driven conditions. This is also the first example of a three-component acyl carboxylation of alkenes.

Background & Results

γ-Keto acids are among the most important chemical motifs widely found in natural products and pharmaceuticals. However, their single-step synthesis is challenging due to the intrinsic mismatch of a 1,4-dicarbonyl skeleton and the need for a carboxylic acid protecting group during the synthesis. Several examples of the single-step synthesis of γ-keto acids have been recently reported. Despite their outstanding achievements, these methods have several drawbacks, specifically, the need for special equipment or harsh reaction conditions (with an excess of hazardous metal reagents or under UV light irradiation) and the use of restricted substrates such as α,β-unsaturated carbonyl compounds, which limit the substrate generality.

In this work, we report the first single-step synthesis of γ-keto acids without ester formation using easily preparable starting materials under mild conditions. Our keys to success consist of three aspects; the use of (1) alkenes as abundant feedstocks that can overcome the narrow substrate generality, (2) benzimidazolines (**BI**s) as easily preparable acyl radical donors and (3) CO_2 as an abundant C1 building block. Our photocatalytic system proceeds under mild conditions (visible-light irradiation and modest temperature), in high to excellent yields (up to 97%), with perfect regioselectivity (>20/1), and broad substrate generality (35 examples). This is also the first example of photocatalytic three-component acylcarboxylation of alkenes. Moreover, a series of mechanistic studies supported our proposed mechanism. This study opens a new avenue to provide a wide range of important structural motifs in a single step from readily available feedstocks in an environmentally friendly manner.

Significance of the research and Future perspective

CO_2 insertion into hydrocarbons is an attractive and environmentally friendly chemical transformation, providing carboxylic acid structures ubiquitous in numerous fine chemicals, while also reducing greenhouse gases. However, this transformation is quite challenging due to the difficulty of activating both stable molecules, hydrocarbons and CO_2. In this context, we have achieved the first three-component acyl carboxylation of hydrocarbon alkenes using CO_2. This is also the first example of a single-step synthesis of γ-keto acids, which are found in many pharmaceuticals. Our system has enabled the CO_2 insertion reaction into hydrocarbons, driven by visible light, which is readily available clean energy from renewable energy sources, under modest temperature conditions. We will contribute to the development of new photo/electro-driven methodologies for the synthesis of high value-added molecules in an environmentally friendly manner.

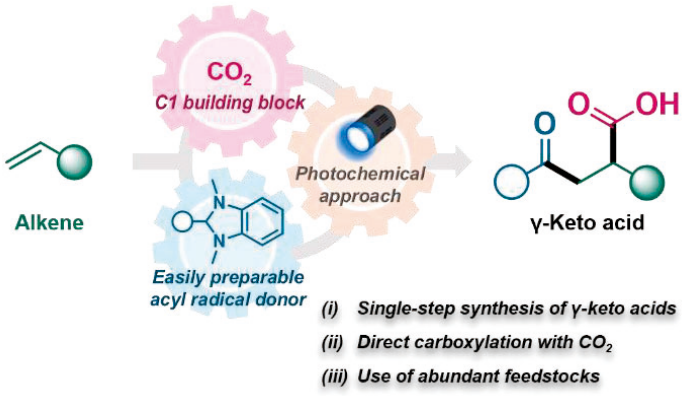

Figure 1. Photocatalytic Three-Component Acylcarboxylation of Alkenes with CO_2

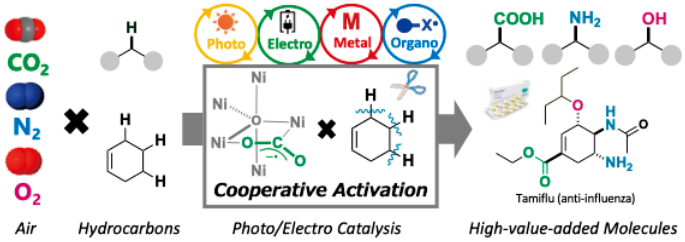

Figure 2. Future Direction: Photo/electrochemical Organic Synthesis of High-value-added Molecules from Abundant Resources

Patent	
Treatise	Saga, Yutaka; Masaoka, Shigeyuki et al. Photocatalytic three-component acylcarboxylation of alkenes with CO_2. Organic Letters. 2024, 26, 6491-6496. doi: 10.1021/acs.orglett.4c02295 Saga, Yutaka; Masaoka, Shigeyuki et al. Electrochemical C(sp^3)-H functionalization using acetic acid as a hydrogen atom transfer reagent. ChemElectroChem. 2024, 11, e202400061. doi: 10.1002/celc.202400061 Saga, Yutaka; Masaoka, Shigeyuki et al. Visible-light-driven hydroacylation of unactivated alkenes using readily available acyl donors. Organic Letters, 2023, 25, 1136-1141. doi: 10.1021/acs.orglett.2c04337
URL	http://www.chem.eng.osaka-u.ac.jp/masaoka_lab/english/index.html
Keyword	CO_2 insertion, CO_2 recycling, photochemical organic synthesis, electrochemical organic synthesis, functionalization of hydrocarbons