Rhodium(I)-Catalysed Aryl C–H Carboxylation of 2-Arylanilines with CO_2

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***Abstract*: An unprecedented amino-group assisted C–H carboxylation of 2-arylanilines with CO_2 under redox-neutral conditions using a Rhodium(I)-catalyst has been developed. This reaction was promoted by a phosphine ligand with *t*-BuOK as the base and did not require the use of an extra strong organometallic reagent. Notably, this protocol may involve an oxidative addition in the C–H bond cleavage step and is distinct from previous Rh(I) or Rh(II)-catalysed methods for C–H carboxylation with CO_2 mechanistically. It enabled an efficient direct conversion of a broad range of 2-(hetero)arylanilines including electron-deficient heteroarenes to various phenanthridinones, which could be further transformed to other synthetically useful compounds readily. Preliminary mechanistic studies were carried out and possible intermediates of the reaction were evaluated, which revealed that the Rh(I)-catalyst is essential for the C–H activation process, providing a promising general type of method for utilization of CO_2 for C–C bond formation.**

Considered as an ideal one-carbon (C1) feedstock, which is abundant, inexpensive and renewable for chemical synthesis, carbon dioxide (CO_2) has been used to produce fine chemicals such as urea and polycarbonate for a long time.[1-13] In the last decades, significant progresses have been made in CO_2 fixation for the formation of C–C bonds, the most fundamental chemical bonds in organic molecules, via transition metal-catalysed cross-coupling reactions with organometallic reagents or preactivated organic (pseudo)halides to produce (hetero)aromatic carboxylic acids and their derivatives.[11-27] In sharp contrast, the method of catalytic fixation of CO_2 for the formation of C–C bonds through the activation of an sp^2 C–H bond with a transition metal is still very limited.[5-10,28-44] Recently, the groups of Nolan[34,35] and Hou,[36,37] disclosed the direct carboxylation of moderately acidic C–H bonds of arenes with CO_2 using the Au(I) or Cu(I)-NHC (*N*-heterocyclic carbene) complexes as the catalysts. Later, a few limited methods of chelation-assisted carboxylation of unactivated aryl C–H bonds with CO_2 were reported by Iwasawa,[38-40] Yu,[43,44] and us,[41,42] using Rh(I), Pd(II), or Rh(II)-catalysts respectively. However, direct carboxylation of

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aryl C–H bonds of amine derivatives via catalytic fixation of CO_2 with a transition metal-catalyst has not yet been resolved.[45-59] In 2011, Iwasawa and co-workers disclosed an elegant Rh(I)-catalysed, nitrogen-based pyridine or pyrazole chelation group assisted C–H bond carboxylation with CO_2 in the presence of a stoichiometric pyrophoric reducing reagent $AlMe_2(OMe)$ (Fig. 1a).[38] Inspired by this pioneering work, we embarked on the development of amino group assisted, Rhodium-catalysed C–H carboxylation of 2-(hetero)arylanilines using CO_2, leading to the production of phenanthridinones (Fig. 1b).[60-64]

