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Palladium-Catalyzed Inert C–H Bond Activation and Cyclocarbonylation of Isoquinolones with Carbon Dioxide Leading to Isoindolo[2,1-*b*]isoquinoline-5,7-diones

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Dedicated to the 100th anniversary of Nankai University.

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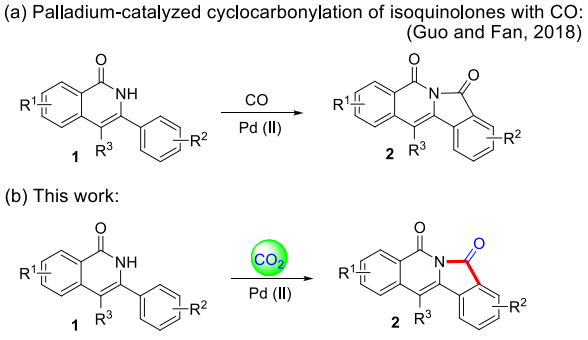
Abstract: A palladium-catalyzed inert C–H bond activation and cyclocarbonylation of isoquinolones leading to isoindolo[2,1-*b*]isoquinoline-5,7-diones under 1 atm of carbon dioxide has been developed. This transformation features high regio- and chemo-selectivity, step-economy, and good functional group tolerance. Most of the corresponding products were obtained in moderate to good yields. It offers an alternative approach for the synthesis of useful diverse isoindolo[2,1-*b*]isoquinoline-5,7-dione derivatives.

Keywords: C–H activation; carbon dioxide; palladium; isoquinolones; isoindolo[2,1-*b*]isoquinoline-5,7-diones

Carbon dioxide (CO_2) is an inexpensive, nontoxic, abundant, and renewable feedstock which can be used as the ideal one-carbon (C1) building block to produce fuels, materials, and commodity chemicals.[1] However, it is challenging to utilize CO_2 under mild reaction conditions because of its thermodynamic stability and kinetic inertness.[2] In the past few decades, novel reagents and various strategies have been developed in promoting the conversion of CO_2 into value-added chemicals.[3-9] However, under transition-metal-free conditions, the site selectivity of several carboxylations of arene substrates with CO_2 is determined by the most nucleophilic site of the arenes and it is difficult to overcome the electronic biases in this type of reactions.[4] In comparison with the transition-metal-free reactions, transition-metal-catalyzed C–H bond activation/functionalization has flourished as a powerful and atom-economical tool to construct C–C and C–heteroatom bonds as it obviates the need for pre-functionalized substrates.[10] This strategy has also been employed in the reactions of CO_2 fixation. Recently, a series of breakthroughs in the transition-metal-catalyzed C–H carboxylation of (hetero)arenes with CO_2 were accomplished.[5] In these examples, the substrates are mainly limited to terminal alkyne, polyhalogenated aromatic hydrocarbons, and heterocyclic rings which possess an acidic C–H bond. However, subsequent reports have shown that these substrates can react with CO_2 in the presence of Cs_2CO_3, LiO^{t}Bu, or other bases, even without adding any transition-metal catalysts.[6] Moreover, for the inert C–H bonds, only few Rh(I),[7] Rh(II),[8] and Pd(II)[9] catalyzed carboxylations with CO_2 have been reported. It can be seen that the utilization of CO_2 still exists a series of challenges need to be solved and it remains in its initial development stage. Therefore, there is still an urgent need to develop new substrates and establish new methods in the fixation of CO_2.

An isoquinolone moiety is an important structural unit, which frequently occurs in various natural products and synthetic compounds.[11-14] Recently,



Scheme 1. Palladium-catalyzed cyclocarbonylation of isoquinolones

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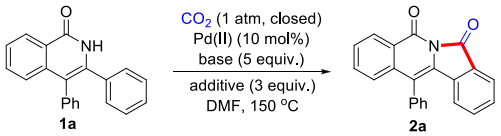
NH isoquinolone unit has emerged as an effective directing group to construct isoquinolone-containing heterocycles through transition metal-catalyzed C–H and N–H bond activation. Li[12] and our group[13] have reported several oxidative annulations of NH isoquinolones with alkynes, olefins, and benzoquinones under the catalysis of Ru(II), Rh(III), or Ir(III). Very recently, Guo and Fan group reported a palladium-catalyzed oxidative cyclocarbonylation of isoquinolones with CO leading to isoindolo[2,1-*b*]isoquinoline-5,7-dione derivatives (Scheme 1a).[14] Although this transformation is step-efficient and atom-economical, the use of highly toxic CO and a stoichiometric oxidant is inevitable. Therefore, it is absolutely essential to explore whether inexpensive and nontoxic CO_2 can be employed instead of CO to synthesize isoindolo[2,1-*b*]isoquinoline-5,7-dione derivatives. Following our growing interest in transition-metal-catalyzed C–H bond activation/functionalization,[13,15] we herein report a palladium-catalyzed cyclocarbonylation of isoquinolones with CO_2 leading to isoindolo[2,1-*b*]isoquinoline-5,7-diones.

