

Research Highlight

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Synergistic photoredox/palladium catalysis enables enantioconvergent carboxylation of racemic heterobiaryl (pseudo)halides with CO₂

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Carbon dioxide (CO₂) is an abundant, non-toxic, and sustainable C1 resource that has garnered significant attention from chemists due to its potential for efficient conversion into various high-value chemicals^[1,2]. In recent decades, researchers have developed various methodologies to convert CO₂ into a range of carboxylic acids^[3-5]. However, the inherent thermodynamic stability and kinetic inertness of CO₂ necessitate harsh reaction conditions for its conversion. Furthermore, the non-polar nature of CO₂ limits its coordination capability with transition metals, presenting a challenge for synthesizing chiral carboxylic acids through transition metal-catalyzed asymmetric carbon-carbon bond formation with CO₂. While there have been advancements in catalytic asymmetric transformations with CO₂, most efforts have concentrated on constructing carboxylic acids with central chirality^[6-8]. In contrast, the catalytic asymmetric synthesis of axially chiral carboxylic acids with CO₂ has received less attention, with only one successful example of nickel-catalyzed asymmetric reductive carboxylation of racemic aza-biaryl triflates with CO₂ reported by Chen *et al.*^[9].



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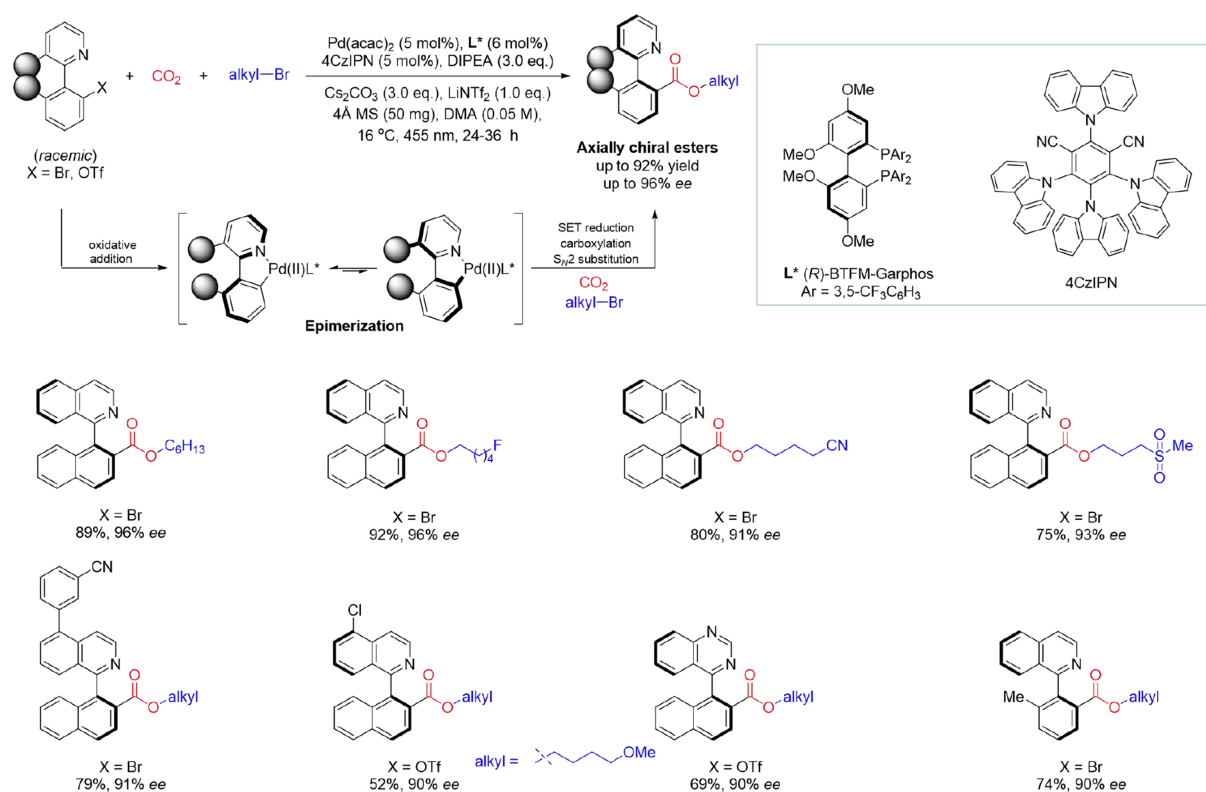


Figure 1. Synergistic photoredox/palladium catalysis for enantioconvergent carboxylation of heterobiaryl (pseudo)halides with CO₂.