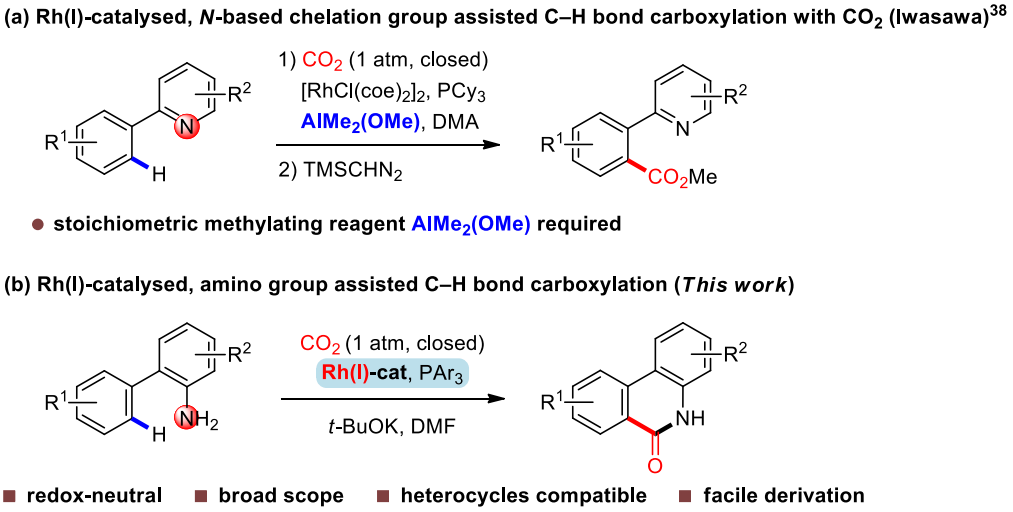


Figure 1. **Rh (I)-catalysed and chelation-assisted aryl C–H carboxylation**. (**a**) The single disclosed method of Rh(I)-catalysed, *N*-based chelation group assisted C–H bond carboxylation with CO_2 requires stochiometric pyrophoric reagent $AlMe_2(OMe)$. (**b**) Our Rh(I)-catalysed, amino group assisted C–H carboxylation of 2-(hetero)arylanilines under redox-neutral conditions.

Phenanthridinone is an important moiety found in natural products and biologically active molecules.[65] Consequently, several methods have been developed for the synthesis of phenanthridinone derivatives.[66-69] However, a general method of using CO_2 for the construction of phenanthridinones has not been reported using a transition metal-catalyst, although electron-rich 2-arylanilines could be converted to phenanthridinones with the hazardous reactive MeOTf as an essential promoter.[66] Based on Iwasawa's pioneering studies and our recent work on Rh(II)-catalysed C–H carboxylation of 2-arylphenols with CO_2,[38-42] we envisioned that Rh-catalysed C–H carboxylation of 2-arylanilines might proceed with a broader substrate scope in a general manner. Another important aspect of the Rh-catalysed process is that it may constitute a fundamental step in the fixation of CO_2, which involves the insertion of

CO_2 into a carbon-metal bond and may provide more hints for mechanistic studies of related transition metal-catalysed C–C bond formation reactions using CO_2.[62-64]

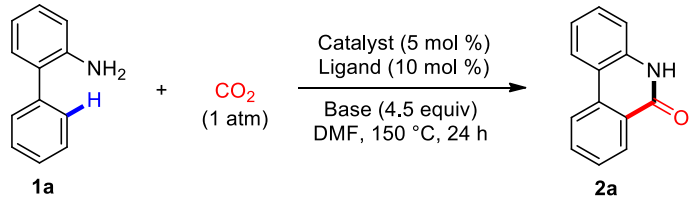
Herein, we report a phosphine ligand-promoted, Rh(I)-catalysed C–H carboxylation of 2-(hetero)arylanilines under atmospheric pressure of CO_2 and redox-neutral conditions, which was assisted by the chelation of the amino group, leading to the production of phenanthridinones (Fig. 1). Notably, unlike Iwasawa's protocol, our method does not require strong organometallic reagent such as $AlMe_2(OMe)$. Importantly, this Rh(I)-catalysed protocol is distinct from our previous protocol with 2-arylphenols as the substrates using a higher valent Rh(II)-catalyst, which probably involves a proton abstraction process in the C–H bond cleavage step rather than a possible oxidative addition process in the current reaction. Moreover, the method converted a broad range of 2-(hetero)arylanilines including challenging electron-deficient (hetero)arenes to various phenanthridinones efficiently, which could be further transformed to other synthetically useful compounds readily. Finally, preliminary mechanistic studies were carried out reveal that the Rh(I)-catalyst is essential for the C–H activation process, leading to a promising general type of method for utilization of CO_2 for C–C bond formation.