We initiated our work by treating 3,4-diphenylisoquinolin-1(2*H*)-one (**1a**) (0.2 mmol, 1.0 equiv.) with 1 atm of CO_2 in the presence of $Pd(TFA)_2$ (10 mol%), KO^{t}Bu (5.0 equiv.), and $ZnMe_2$ (3 equiv.) in DMF (*N*,*N*-dimethylformamide) (2.0 mL) at 150 °C for 20 h, and the desired product 12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (**2a**) was obtained in 33% yield (Table 1, entry 1). The effect of catalysts was firstly investigated, which revealed that $Pd(OAc)_2$ was the most effective catalyst (36%, entries 1–4). No product was observed in the absence of catalyst or base (entries 5–6). Then, other bases including LiO^{t}Bu and NaO^{t}Bu were tested (entries 2, 7–8). To our delight, the reaction employing LiO^{t}Bu as the base provided product **2a** in 74% yield. In addition, different solvents were investigated, and DMF was discovered to be more suitable for this transformation (entries 7, 9–10). Other additives such as $ZnEt_2$ and $AlMe_3$ gave low yields or no product under the present reaction conditions (entries 11–12). Finally, we chose the reaction conditions of entry 7 as the standard conditions.

Table 1. Optimization of the reaction conditions.[a]

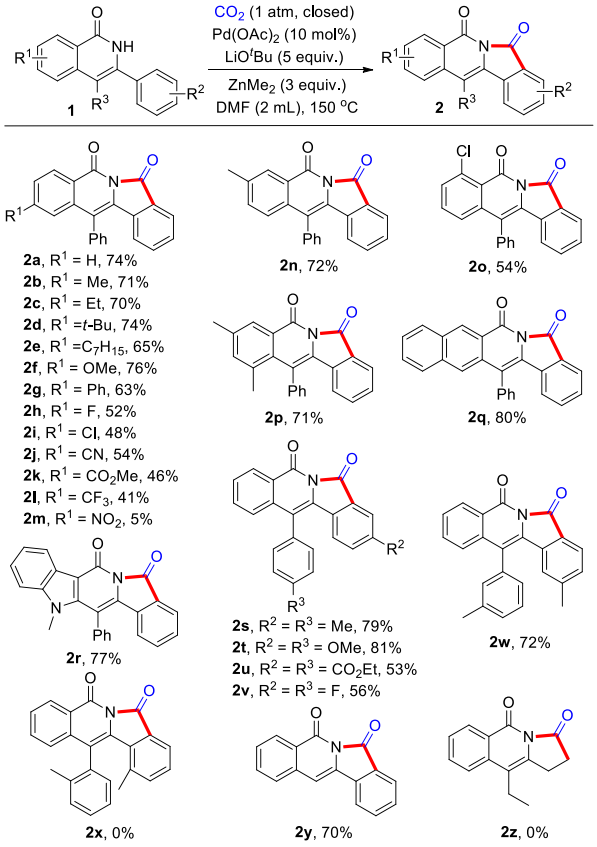


Entry	Catalyst	Base	Solvent	Additive	Yield[b]
1	$Pd(TFA)_2$	KO^{t}Bu	DMF	$ZnMe_2$	33
2	$Pd(OAc)_2$	KO^{t}Bu	DMF	$ZnMe_2$	36
3	$PdCl_2$	KO^{t}Bu	DMF	$ZnMe_2$	29
4	$Pd(PPh_3)_2$	KO^{t}Bu	DMF	$ZnMe_2$	31
5	-	KO^{t}Bu	DMF	$ZnMe_2$	0
6	$Pd(OAc)_2$	-	DMF	$ZnMe_2$	0
7	**$Pd(OAc)_2$**	**LiO^{t}Bu**	**DMF**	**$ZnMe_2$**	**74**
8	$Pd(OAc)_2$	NaO^{t}Bu	DMF	$ZnMe_2$	0
9	$Pd(OAc)_2$	LiO^{t}Bu	DMA	$ZnMe_2$	42
10	$Pd(OAc)_2$	LiO^{t}Bu	DMSO	$ZnMe_2$	0
11	$Pd(OAc)_2$	LiO^{t}Bu	DMF	$ZnEt_2$	65
12	$Pd(OAc)_2$	LiO^{t}Bu	DMF	$AlMe_3$	0

