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研究課題名(和文) Dual Catalysis with Photoredox Catalysts for Organic Transformations Mediated by Single-Electron Transfer Processes

研究課題名(英文) Dual Catalysis with Photoredox Catalysts for Organic Transformations Mediated by Single-Electron Transfer Processes

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研究成果の概要(和文)：二酸化炭素と容易に入手可能な原料からのラクトンの合成研究として、C-H活性化の化学と銅触媒によるカルボキシル化反応とを組み合わせたベンジルアルコール類のフタリド類への変換、及び、連続的なトランス選択的のヒドロアルミニウム化に次ぐ銅触媒によるカルボキシル化反応によるプロパルギルアルコール類のブテノライド類への変換を試みた。

最後に、複雑な有機分子を構築するための二酸化炭素との多成分カップリング反応の開発に興味を持ち研究を行った。二酸化炭素およびフッ化セシウムとの1-アリール-2,2-ジフルオロアルケンのフルオロカルボキシル化により、トリフルオロメチルカルボン酸が良好な収率で得られることを見出した。

研究成果の学術的意義や社会的意義

Various strategies of utilizing carbon dioxide as a sustainable source of a carbon feedstock to synthesize various value-added organic substrates have been discovered through our studies, and it is anticipated that our finding can be used to sustainably synthesis other complex organic molecules.

研究成果の概要(英文)：I investigated the synthesis of lactones from carbon dioxide and readily available starting materials by two different strategies. The first approach involved combining C-H activation (C-H silylation) chemistry with copper-catalyzed carboxylation reaction to convert benzyl alcohols to phthalides. The second approach involved a sequential trans-hydroalumination and copper-catalyzed carboxylation reaction to convert propargyl alcohols into butenolides.

Finally, I have interest in developing multi-component coupling reactions with carbon dioxide to make complex organic molecules. I found that 1-aryl-2,2-difluoroalkenes can undergo fluorocarboxylation with carbon dioxide and cesium fluoride to provide trifluoromethyl carboxylic acids in good yields.

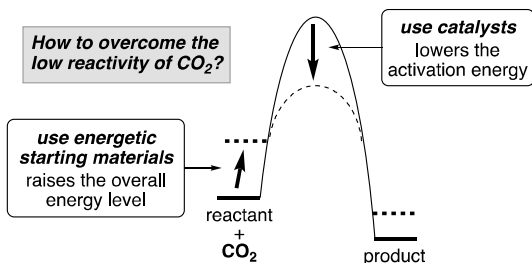
研究分野：有機合成化学

キーワード：carbon dioxide multi-component coupling copper fluorine lactone

1. 研究開始当初の背景

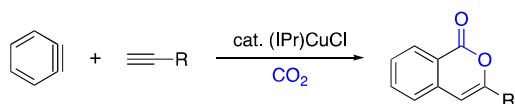
Synthetic organic chemistry provides the foundation in which modern society is built upon by providing the tools for the fabrication of the functional materials and organic compounds that improves the quality of human life. However, the rate of consumption of raw materials that fuel the needs of human beings is unsustainable, and chemist must seek new methods to make reactions more efficient, or develop methods that can make use of renewable resources. Carbon dioxide (CO₂) is a naturally occurring gas that is the by-product of combustion. As such, it is a readily available and renewable C1 source in organic synthesis. However, due to its intrinsic thermodynamic stability and kinetic inertness, the use of CO₂ as a renewable resource in organic chemistry is limited. In order to overcome the thermodynamic stability of CO₂, highly reactive substrates/reagents are needed, while the kinetic barriers can be surmounted by the use of catalysts (Scheme 1).

Scheme 1. General approach to solve low reactivity of CO₂



Recent advancements in CO₂ chemistry has been focused on transition metal-catalyzed carboxylation reactions of reactive organometallic nucleophiles for the preparation of simple benzoic acid derivatives. To synthesize more complex organic compounds with CO₂, the development of multi-component coupling reactions are needed. Previously, we reported the use of benzynes, as energetic compounds, that could be incorporated into multi-component coupling reactions with terminal alkynes and CO₂ to prepare various isocoumarines (Scheme 2). This research is a continuation of the theme of preparing complex organic compounds from CO₂ through multi-component coupling reactions.

Scheme 2. Multi-component coupling reaction with CO₂



2. 研究の目的

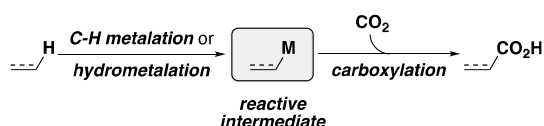
The purpose of this research is the development of new carboxylation reactions in multi-component coupling reaction to prepare complex organic compounds. Particular focus

was placed on synthesizing heterocycles and fluorine-containing compounds, since these types of molecules are important motifs found in pharmaceutical and agricultural sciences.

3. 研究の方法

To achieve this goal, the plan was to combine efficient metallation chemistry (C-H activation or hydrometallation) with carboxylation chemistry to efficiently prepare complex organic molecules with CO₂ (Scheme 3).

Scheme 3. Combination of metallation chemistry with CO₂



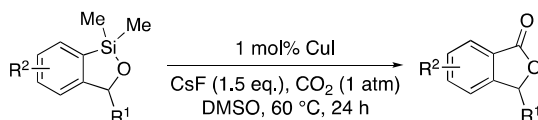
4. 研究成果

During the funding period, several different projects were completed that makes use of the above stated concept and are described below.