In recent years, there has been growing interest in the synergistic catalytic system that combines photocatalysis with transition metal catalysis^[10,11]. This dual catalytic approach offers a unique blend of advantages from both systems, disrupting conventional metal catalysis reaction pathways and enhancing the flexibility in controlling catalytic metal oxidation states by incorporating photocatalytic generated species. As a result, novel reactivity pathways are introduced. Moreover, the synergistic catalysis of photocatalysis and metal catalysis enables a more accurate regulation of reaction reactivity and selectivity. Among these, photoredox/palladium dual catalysis has also been recently adopted in the challenging reductive carboxylations of organohalides with CO₂ under mild conditions^[12-14]. Following this logic, recently, Liu *et al.* have developed a novel tandem asymmetric carboxylation and *in situ* esterification reaction of aryl/heteroaryl halides and pseudohalides with CO₂ and alkyl bromides using a synergistic photoredox/palladium catalytic system through a dynamic kinetic asymmetric transformation process [Figure 1]^[15]. Using 2,4,5,6-tetrakis(carbazol-9-yl)isophthalonitrile (4CzIPN) as the photocatalyst, palladium(II) acetylacetonate [Pd(acac)₂] as the palladium catalyst precursor, (*R*)-(4,4',6,6'-tetramethoxy-1,1'-biphenyl-2,2'-diyl)bis(bis(3,5-bis(trifluoromethyl)phenyl)phosphine) [(*R*)-BTFM-Garphos] (L*) as the chiral ligand, *N,N*-diisopropylethylamine (DIPEA) as the reducing agent, cesium carbonate as the base, lithium bis(trifluoromethanesulfonyl)imide and 4 Å molecular sieves as reaction additives, *N,N*-dimethylacetamide as the solvent, under an atmospheric CO₂ environment with 455 nm blue light irradiation at 16 °C for 24 h, the model reaction gave the corresponding ester product with 89% yield and 96% enantiomeric excess (ee). Under the optimized conditions, various heterobiaryl, including isoquinoline and quinazoline, bromides or triflates with different functional groups such as ester, cyano, chloride, and ketone substituents were well tolerated. Additionally, when the naphthalene ring was replaced with a 6-methylphenyl group, the reaction

