

# Development of Novel Efficient Palladium-Catalyzed Carbonylation Reactions in Combination with Copper Salts

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# DISSERTATION ABSTRACT

題名 (Title) Development of Novel and Efficient Palladium-Catalyzed Carbonylation  
Reactions in Combination with Copper Salts

(邦題訳) 新規かつ効率的な銅塩協働パラジウム触媒によるカルボニル化反応の開発

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## ABSTRACT

Palladium-catalyzed carbonylations of alkenes have acquired a growing importance in recent years, which provides a versatile method for the direct functionalization of C=C double bond to produce efficient entries to a variety of useful carbon-homologated compounds with oxygen-functional groups. The development of novel methods with high efficiency, selectivity, and large substrate scope are of immense importance for continued progress in this field.

Based on earlier works in our laboratory, the combination of palladium (II) with copper salt has realized to catalyze alkoxy-carbonylation and related reactions under normal pressure of carbon monoxide and oxygen. Considering the great synthetic value of the carbonylation reactions, the aim of the present study was decided to develop novel and efficient palladium-catalyzed carbonylation reactions in the presence of copper salts.

In this research, a novel asymmetric intra- and intermolecular palladium-catalyzed dicarbonylation reaction of homoallylic amine derivatives is developed to provide straightforward entry to optically active  $\gamma$ -lactams, which have biological activity and are versatile building blocks for nitrogen-containing chemicals. In addition, an extensive study on palladium-catalyzed intermolecular alkoxy-alkoxy-carbonylation reaction of vinylphenols in the presence of copper salt is also described. The applications of  $\beta$ -alkoxy ester products are demonstrated for their further transformations towards various useful chemicals and bioactive agents.

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## DISSERTATION ABSTRACT

The development of sustainable and efficient methodologies based on catalysis and organometallic chemistry has gained considerable attention. In this regard, carbonylation reactions catalyzed by transition metal are now widely recognized as a powerful tool in advanced organic synthesis to provide efficient entries to a variety of useful homologated carbonyl compounds utilizing carbon monoxide (CO) as an inexpensive and readily available C1 unit, which also meets the principles of “atom economy”, “step economy”, and “green chemistry”. Among the different types of carbonylation reactions, palladium-catalyzed oxidative carbonylation of alkenes have attracted much attention from both academia and industry in recent years since they allow the direct functionalization of C=C double bond with CO in the presence of suitable nucleophiles and oxidation reagents to produce more valuable products such as aldehydes, esters, and carboxylic acid derivatives. The development of novel methods with high efficiency, selectivity, and larger substrate scope is of immense importance for continued progress in this field.

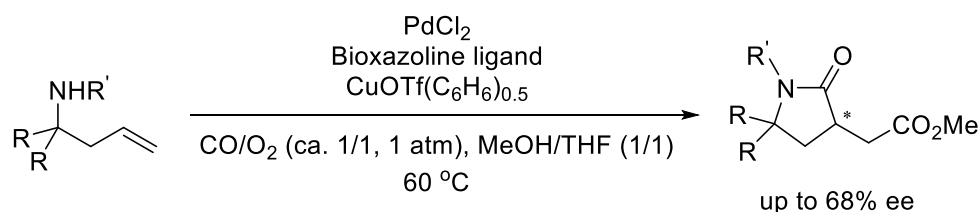
Our laboratory has studied palladium-catalyzed mono- and dicarbonylation of terminal olefins, homoallylic alcohols, homoallylic amine derivatives and already reported several asymmetric versions for dicarbonylation reactions. The combination of palladium (II) and copper (I) salt catalyzed these carbonylations under mild conditions.

Regarding to such perspectives, the aim of the study presented in this dissertation was to develop novel and efficient palladium-catalyzed oxidative carbonylation reactions in the combination with copper salts. The work involved in achieving the aim led to two main research contents as follows.

### A. Asymmetric Palladium-Catalyzed Intra- and Intermolecular Dicarbonylation of Homoallylic Amine Derivatives

The  $\gamma$ -lactams can probably be considered as one of the most important heterocyclic motifs used in synthetic and medicinal chemistry, which can be found in a very large number of biologically and pharmaceutically active compounds, and also serve as versatile building blocks for the synthesis of complex molecules. The development of methodologies allowing their synthesis is therefore of highly interest. Many synthetic approaches to  $\gamma$ -lactam compounds via metal-catalyzed cyclocarbonylation have been reported over the years. To the contrary, the enantioselective synthesis of  $\gamma$ -lactams has limited. Being encouraged by our previously results on asymmetric dicarbonylation reactions, an asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives was envisioned to produce optically active  $\gamma$ -lactams in single step. In this work, asymmetric intra- and intermolecular dicarbonylation of homoallylic amine derivatives catalyzed by palladium (II) and copper (I) salt under normal pressure of CO and O<sub>2</sub> has been achieved by using (*S,S*)-benzyl-substituted bioxazoline as a ligand. A variety of