(1) Copper-Catalyzed Carboxylation of Benzoxasiloles

Phthalides are an important class of lactones that are commonly found in numerous biologically active compounds, and is the target of many synthetic methodologies. Our hypothesis was that these heterocycles could be constructed from readily available benzyl alcohols and CO₂ through a sequential C-H silylation, followed by carboxylation of the corresponding benzoxasiloles. Although the C-H activation of benzyl alcohol is established, the carboxylation of aryl silanes has been hardly explored. We found that by utilizing catalytic amounts of CuI, the desired transformation can be achieved to furnish a large variety of phthalides in good yields. Furthermore, we demonstrated the synthetic utility of our methodology by preparing natural products, such as Marilone C (Scheme 4).

Scheme 4. Cu-catalyzed carboxylation of benzoxasiloles

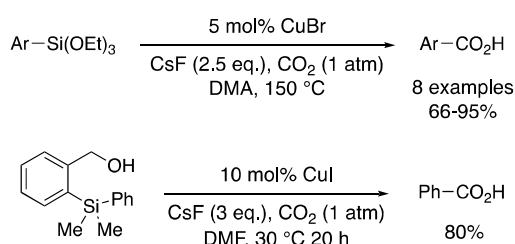


(2) Copper-Catalyzed Carboxylation of Aryl Silanes

Due to our previous work with the carboxylation of benzoxasiloles, we found that the carboxylation of aryl silanes hardly proceeded. As such, we decided to investigate the copper-catalyzed carboxylation of aryl silanes. In our first generation system, we found that simple copper bromide could catalyze the carboxylation of aryl triethoxysilanes, but

required very high reaction temperatures (150 °C) (Scheme 5, above). This was in stark contrast with the carboxylation of benzoxasiloles (60 °C). Since the major difference between benzoxasiloles and aryl trialkoxysilanes is the pendent hydroxyl group, we hypothesized that 2-hydroxymethylaryl dimethylsilanes (HOMSi) could be a reactive nucleophile for the carboxylation reaction to prepare benzoic acids. We found that the use of HOMSi reagents, in conjugation with CuI as a catalyst, allows for the carboxylation reaction to occur under mild reaction temperatures, and further optimization is now on-going (Scheme 5, below).

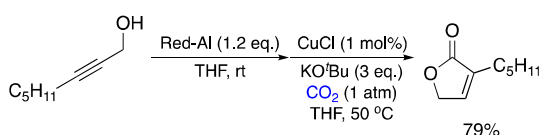
Scheme 5. Cu-catalyzed carboxylation of aryl silanes



(3) Synthesis of Butenolides via Hydrometallation/Carboxylation Strategy.

Since we achieved the synthesis of phthalides through a C–H activation/carboxylation strategy, we considered utilizing this same approach for the synthesis of structurally related lactone, butenolides. However, our initial trials failed, due to our inability to conduct the C–H silylation of allylic alcohols. As such, we changed our approach and decided to prepare the key metallated species through a hydrometallation strategy starting from propargyl alcohols as a readily available starting material. The key challenge with this method was to achieve the hydrometallation in a *trans*-selective manner, which is normally difficult since metallation processes often occurs in a *syn*-fashion. However, we based on the literature, hydroalumination of propargyl alcohols with Red-Al is *trans*-selective, and in order to achieve our goal, we required a catalytic method that readily would convert the corresponding alanes into the carboxylic acid with CO₂. We found that by using CuI as a catalyst, the carboxylation of the in situ-prepared alane could undergo carboxylation to furnish the desired butenolide in an excellent yield (Scheme 6). Further investigations are now on-going to flesh out the substrate scope.

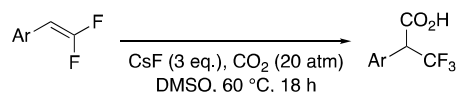
Scheme 6. Sequential *trans*-hydrometallation/copper-catalyzed carboxylation



(4) Synthesis of α -Trifluoromethyl Carboxylic Acids via Fluorocarboxylation of β,β -Difluoroalkenes.

Trifluoromethyl (CF₃) groups are known to significantly modify the chemical properties, such as lipophilicity, metabolic stability, and bioavailability, of organic compounds and there is significant interest in developing new methods that enable facile access to CF₃ moieties. With this in mind, we became interested in the preparation of α -trifluoromethyl carboxylic acids since these molecules can act as versatile building blocks for the synthesis of CF₃-containing drugs and other fluorinated compounds. Although several synthetic methods have been reported, the drawback to these approaches are the long synthetic steps, the use of transition metal catalysts, and/or the use of expensive electrophilic fluorinating reagents. In order to overcome these challenges, we found that 1-aryl-2,2-difluoroalkenes can undergo a three-component coupling reaction with CsF and CO₂ to provide readily access to the target molecule in good yields (Scheme 7). We found that gem-difluoroalkenes, bearing electron-withdrawing groups, could undergo the fluorocarboxylation reaction under 1 atm of CO₂. However, less reactive difluoroalkenes, bearing electron-rich moieties required pressurized CO₂ to undergo the three-component coupling reaction.

Scheme 7. Fluorocarboxylation of β,β -difluoroalkenes



5. 主な発表論文等

(研究代表者、研究分担者及び連携研究者には下線)

[雑誌論文](計2件)

"Copper-Catalyzed Carboxylation of Aryl- and Alkenyltrialkoxysilanes" Thanh V. Q. Nguyen, Woo-Jin Yoo, Shū Kobayashi, *Asian Journal of Organic Chemistry*, **2018**, 7, 116-118. DOI: 10.1021/ajoc.201700519. (peer-reviewed)

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6 . 研究組織

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