Stereoselective alkoxy carbonylation of unactivated C(sp³)–H bonds with alkyl chloroformates via Pd(II)/Pd(IV) catalysis

Several examples of Pd-catalysed carbonylation of methyl C(sp³)–H bonds with gaseous CO via Pd(II)/Pd(0) catalysis have been reported. However, methylene C(sp³)–H carbonylation remains a great challenge, largely due to the lack of reactivity of C–H bonds and the difficulty in CO migratory insertion. Herein, we report the stereoselective alkoxy carbonylation of both methyl and methylene C(sp³)–H bonds with alkyl chloroformates through a Pd(II)/Pd(IV) catalytic cycle. A broad range of aliphatic carboxamides and alkyl chloroformates are compatible with this protocol. In addition, this process is scalable and the directing group could be easily removed under mild conditions with complete retention of configuration.
Over the past few decades, Pd-catalysed C–H functionalization has emerged as a powerful tool for the direct conversion of ubiquitous C–H bonds into diverse functional groups. Among various C–H functionalization reactions, the direct alkoxycarbonylation of C–H bonds is particularly valuable, since the resulting products, esters, are among the most important functional groups that appear commonly in agrochemicals, fine chemicals, natural products and pharmaceuticals.

Although Pd-catalysed carbonylation of aromatic C–H bonds has been extensively investigated, the direct carbonylation of aliphatic C–H bonds is limited and still represents a tremendous challenge in organic synthesis. Pd-catalysed carbonylation of methyl C(sp³)–H bonds of aliphatic amides or amines with CO for the synthesis of succinimides or lactams has been achieved recently. Generally, these reactions proceed through a Pd(II)/Pd(0) catalytic cycle. While these elegant methods are efficient to introduce carbonyl groups and have greatly enriched the reaction scope, the use of CO is still relatively inconvenient on laboratory-scale due to its gaseous form, toxic nature and flammability. In addition, the carbonylation reactions were limited to those functionalizing methyl C(sp³)–H bonds, which are more inert and sterically hindered than methyl C(sp³)–H bonds, remains unexplored.

Pd-catalysed alkoxycarbonylation of C(sp³)–H bonds with other carbonyl reagents, such as potassium oxalate monoester, DMF, formates, azodicarboxylates, α-keto esters, glyoxylates and oxaziridine has been reported. Ru-catalysed alkoxycarbonylation of 2-arylpyrindines with alkyl chloroformates was disclosed by Kakiuchi and co-workers. Inspired by these excellent precedents and based on our recent work on Pd-catalysed alkoxycarbonylation of unactivated C(sp³)–H bonds with less toxic, more easy to handle and readily available carbonyl reagents, we were eager to develop the catalytic carbonylation of methylene C(sp³)–H bonds with carbon monoxide through the traditional Pd(II)/Pd(0) pathway. Previously, we have found that the reaction of N-phthaloyl phenylalanine derivative 1a and stoichiometric Pd(OAc)₂ could form the stable palladacycle I in MeCN with CO coordinated as an L-type ligand was obtained as a pale yellow solid in 80% yield. However, when we treated palladacycle I with carbon monoxide under various conditions, no desired carbonylation product 3ab was observed. Complex II with CO coordinated as an L-type ligand was obtained as a pale yellow solid in 80% yield (Fig. 2b). This complex showed unexpected resistance to migratory insertion under various conditions, and proved stable to air and moisture, withstanding shelf storage without noticeable decomposition. The coordination of CO as a neutral ligand without migratory insertion was confirmed by the characteristic infrared absorption of terminally coordinated CO ligand (2095 cm⁻¹, Supplementary Fig. 2), and, the ease formation of complex III via ligand exchange with pyridine.

**Results**

**Proof of concept on methylene C(sp³)–H alkoxycarbonylation.** We began our investigation by using N-phthaloyl phenylalanine derivative 1a bearing an 8-aminoquinoline (AQ) auxiliary as a model substrate. This auxiliary was first introduced by Daugulis and has been proved to be effective in the direct functionalization of methylene C(sp³)–H bonds. We first explored the carbonylation with carbon monoxide through the traditional Pd(II)/Pd(0) pathway. Previously, we have found that the reaction of N-phthaloyl phenylalanine derivative 1a and stoichiometric Pd(OAc)₂ could form the stable palladacycle I in MeCN (Fig. 2a). However, when we treated palladacycle I with carbon monoxide under various conditions, no desired carbonylation product 3ab was observed. Complex II with CO coordinated as an L-type ligand was obtained as a pale yellow solid in 80% yield (Fig. 2b). This complex showed unexpected resistance to migratory insertion under various conditions, and proved stable to air and moisture, withstanding shelf storage without noticeable decomposition. The coordination of CO as a neutral ligand without migratory insertion was confirmed by the characteristic infrared absorption of terminally coordinated CO ligand (2095 cm⁻¹, Supplementary Fig. 2), and, the ease formation of complex III via ligand exchange with pyridine.