Results

Screening of reaction conditions. To start our investigation, 2-phenylaniline (**1a**) was chosen as the model substrate (Table 1). Initially, various rhodium catalysts including Rh(I), Rh(II) and Rh(III) catalysts were examined (entries 1-4). Much to our delight, desired lactamization product **2a** generated after C–H carboxylation was obtained in 44% yield with $[RhCl(cod)]_2$ as the catalyst and 4.5 equivalents of *t*-BuOK as the base under atmospheric pressure of CO_2 after 24 hours in DMF at 150 °C (entry 3). Since electron-rich ligands such as phosphine and NHC ligands might increase the nucleophilicity of the Rh-complex intermediate towards CO_2, a series of phosphine and NHC ligands were examined revealing that **L4** was the best choice that led to 69% yield of **2a** (entries 5-9, see also Supplementary Table 1). Notably, the reaction was shut down in the absence of a Rh salt (entries 10−11), indicating that base or phosphine ligand could not promote the reaction alone without a Rh catalyst. Moreover, the reaction was

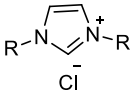
sensitive to the base since no desired product was obtained when Cs_2CO_3 or EtONa was employed as the base (entries 12 and 13)

Table 1. Optimization of reaction conditions.

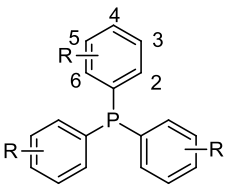


1a **2a**

Entry	Catalyst	Ligand	Base	Yield (%)
1	$[RhCl_2Cp^*]_2$	-	*t*-BuOK	11
2	$RhCl(PPh_3)_3$	-	*t*-BuOK	19
3	$[RhCl(cod)]_2$	-	*t*-BuOK	44
4	$[Rh(OAc)_2]_2$	-	*t*-BuOK	13
5	$[RhCl(cod)]_2$	**L1**	*t*-BuOK	8
6	$[RhCl(cod)]_2$	**L2**	*t*-BuOK	38
7	$[RhCl(cod)]_2$	**L3**	*t*-BuOK	30
8	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	69
9	$[RhCl(cod)]_2$	**L5**	*t*-BuOK	52
10	-	-	*t*-BuOK	0
11	-	**L4**	*t*-BuOK	0
12	$[RhCl(cod)]_2$	**L4**	Cs_2CO_3	0
13	$[RhCl(cod)]_2$	**L4**	EtONa	0
14	$[RhCl(cod)]_2$	**L4**	*t*-BuONa	34
15[a]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	1
16[b]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	27
17[c]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	75
18[d]	**$[RhCl(cod)]_2$**	**L4**	***t*-BuOK**	**84 (83)**
19[e]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	67
20[f]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	56
21[g]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	62
22[h]	$[RhCl(cod)]_2$	**L4**	*t*-BuOK	56



L1: R = cyclohexyl
L2: R = isopropyl



L3: R = 4-F
L4: R = 4-CF_3
L5: R = 3,5-di-CF_3

Reaction conditions: **1a** (0.2 mmol), CO_2 (1 atm, closed), catalyst (5 mol %), **L** (10 mol %), base (4.5 equiv), DMF (2 mL), 150 °C, 24 h. Yield was determined by ^1H NMR with CH_2Br_2 as the internal standard. [a]DMA was used as solvent. [b]Diglyme was used as solvent. [c]*t*-BuOK (6.0 equiv). [d]*t*-BuOK (6.5 equiv). [e]*t*-BuOK (7.0 equiv). [f]*t*-BuOK (8.0 equiv). [g]$[RhCl(cod)]_2$ (2.5 mol %), **L4** (5 mol %). [h]140 °C. Cp*: pentamethylcyclopentadienyl; cod: 1,5-cyclooctadiene.

and only low yield of **2a** was received while using *t*-BuONa as the base (entry 14). Screening other solvents, such as DMA and Diglyme, revealed that DMF was the best one (entries 15 and 16). The loading of *t*-BuOK was then increased gradually (entries 17-20), and it was found that the best result was afforded when 6.5 equivalents of *t*-BuOK was employed, leading to 83% isolated yield of **2a** (entry 18). In addition, an acceptable yield of **2a** could also be generated when the loading of $[RhCl(cod)]_2$ was decreased to 2.5 mol % (entry 21). Finally, attempts to reduce the reaction temperature failed, resulting in a lower yield of **2a** (entry 22).