[a] Conditions: **1a** (0.2 mmol), CO_2 (1 atm), catalyst (0.02 mmol), base (1.0 mmol), additive (0.6 mmol), solvent (2 mL), 150 °C, 20 h. [b] Isolated yields.

With the establishment of the optimized conditions in hand, we explored the applicability of the scope of diversely substituted 3,4-diphenylisoquinolin-1(2*H*)-ones (**1a**–**1v**), and the results are summarized in Table 2. To our delight, most reactions proceeded smoothly to afford corresponding products in moderate to good yields. The cyclocarbonylation of substituted 3,4-diphenylisoquinolin-1(2*H*)-ones bearing alkyl, methoxyl, and phenyl groups at the C6-position afforded corresponding products in good yields (63–76%, **2a**–**2g**). While, introducing an electron-withdrawing substituent such as halogen, cyano, methoxycarbonyl, and trifluoromethyl at the C6-position of 3,4-diphenylisoquinolin-1(2*H*)-ones afforded corresponding products (**2h**–**2l**) in moderate yields (41–54%). The corresponding product **2m** was obtained in only 5% yield, when 2-nitro-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (**1m**) with a nitro at the C6-position was employed. This may be because the strong electron-withdrawing ability of the nitro group reduces the nucleophilic

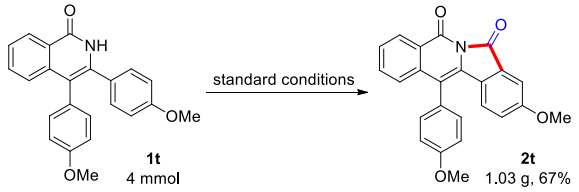
Table 2. Substrate scope of isoquinolones.[a]



[a] Reaction conditions: **1** (0.2 mmol), CO_2 (1 atm), $Pd(OAc)_2$ (0.02 mmol), LiO^{t}Bu (1.0 mmol), $ZnMe_2$ (0.6 mmol), DMF (2 mL), 150 °C, 20 h, isolated yields.

attack of the nitrogen atom on the substrate to CO_2. When a methyl was placed at the C7 position of 3,4-diphenylisoquinolin-1(2*H*)-one, product **2n** was obtained in 72% yield. As expected, the corresponding product **2o** was also obtained smoothly (54%), when the substrate 8-chloro-3,4-diphenylisoquinolin-1(2*H*)-one (**1o**) with a chloro substituent at the C8-position was employed. Meanwhile, the study of substrate with two substituents at the C5/7-position was also examined and the corresponding product **2p** was obtained in 71% yield. Besides isoquinolones, other fused pyridones (**1q**–**1r**) were also proved to be good substrates. When 3,4-diphenylbenzo[*g*]isoquinolin-1(2*H*)-one (**1q**) and 5-methyl-3,4-diphenyl-2,5-dihydro-1*H*-pyrido[4,3-*b*]indol-1-one (**1r**) were employed as the substrates, the corresponding products **2q** and **2r** were obtained in 80% and 77% yields, respectively. In addition, we also investigated the palladium-catalyzed cyclocarbonylation of isoquinolones with different R^2 substituents (**1s**–**1x**). The results suggested that isoquinolone substrates bearing a substituent such as methyl, methoxy, ethoxycarbonyl, and fluorine at the *para*-position of the 3-phenyl moiety took part in this reaction smoothly and afforded corresponding products (**2s**–**2w**) in 53–81% yields. The cyclocarbonylation of 3,4-di(*m*-tolyl)isoquinolin-1(2*H*)-one (**1w**) with a methyl at the *meta*-position of the 3-phenyl moiety afforded regioselective product **2w** in 72% yield, no other regioisomer of **2w** was detected. This indicated that the reaction is sensitive to the steric hindrance and favors to form the less hindered product. However, when substrate **1x** which bearing a methyl group in the *ortho*-position of the 3-phenyl moiety was employed, no corresponding product was observed. This may be due to the steric effect of the *ortho* substituent which may affect the coplanarity of the phenyl ring and the isoquinolinone ring and depress the C–H activation and cyclocarbonylation. Furthermore, 3-phenylisoquinolin-1(2*H*)-one (**1y**) derived from an unsymmetrical substituted alkyne proceeded this reaction smoothly to give product **2y** in 70% yield. No corresponding product was detected when the isoquinolinone **1z** which bearing a $C(sp^3)$–H reaction site was used as the substrate.