Figure 1 | Pd-catalyzed carbonylation of C(sp³)–H bonds. (a) Previous reports on Pd-catalyzed carbonylation of methyl C(sp³)–H bonds with carbon monoxide through a Pd(0)/Pd(II) catalytic cycle. (b) Our work on Pd-catalyzed alkoxycarbonylation of unactivated C(sp³)–H bonds with alkyl chloroformates through a Pd(II)/Pd(IV) catalytic cycle.
which was characterized by X-ray crystallography (Fig. 2d). It is noteworthy that complex III could also be generated via the reaction of 1a with 1 equiv. of Pd(OAc)_2 under 1 atm CO and pyridine (see Supplementary Methods for details). Moreover, the reaction of 1a with stoichiometric Pd(OAc)_2 under 1 atm CO could also give complex II in 80% yield without the detection of any carbonylated product 3ab (Fig. 2c). Thus, the carbonylation of β-methylene C(sp^3)-H bonds of 1a through Pd(II)/Pd(0) was unfeasible due to the difficulty in CO migratory insertion and subsequent reductive elimination. 

It has been proven that high-valent Pd(IV) species undergo facile reductive elimination. We speculated that the use of alkyl chloroformates as carbonylation reagent might enable the desired alkoxycarbonylation via oxidative addition of palladacycle I to form a highly reactive Pd(IV) intermediate IV, which could then undergo reductive elimination to give the corresponding ester (Scheme 1, Pd(II)/Pd(IV) pathway). To our delight, treatment of complex I with 3 equiv. of CICO_2Et (2ab) or CICO_2Me (2b) in the presence of 2 equiv. of silver carbonate gives the expected alkoxycarbonylation product 3a and 4b in 25% and 18% yield, respectively. The relative and absolute stereochemistry of 3a and 4b was unambiguously determined by X-ray crystallography (Fig. 2e). Inspired by this promising result, we next sought to identify suitable reaction conditions to render this reaction catalytically (Table 1). When 1a was treated with 10 mol% Pd(OAc)_2, 3 equiv. of CICO_2Et and 2 equiv. Ag_2CO_3 in DCM, the desired product 3a was obtained in 40% yield, along with trace of undesired β-lactam 3aa generated by the competitive intramolecular C=N bond reductive elimination (entry 1). Toluene was found to be the ideal solvent for this transformation (entry 7, 65% yield). Further screening of additives then established that the addition of I_2 could significantly improved the efficiency and 3a was obtained in 76% isolated yield (entry 11). It is worth noting that the alkoxycarbonylation reaction was quite sensitive to the amount of Ag_2CO_3. Attempts to lower the Ag_2CO_3 loading led to the inhibition of the desired reaction and the competitive intramolecular C=N bond reductive elimination occurred predominantly (entry 12, 3a, <5%; 3aa, 30%).
Substrate scope of methylene C(sp³)–H alkoxy carbonylation.

With the optimal reaction conditions in hand, the scope of this alkoxy carbonylation reaction was investigated (Fig. 3). The reaction was found to be compatible with a broad range of phenylalanine derivatives with various electron-donating and electron-withdrawing substituents (3b–3q). Various functional groups, such as methoxy (3e–3g), trifluoromethyl (3h), acetyl (3i), methoxycarbonyl (3j), fluoro (3k and 3l), chloro (3m) and bromo (3n) were tolerated, furnishing the desired products in moderate to good yields. The tolerance of halides was particularly noteworthy since such substituents could serve as versatile handles for further elaboration via cross-coupling. It is noteworthy that arylalanine derivatives (1b–1q) were prepared by arylation of the alanine derivative (5a) using our previously established conditions. Therefore, this protocol also showcases the synthesis of chiral aspartic acid derivatives via a two-step C–H functionalization sequence. Importantly, the alkoxy carbonylation of aliphatic secondary C(sp³)–H bonds could also be achieved when 0.2 equiv. of succinic anhydride was included (3r–3w). Alkoxy carbonylation of sterically hindered L-leucine derivative containing adjacent secondary alkyl group occurred smoothly under a slightly higher temperature (3t, 50%). The alkoxy carbonylation reaction was found to be highly diastereoselective, furnishing a single diastereoisomer as the sole product. The relative and absolute stereochemistry of 3a, 3d, 3k and 4b, was unambiguously determined by X-ray diffraction, and all other alkoxy carbonylation products were assigned analogically. The trans orientation of the N-phthaloyl group and the newly incorporated alkoxy carbonyl group was consistent with the proposed stereochemical model and previous reports.