Substrate scope of the C–H carboxylation of 2-arylanilines. With the optimized reaction conditions in hand, we investigated the scope of this Rh(I)-catalysed C–H carboxylation of 2-arylanilines with CO_2 (Fig. 2). Firstly, substrates with various electron-donating or electron-withdrawing substituents at the *meta*-position of the phenyl ring (**1b-1d**), as well as at the *para*-position (**1e-1o**) were well tolerated under the reaction conditions, leading to generally good to excellent yields of desired phenanthridinones. Notably, the electron-withdrawing groups, such as trifluoromethyl (**2c** and **2o**), amide (**2k**), and cyanide (**2n**) groups were compatible with the reaction and high yields of desired products were smoothly afforded. In sharp contrast, electron-withdrawing groups decreased the efficiency of the lactamization dramatically in the previous work using MeOTf as the promoter, where the key step of the reaction was probably an electrophilic annulation of an isocyanate intermediate.[66] Meanwhile, it is also worth noting that the base sensitive amide (**2k**) and cyanide(**2n**) groups were tolerated in this reaction. These different results suggested that the Rh(I)-catalysed carboxylation should undergo a much different reaction pathway from the base-promoted fixation of CO_2 with a much broader scope. Subsequently, polycyclic arene was also a viable substrate (**2p**), albeit in a modest yield. Moreover, the method was extended to substrates with various substituents on the aniline ring, giving the desired products **2q**-**2x** in generally satisfied yields. However, it should be noted that the steric hindrance was not well tolerated, and only the substrate with a fluoro group at *ortho*-position of the phenyl substituent could lead to some desired product (**2x**).