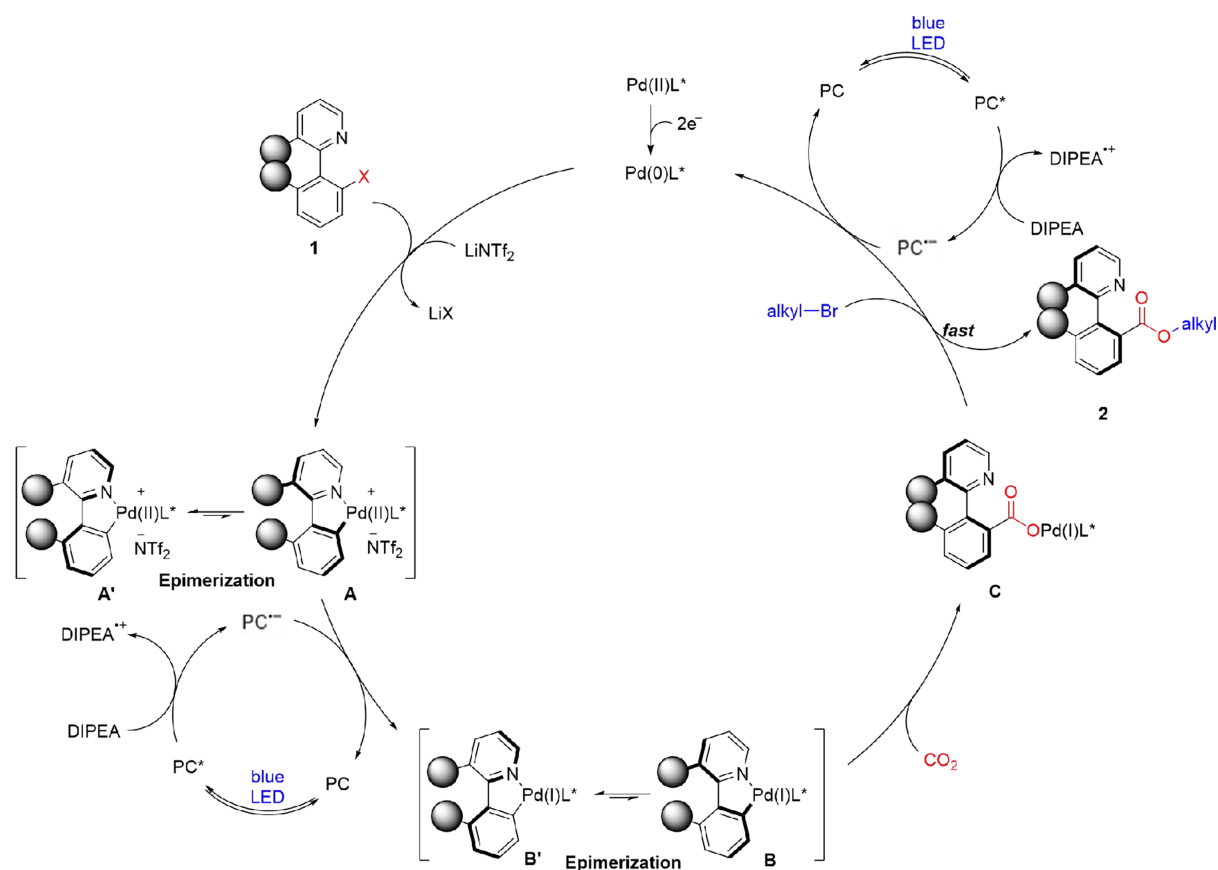


Figure 2. A possible catalytic cycle.

also proceeded with good yield and enantioselectivity.

Controlled experiments were carried out to gain a deeper understanding of the impact of the synergistic photoredox/palladium catalytic system on the reaction. The 1:1 ratio between the palladium catalyst (Pd/L^*) and the photocatalyst (4CzIPN) resulted in the highest product yield and ee, suggesting that the synergistic effect was optimal at this catalyst ratio. Kinetic studies revealed that the ee value of the recovered starting material remained relatively low, suggesting that in the presence of Pd/L^* , the carboxylation reaction undergoes a non-ideal kinetic resolution process. Lastly, the authors noted that the rapid *in situ* trapping of chiral carboxylate intermediates by alkyl bromide is crucial for successfully producing conformationally stable axially chiral esters, as the carboxylate undergoes racemization gradually under standard conditions. Based on the experimental results and previous literature reports^[16,17], the authors propose a potential catalytic cycle [Figure 2]. Initially, the Pd(II)/L^* complex is reduced to Pd(0)/L^* , which then coordinates with the racemic heterobiaryl bromide **1a** and undergoes oxidative addition to form palladacyclic species **A** and **A'**. Previous studies have indicated that the divalent palladacyclic species **A** or **A'** do not undergo carboxylation with CO_2 due to the high reaction barrier^[18]. Therefore, they undergo a photocatalytic single-electron reduction process, forming the monovalent aryl palladium species ArPd(I)L^* (**B** and **B'**), which coordinate and migrate insert with CO_2 to form intermediate **C**. The palladium carboxylate **C** is captured *in situ* by alkyl bromide via a rapid $\text{S}_{\text{N}}2$ reaction to yield the corresponding axially chiral ester **2a**. Finally, the released Pd(I)L^* species is reduced to Pd(0)L^* , completing the entire catalytic cycle.

In summary, this work by Liu *et al.* provides an effective synergistic photoredox/palladium approach for the enantioconvergent carboxylation-alkylation of racemic aryl/heteroaryl halides and pseudohalides with CO₂ and alkyl bromides, yielding a variety of axially chiral esters in good to high yields with excellent enantioselectivities^[15]. This process features mild reaction conditions and wide substrate compatibility. The combined use of photoredox and palladium catalysts in this research not only advances the field of axially chiral carboxylic acids but also contributes to the efficient utilization of CO₂ in asymmetric transformations.

DECLARATIONS

Authors' contributions

Wrote the draft manuscript: Gui YY, Chen XW, Yue JP

Revised and rewrote the manuscript: Yu DG

Availability of data and materials

Not applicable.

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Conflicts of interest

Yu DG is the Associate Editor of *Chemical Synthesis*, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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