Next, we explored the synthetic applicability of this method. As shown in Scheme 2, the gram-scale reaction successfully afforded **2t** in 67% yield (1.03 g) at standard conditions. This result clearly proved the practical aspect of this newly developed method. Furthermore, the structure of **2t** was further confirmed by its single-crystal X-ray diffraction analysis (Figure 1).[16]



Scheme 2. Synthesis of **2t** on gram-scale.

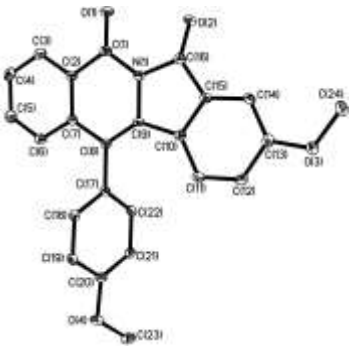
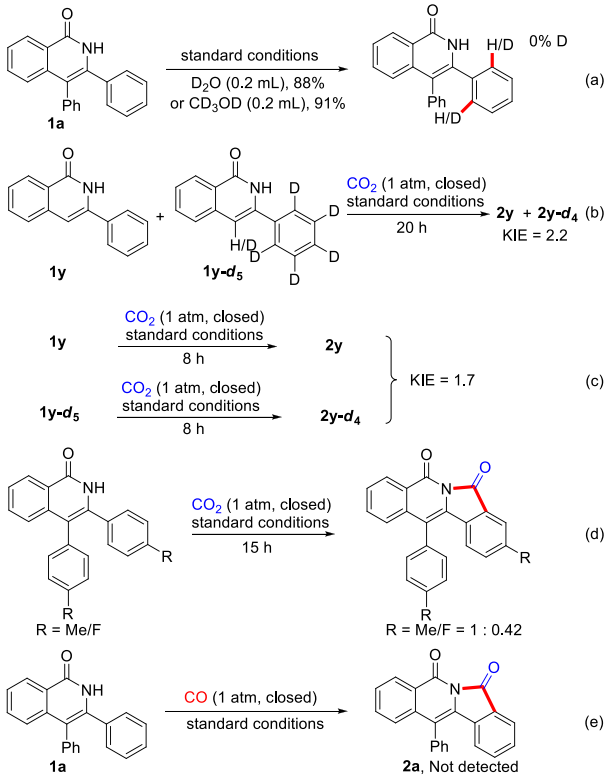


Figure 1. The molecular structure of **2t**.

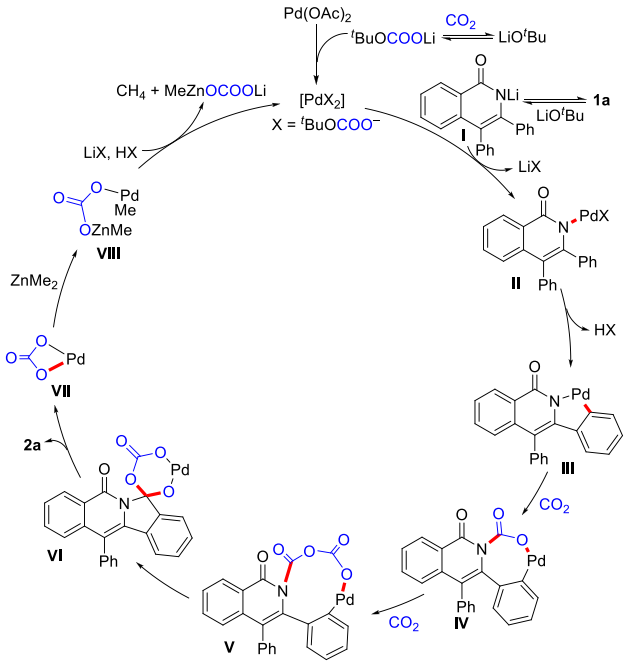
To gain more insight into the mechanism, a series of experiments have been conducted to probe the reaction mechanism. A H/D exchange experiment of **1a** using 0.2 mL of D_2O or CD_3OD was performed under standard conditions, and no H/D exchange was detected (Scheme 3a). This result indicated that the cleavage of the relevant C−H bond was an irreversible process. Then, a deuterium competition experiment between substrate **1y** and **1y-*d*$_5$** was performed, and a kinetic isotope effect (KIE) of 2.2 was observed (Scheme 3b). Meanwhile, two parallel independent reactions of **1y** and **1y-*d*$_5$** illustrated a KIE of 1.7 **(**Scheme 3c**)**. Both results indicated that the $C(sp^2)$–H bond cleavage of this transformation might be involved in the rate-determining step. In addition, we performed the intermolecular competition experiment between electronically differentiated 3,4-di(*p*-tolyl)isoquinolin-1(2*H*)-one (**1s**) and 3,4-bis(4-fluorophenyl)isoquinolin-1(2*H*)-