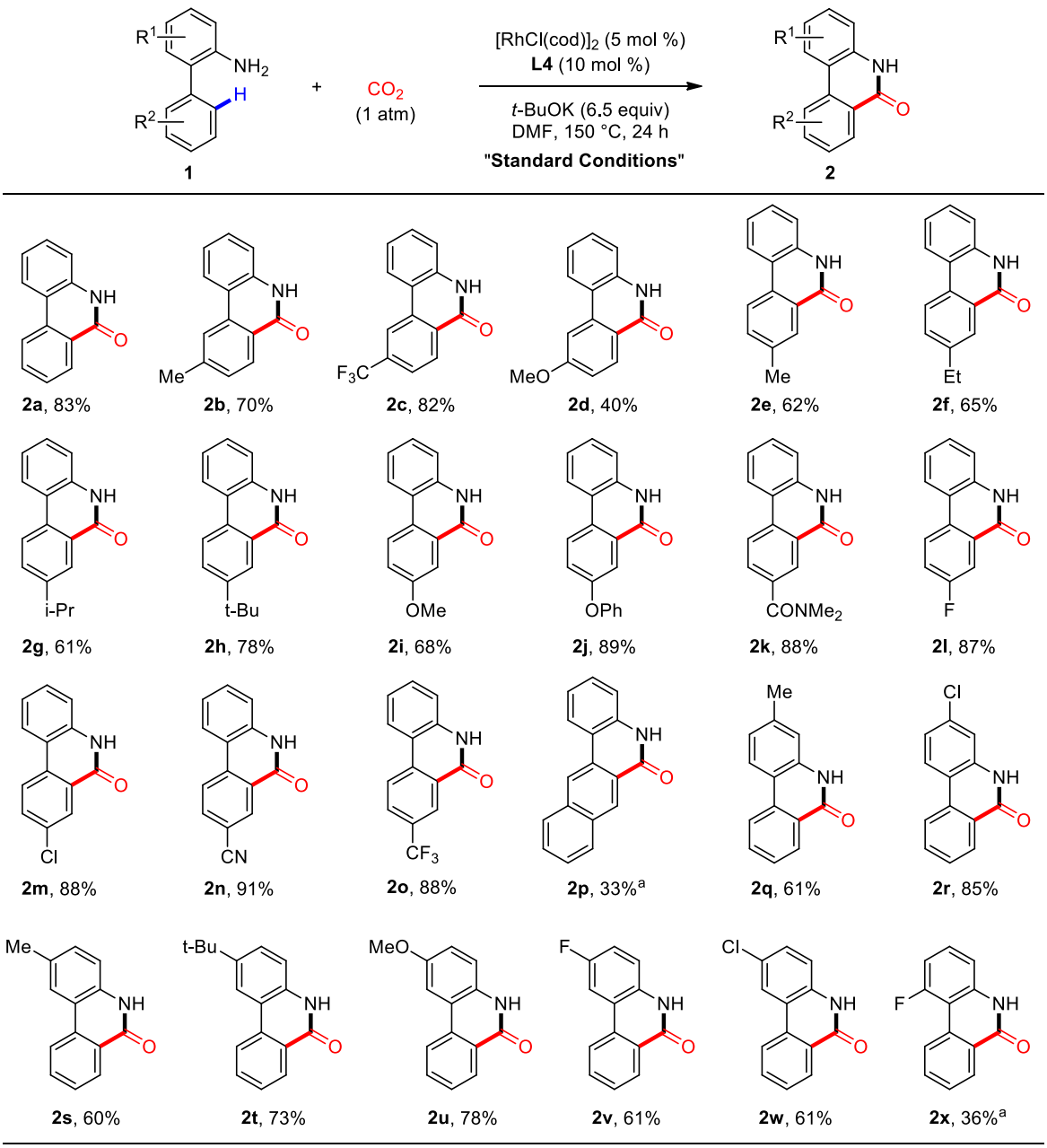


Figure 2. The scope of Rh(I)-catalysed C–H carboxylation of 2-arylanilines. Reaction conditions: **1** (0.2 mmol), CO_2 (1 atm, closed), $[RhCl(cod)]_2$ (5 mol %), **L4** (10 mol %), *t*-BuOK (6.5 equiv), DMF (2 mL), 150 °C, 24 h. Isolated yields. [a]Some urea side product was found with these two examples.

Substrate scope of the C–H carboxylation of 2-heteroarylanilines. Encouraged by the above success with 2-arylanilines, we further investigated the reaction with 2-heteroarylanilines (Fig. 3a), products of which may be of interest for the synthesis of biological compounds.[70] Firstly, we were pleased to find the electron-deficient 4-pyridyl and 3-pyridyl groups, which might compete with amino group via coordination with the Rh(I)-catalyst to impede the desired reaction, could be tolerated in this reaction (**4a**-