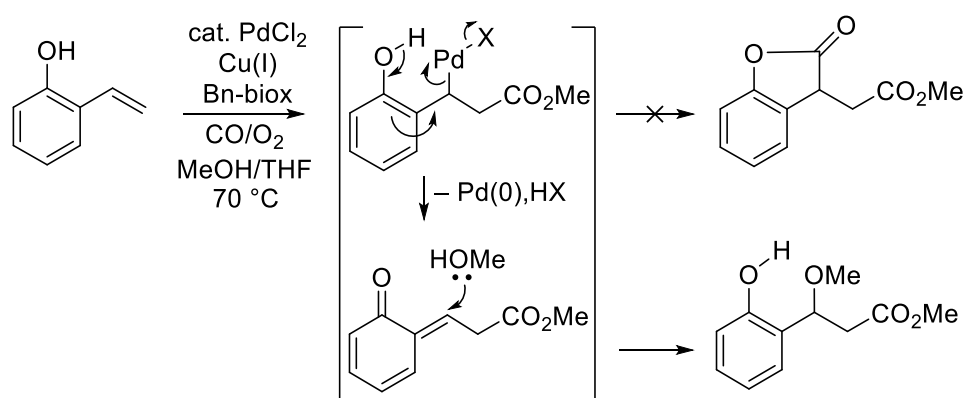
*N*-substituted homoallylic amine derivatives was applicable to the present reaction to give the corresponding optically active  $\gamma$ -lactams up to 68% ee (Scheme 1).



**Scheme 1.** Asymmetric palladium-catalyzed dicarbonylation of homoallylic amine derivatives.

### B. Palladium-Catalyzed Intermolecular Alkoxy-Alkoxy-carbonylation of Vinylphenols in the Presence of Copper Salt: Unexpected Cooperative Effect of Tin Salt

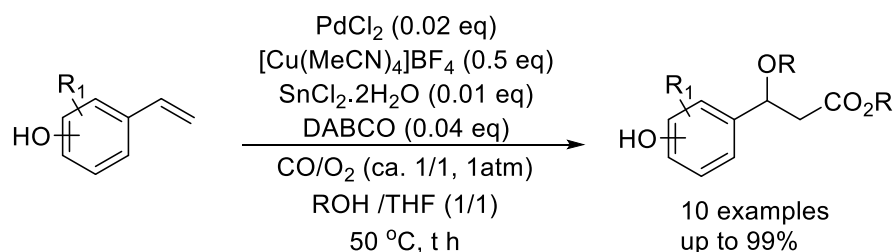
Concerning palladium-catalyzed carbonylation of unsaturated alcohols, intramolecular alkoxy-carbonylation often proceeds to furnish cyclic ethers, such as tetrahydrofurans or tetrahydropyrans. However, the intermolecular version of the alkoxy-carbonylation of alkenes is quite limited. In light of the successful development of a palladium-catalyzed intra- and intermolecular dicarbonylation protocol for homoallylic alcohols from earlier work in our laboratory, the idea of expanding the range of vinylphenols as substrates in the reaction emerged. The study was initiated with the asymmetric intra- and intermolecular bis(alkoxy-carbonylation) of 2-vinylphenol. Interestingly, although the carbonylation proceeded smoothly, the expected lactone was not formed, but 3-aryl-3-methoxypropanoic acid methyl ester was obtained instead. This ester might be derived from regioselective carbopalladation followed by reductive elimination and subsequent addition of MeOH to the resulting quinonemethide before the second carbonylation (Scheme 2).