Scheme 3. The mechanism study experiments.

one (**1v**) to determine the electronic preference of the reaction. The ^{1}H NMR spectrum of the obtained products showed that the corresponding products **2s** and **2v** were produced in a ratio of 1:0.42, which indicated that the reaction favored the electron-rich isoquinolones (Scheme 3d). Considering CO_2 can be converted to CO under certain conditions and then participates in the carbonylation reaction,[17] 1 atm of CO was used instead of CO_2 to react with **1a** in standard conditions. Product **2a** was not detected by HRMS (Scheme 3e). This result excluded the possibility of CO, converted from CO_2, as the active carbonylation reagent in this transformation.

Recently, Yu and coworkers reported a lactonization reaction of unactivated aryl C–H bond with CO_2. They proposed a mechanism based on the DFT calculation.[9c] Referring to their work and our preliminary mechanistic studies, a possible mechanism is proposed for this present catalytic reaction (Scheme 4). First of all, the combination of ^{t}BuO$^-$ ion and CO_2 leads to the formation of hemicarbonate ion. The starting active catalytic complex hemicarbonate−Pd could be generated after ligand exchange. At the same time, the proton exchange between solvated LiO^tBu and reactant **1a** could afford the intermediate **I**. Then, the counter anion exchange of starting active catalytic complex with **I** affords ^{t}BuOCOOLi and palladium intermediate **II**. Then, intermediate **II** undergo a concerted-metalation−deprotonation (CMD) process leads to the palladacycle intermediate **III** and ^{t}BuOCOOH. According to the previous reports,[18] the activity of CO_2 insertion into the N–Pd bond is higher than the insertion into the C–Pd bond. So, the next step of this reaction is the insertion of CO_2 into the N–Pd bond and generation intermediate **IV**.



Scheme 4. Proposed mechanistic pathway.

Subsequently, the second CO_2 insertion into the O–Pd bond could form a nine-membered palladacycle intermediate **V**. The spiroheterocyclic intermediate **VI** is generated by intramolecular nucleophilic addition of **V**. Subsequently, the decarbonization releases lactam product **2a** and concomitantly generates carbonate palladium intermediate **VII**. Transmetalation between **VII** and $ZnMe_2$ would give the intermediate **VIII**. Finally, the active catalyst would be regenerated after an acid−base exchange.

In conclusion, we have successfully developed a novel and efficient approach to build substituted isoindolo[2,1-*b*]isoquinoline-5,7-diones from readily available isoquinolones and CO_2 *via* palladium-catalyzed inert C–H bond activation. Various regioselective products were prepared smoothly in moderate to good yields. Further research on the reaction mechanism and applications of this method in the synthesis of more complex heterocycles are in progress in our laboratory.

Experimental Section

A mixture of isoquinolones (**1**) (0.2 mmol, 1.0 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), LiO^tBu (80.0 mg, 1.0 mmol, 5.0 equiv.) were weighed in a Schlenk sealed tube equipped with a stir bar. The tube was then evacuated and back-filled with CO_2 for 3 times, dry DMF (2.0 mL) and $ZnMe_2$ (1 M) in toluene (0.6 mL, 0.6 mmol, 3.0 equiv.) were added. The Schlenk tube was sealed at 1 atmospheric pressure of CO_2 and the mixture was stirred at 150 °C for 20 h. Then, the mixture was cooled to room temperature, concentrated in vacuo, and the resulting residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether.

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[16] CCDC-1891840 (**2q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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