In addition, the more remote γ-methyl C(sp³)–H bond was also reactive, provided that no reactive β–C–H bonds were present. The alkoxy carbonylation of L-tert-Leucine (3u), L-isoleucine (3v) and L-valine (3w) proceeded effectively, albeit affording the products in reduced yields.

The scope of the alkyl chloroformates coupling partners was examined subsequently (Fig. 4). The reaction was found to be compatible with a variety of simple and more complex chloroformates. Methoxycarbonylation of phenylalanine derivative proceeded smoothly to provide product 4b in 72% yield. A number of linear alkyl chloroformates gave the corresponding products in good yields (4b–4e). Interestingly, the more sterically hindered branched-alkyl chloroformates, such as iPr (2f), iBu (2g), and cyclopentyl (2h) were more reactive, giving the

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Figure 3 | Pd-catalyzed alkoxy carbonylation of β-methylene C(sp³)–H bonds and γ-methyl C(sp³)–H bonds. Reaction conditions: 1 (0.15 mmol), Pd(OAc)₂ (10 mol%), Ag₂CO₃ (2.0 equiv.), I₂ (1.0 equiv.), ClCO₂R (3.0 equiv.), toluene (2.0 ml), 120 °C, air, 16 h. Isolated yield. *20 mol% succinc anhydride was used. *¹40 °C.

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corresponding products in higher yields (4f–4h, 82–96% yield). The synthetic potential of this alkoxycarbonylation strategy was further demonstrated by the effective reaction with more complex chloroformates, such as methyl chloroformate (2j) and Fmoc-Cl (2j).

**Figure 4** | **Scope of alkyl chloroformates.** Reaction conditions: 1a (0.15 mmol), Pd(OAc)₂ (10 mol%), Ag₂CO₃ (2.0 equiv.), I₂ (1.0 equiv.), CICO₂R (3.0 equiv.), toluene (2.0 ml), 120 °C, air, 16 h. Isolated yield.

**T**he competitive intramolecular C–N bond reductive elimination product 3aa was also produced in 12% yield when the reaction was scaled up. The desired product 3a was obtained without any racemization. Moreover, we also found that no epimerization of 3a has been observed upon prolonged heating under the reaction conditions (Supplementary Figs 8–10).

The ability to easily remove the directing group from the final product is crucial for synthetic applications of this reaction. Previously, we reported that 2-pyridinylisopropyl bidentate auxiliary introduced by us could be removed through a nitrosylation/hydrolysis sequence with a mixture of NaNO₂/AcOH/AcO (refs 39,40). Baudoin and co-workers has improved the procedure by using NOBF₄ as a nitrosation agent and pyridine at low temperature⁶¹,⁶². We envisioned that novel process could also be applied to the removal of AQ. As expected, the corresponding carboxylic acid 7 was obtained in 62% yield without further optimization. Following esterification, the corresponding methyl ester 8 was obtained in 91% yield with the retention of configuration (Scheme 3, see Supplementary Methods and Supplementary Fig. 61 for details). It is worth noting that all of the alkoxycarbonylation reactions were operationally simple, without the need for an inert-atmosphere or rigorously moisture-free conditions.

**Mechanistic investigations.** To shed light on the mechanism, several experiments were performed (Fig. 7). First, kinetic isotopic effect (KIE) experiments were conducted by treatment of compound 1a and its deuterated analogue 1a-d₂ under the standard reaction conditions for 10 min. A k_H/k_D value of 1.5 was obtained in a competitive reaction and 1.7 in parallel reactions on the basis of ¹H nuclear magnetic resonance (NMR) analysis (Fig. 7a), which is indicative of a secondary kinetic isotope effect. This result also suggests that the cleavage of C–H is not the rate-determining step of the reaction.
Second, a stoichiometric reaction of complex I with 3 equivalents of ClCO₂Et (2a) under the optimized reaction conditions was performed, and the alkoxy carbonylated product 3a was obtained in 40% yield. However, β-lactam 3aa was produced in 48% yield and no desired product 3a was observed when complex I was treated with iodine in the absence of silver carbonate (Fig. 7b). These results clearly indicated that the addition of silver carbonate was crucial for the success of this transformation. Although the exact role of the silver salt may simply be a halide scavenger, it is also proposed to form a bimetallic complex with palladium, which might be important for the reaction.