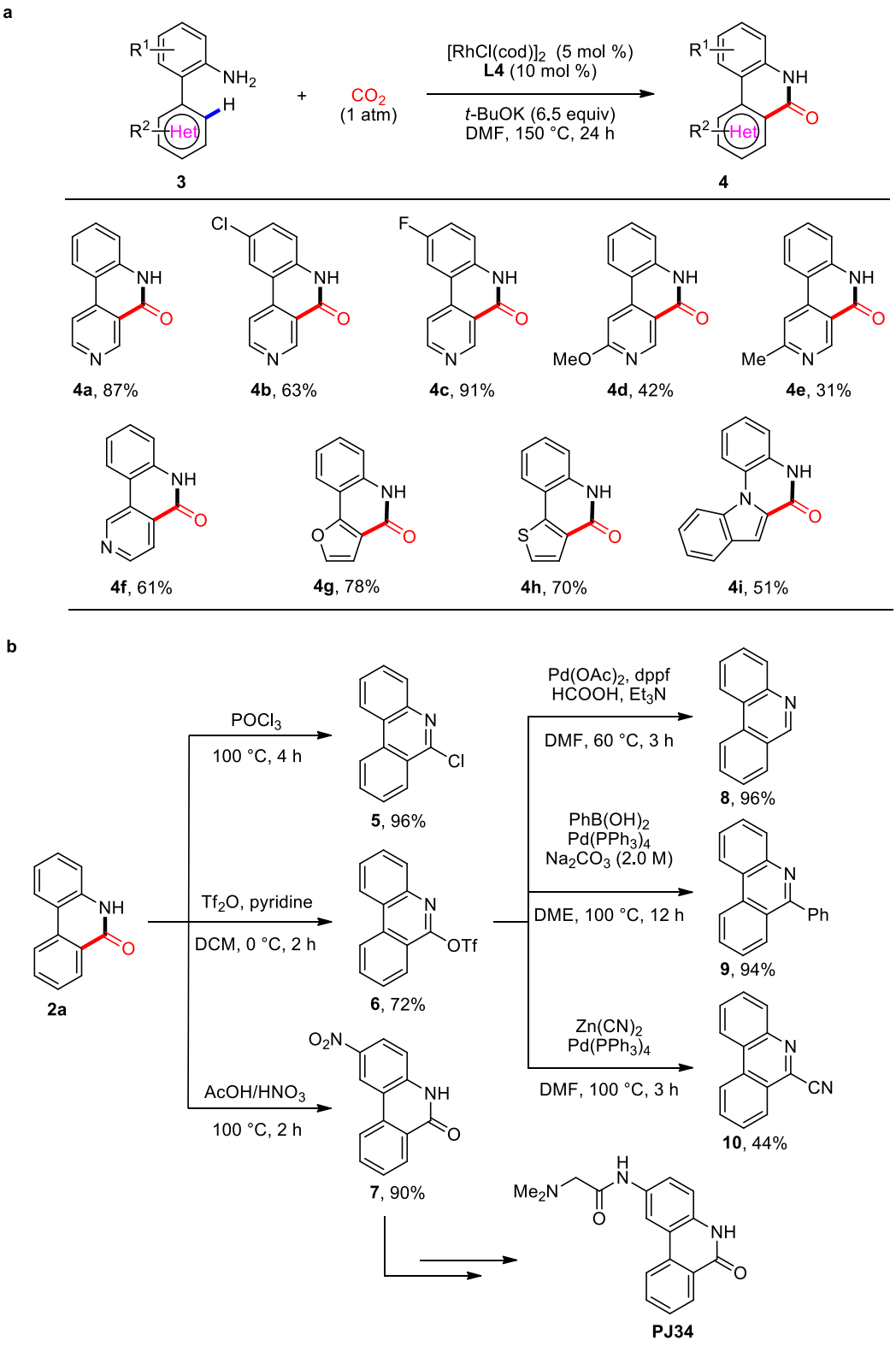


Figure 3. The scope of Rh(I)-catalysed C–H carboxylation of 2-heteroarylanilines and synthetic elaborations of the product. (**a**) scope of 2-heteroarylanilines. Reaction conditions: **3** (0.2 mmol), CO_2 (1 atm, closed), $[RhCl(cod)]_2$ (5 mol %), **L4** (10 mol %), *t*-BuOK (6.5 equiv), DMF (2 mL), 150 °C, 24 h. Isolated yields. No desired products were obtained without adding $[RhCl(cod)]_2$ and **L4**. (**b**) Application potential of C–H carboxylation of 2-arylanilines with CO_2.

4f), albeit the reaction was less efficient with substrates bearing substituents on the pyridyl ring (**4d** and **4e**). In addition, 2-(furan-2-yl)aniline and 2-(thiophen-3-yl)aniline could also react smoothly to afford the expected products (**4g** and **4h**) in satisfied yields. Finally, the reaction could also be extended to an indole derivative to produce the desired product successfully (**4i**). Notably, it should be mentioned that no desired product could be generated from these heterocycle substrates under basic conditions in the absence of $[RhCl(cod)]_2$ and the **L4** ligand.

Synthetic elaboration. To demonstrate the utility of our C–H carboxylation method, further elaboration was carried out for the synthesis of several synthetically useful compounds (Fig. 3b). Firstly, 6-chlorophenanthridine **5** was afforded in excellent yield by subjecting **2a** to $POCl_3$. Moreover, phenanthridine **8** and 6-substituted phenanthridines (**9** and **10**) could be obtained readily with well-established reaction conditions from triflate **6** that was generated from **2a** with triflate anhydride in good yields. Finally, nitration of **2a** in the presence of $AcOH/HNO_3$ provided 2-nitrophenanthridin-6(5*H*)-one **7** in 90% yield which is a key precursor for the preparation of a highly selective PARP-1 inhibitor **PJ34** which also possesses anti-cancer activity.[65]