**Scheme 2.** Methoxy-methoxy-carbonylation of 2-vinylphenol.

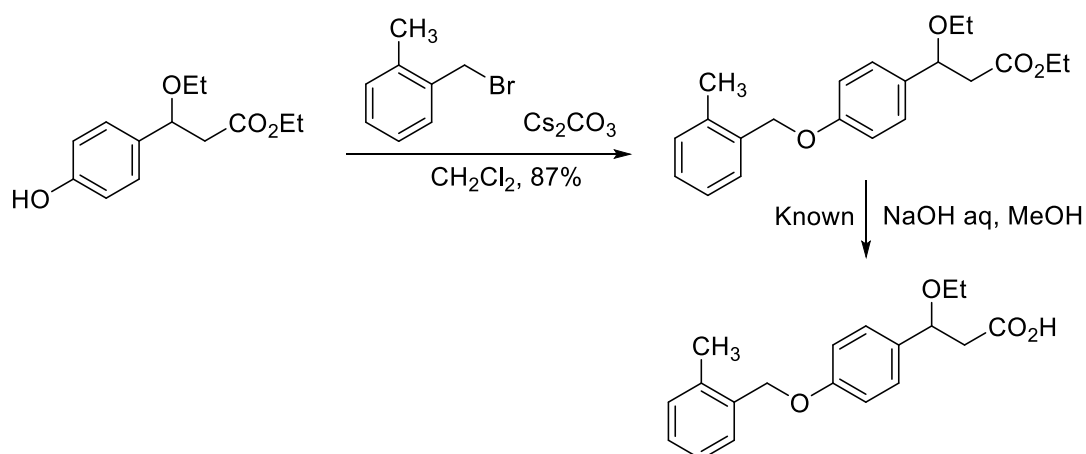
The unexpected result triggered the original objective to an extensive study on new intermolecular alkoxy-alkoxy-carbonylation reaction. Consequently, the efficient palladium-catalyzed intermolecular alkoxy-alkoxy-carbonylation of vinylphenols was developed to afford the corresponding 3-alkoxy-3-

arylpropanoic acid esters in good to high yields under optimized conditions as shown in scheme 3. Not only primary alcohols but also secondary alcohols were applicable to the present reaction. In this work, an unexpected effect of tin salt was discovered. The presence of a tin salt was crucial to realize reproducibly high yields.



**Scheme 3.** Alkoxy-alkoxycarbonylation of vinylphenols.

Furthermore, the 3-alkoxy-3-(4-hydroxyphenyl)propanoic acid esters obtained by the present alkoxy-alkoxycarbonylation was readily applied to the preparation of valuable chemicals and useful synthetic intermediates for biologically active compounds, such as GPR40 agonists for treatment of diabetes (Scheme 4).



GPR40 agonists for treatment of diabetes  
(*Bioorg. Med. Chem.* **2015**, *23*, 5546)

**Scheme 4.** Transformation of 3-ethoxy-3-(4-hydroxyphenyl)propanoate.

In summary, novel and efficient palladium-catalyzed carbonylation reactions have successfully developed. The combination of palladium (II) with copper (I) salt has realized to catalyze these reactions under normal pressure of CO and O<sub>2</sub>. Notably, the methods developed from this research could find great interest in the synthesis of highly functionalized molecules and especially in the synthesis of biologically active compounds. Thus, these results add value to the scope of palladium-catalyzed carbonylation.

With respect to the contents, the dissertation includes following parts:

**Chapter I** provides general introduction, including context of the research area, relevant basic concepts, background of research and aims of the present work.

**Chapter II** focuses on the development of asymmetric palladium-catalyzed intra- and intermolecular dicarbonylation of homoallylic amine derivatives.

**Chapter III** presents the successful strategy for palladium-catalyzed intermolecular alkoxy-alkoxycarbonylation of vinylphenols.

**Chapter IV** provides a summary of fruitful outcomes of the present study, a proposal for extensive study, and general conclusion.

**Experimental Section** provides detailed experiment procedures, full spectra data for identification of new and important compounds.

## 学位論文審査報告書（甲）

1. 学位論文題目（外国語の場合は和訳を付けること。）

Development of Novel Efficient Palladium-Catalyzed Carbonylation Reactions in Combination with Copper Salts（新規かつ効率的な銅塩協働パラジウム触媒によるカルボニル化反応の開発）

2. 論文提出者 (1) 所属 物質化学専攻

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Phan Thi Hang Nga

3. 審査結果の要旨

提出学位論文について、各審査委員により個別に予備審査を実施するとともに、平成30年1月31日に開催された口頭発表の結果を踏まえて、同日に論文審査委員会を開催して協議を行った。その結果、以下の様に判定した。

遷移金属触媒による一酸化炭素の導入反応は、炭素一つを増やしながらカルボニルなどの酸素官能基を導入できる反応として、工業的にも極めて重要である。オレフィンを基質とするカルボニル化反応において、カルボニルを導入しながら他の官能基も同時に導入することは、従来困難であった。本論文では、パラジウム触媒を用い、銅塩の協働作用を利用することにより、二つめのカルボニル基も導入可能とするジカルボニル化反応と、エーテル結合も同時に生成するアルコキシカルボニル化反応を開発した。前者では不斉配位子存在下において光学活性 $\gamma$ -ラクタムの合成を達成し、後者では $\beta$ -アルコキシプロピオン酸骨格を有する生理活性物質合成中間体の合成への応用を実現した。本論文の内容は、一酸化炭素導入により高度に酸素官能基化されたカルボニル化合物の合成法を開発した研究として非常に意義深いことから、博士（理学）の学位に値するものと判断した。

4. 審査結果 (1) 判定（いずれかに○印） 合格 ・ 不合格

(2) 授与学位 博士（理学）