Figure 5 | Pd-catalysed alkoxy carbonylation of β-Methylene C(sp³)-H Bonds. Reaction conditions: 5 (0.15 mmol), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (2.0 equiv.), Na₃PO₄ (1.0 equiv.), ClCO₂Me (3.0 equiv.), toluene (1.5 ml), 120 °C, air, 20 h. Isolated yield. In the absence of Na₃PO₄.

Figure 6 | Gram-scale synthesis and the removal of directing group. (a) Alkoxy carbonylation of N-phthaloyl phenylalanine derivative 1a in gram scale. (b) The removal of AQ under mild conditions with the retention of configuration.
Finally, we found that palladacycle I was a viable precatalyst for the alkoxy carbonylation of 1a, providing the desired product in 70% yield, which was comparable with the result under the standard conditions (Fig. 7c).

**Discussion**

In conclusion, we have developed a new protocol for the direct alkoxy carbonylation of both methylene and methyl C(sp3)–H bonds through a Pd(II)/Pd(IV) catalytic cycle. A variety of operationally simple and readily available alkyl chloroformates were used as carbonyl sources. The reaction proceeded with high functional compatibility. Furthermore, this efficient and stereoselective protocol to access orthogonally protected chiral aspartic acid derivatives may find applications in the synthesis of complex molecules. Compared with the well-established C–H carbonylation with CO via Pd(II)/Pd(0) catalysis, the direct alkoxy carbonylation of unactivated C–H bonds through a Pd(II)/Pd(IV) catalytic cycle provides a new mode of reaction and might offer a distinct platform for reaction development. Further studies toward the application of this new strategy to other reaction systems are currently underway.

**Methods**

**General methods.** For NMR spectra, high-performance liquid chromatography (HPLC) data, and X-ray analysis of compounds in this manuscript and detailed experimental procedures, see Supplementary Figs 1–67, Supplementary Tables 1–12 and Supplementary Methods. See Supplementary Datasets 1–6 for X-ray CIF files of compounds III, 3a, 3d, 3k, 4b and 6a (CCDC 1446624, 1487147, 1486639, 1486599, 1446623, 1475241).

**General procedure for secondary C–H alkoxy carbonylation.** To a 50 ml Schlenk tube, were added I (0.15 mmol), Pd(OAc)2 (3.5 mg, 0.015 mmol), Ag2CO3 (82.7 mg, 0.3 mmol), Na3PO4 (49.0 mg, 0.3 mmol), ClCO2Me (0.45 mmol, 3.0 equiv.) and toluene (2.0 ml). The tube was sealed under air. The mixture was stirred at room temperature for 5 min then heated at 120 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 ml) and filtered through a pad of Celite. After concentration in vacuo, the crude reaction mixture was purified by silica gel flash chromatography.

**General Procedure for Primary C–H Alkoxy carbonylation.** To a 50 ml Schlenk tube, were added I (0.15 mmol), Pd(OTFA)2 (5.0 mg, 0.015 mmol), Ag2CO3 (82.7 mg, 0.3 mmol), Na3PO4 (49.0 mg, 0.3 mmol), ClCO2Me (0.45 mmol, 3.0 equiv.) and toluene (2.0 ml). The tube was sealed under air. The mixture was stirred at room temperature for 5 min then heated at 120 °C for 20 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 ml) and filtered through a pad of Celite. After concentration in vacuo, the crude reaction mixture was purified by silica gel flash chromatography.

**Data availability.** The X-ray crystallographic structures for compounds III, 3a, 3d, 3k, 4b, 6a reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), with the accession codes CCDC 1446624, 1487147, 1486639, 1486599, 1446623, 1475241 (http://www.ccdc.cam.ac.uk/data_request/cif). The authors declare that all other relevant data supporting the findings of this study are available within the article and its Supplementary Information files.
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Author contributions

G.L. and B.-F.S. conceived and designed the study. G.L. principally performed the experiments. X.-S.Y., K.C., Q.Z. and S.-Q.Z. helped to conduct some experiments and collect data. B.-F.S. provided overall supervision and wrote the manuscript.

Additional information

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