Mechanistic investigation and the proposed catalytic cycle. Preliminary studies were then carried out to obtain some mechanistic hints of this reaction (Fig. 4a-d). Firstly, $^{13}CO_2$ was utilized to confirmed that the carbonyl source in **2a** was CO_2 (Fig. 4a). Moreover, significant amount of D/H exchange was observed in the product of the isotopically labeled **1a**-d_5 indicating that the C–H metalation step is reversible (Fig. 4b). Subsequently, when the reaction was stopped before completion or carried out without adding a Rh catalyst and the **L4** ligand, undesired urea **11** and carbamate **12** could be obtained, which were often observed in the reaction of amines with CO_2 under basic conditions (Fig. 4c).[1,2] When **11** and **12** were subjected to the standard reaction conditions (Fig. 4d), however, lower yields of **2a** were obtained from **11** or **12** than that of the reaction with **1a** as the substrate. These results suggested that the generation of side products **11** or **12** might retard the reaction and they should not be the intermediates. **11** or **12** may first need to decompose into **1a** which should actually account for the production of stable lactam **2a** in these two reactions. Moreover, trace of product **2a** was formed with **11** or **12** when the

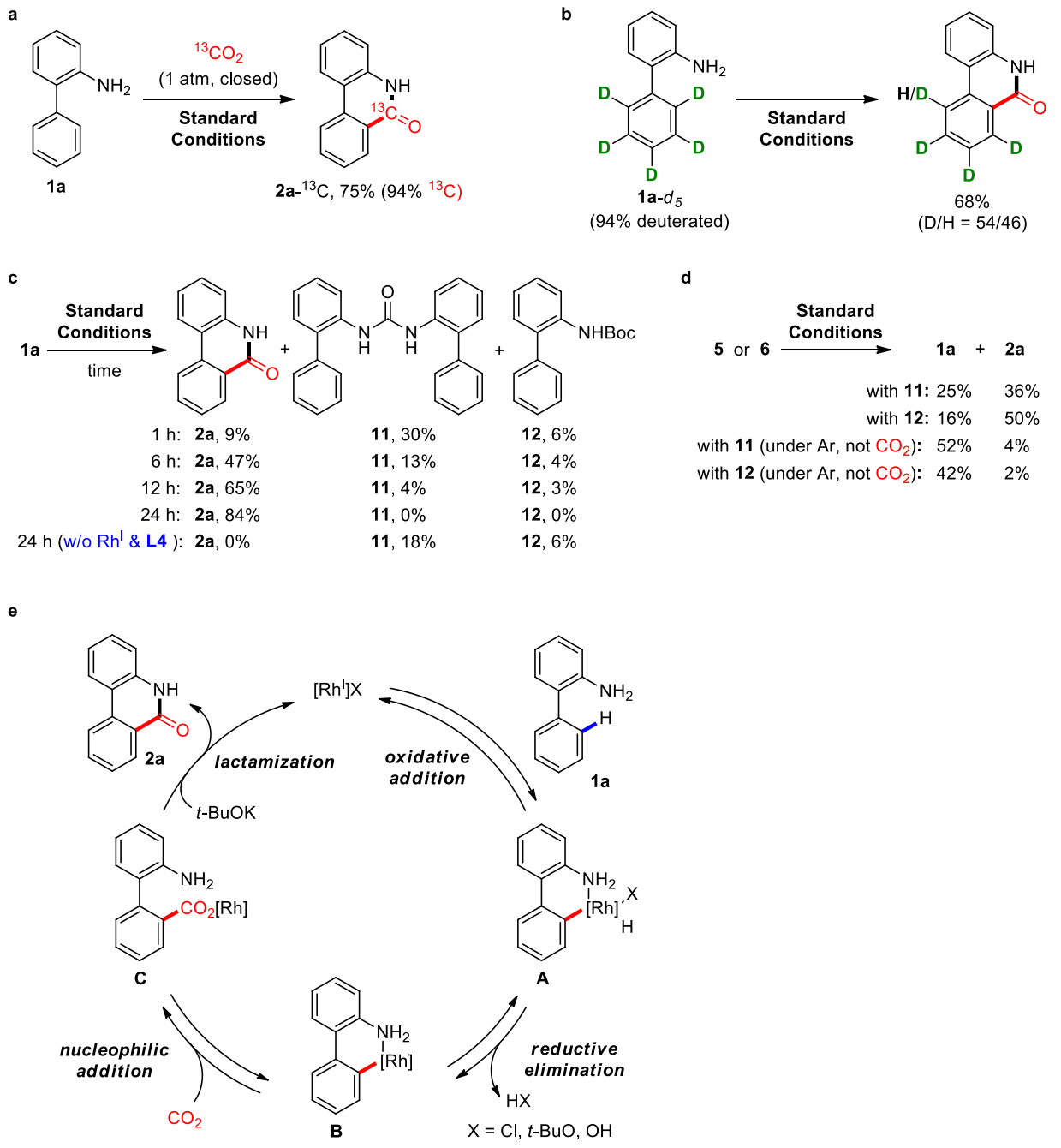


Figure 4. Mechanistic investigation and the proposed catalytic cycle. (a) The reaction using ^{13}C-labeled CO_2 revealed the incorporation of $^{13}CO_2$ in the product. (b) Significant H/D exchange occurred in the C–H carboxylation of the isotopically labelled **1a**-d_5. (c) Urea **11** and carbamate **12** were formed in the course of the reaction. (d) Both substrate **1a** and desired product **2a** could be generated from **11** or **12,** however, in a low yield. (e) The proposed reaction mechanism involves an oxidative addition of a Rh(I) species in the C–H bond cleavage.

reactions were run under argon without adding CO_2 (Fig. 4d), which might due to that small amount of CO_2 was produced when **11** or **12** decomposed into **1a** with *t*-BuOK. It should also be noted that **2a** could not be obtained from **11** or **12** when the Rh(I)-catalyst and the **L4** ligand were removed from the reaction

(see Supplementary Methods), suggesting the formation of **2a** from **11**or **12** was not based-promoted. Moreover, unlike the proposed base-promoted electrophilic annulation of an isocyanate intermediate in the previous report,[66] an isocyanate (see Supplementary Methods for the use of isocyanate as the substrate), which was not observed in the control experiments, is not likely an intermediate in our reaction since the electron-deficient substrates generally gave even higher yields than the electron-rich substrates (see Fig. 2). This mechanistic difference also indicated our method is more general than base-promoted use of CO_2 for C–C bond formation.

Based on the above results, a tentative reaction mechanism is proposed (Fig. 4e). Reversible oxidative addition of a Rh(I) species followed by the reductive elimination of HX would generate rhodacycle **B**, which undergoes reversible nucleophilic carboxylation with CO_2 to form rhodium carboxylate **C**. Final lactamization of **C** assisted by *t*-BuOK gives product **2a** and regenerates the Rh(I)-catalyst.

Discussion

In summary, we have developed the first efficient amino-group assisted C–H carboxylation with CO_2 under redox-neutral conditions utilizing a Rh(I)-catalyst. This reaction was promoted by a phosphine ligand using *t*-BuOK as the base without using an additional strong organometallic reagent. Notably, compared with previous Rh(I) or Rh(II)-catalysed methods for C–H carboxylation with CO_2, this protocol introduced a distinctly new recipe of reaction conditions and may involve a mechanistically different oxidative addition pathway in the C–H bond cleavage step. It was compatible with a broad range of substrates including electron-deficient heteroarenes, and further synthetic elaboration demonstrated its good potential in achieving synthetically useful compounds. Importantly, preliminary mechanistic studies revealed that the Rh(I)-catalyst is essential for this reaction and our method is a promising general method of utilizing CO_2 for C–C bond formation. Further exploration of this reaction with other classes of substrates and investigation into the detailed reaction mechanism are intensively under way in our laboratory.

Methods

General. For ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of compounds in this manuscript and details of the synthetic procedures, see Supplementary Figs 1–41 and Supplementary Methods.

General procedure for Rh(I)-catalysed C–H carboxylation of 2-(hetero)arylanilines. In a glove box, to an oven-dried 50 mL Schlenk sealed tube (with a Teflon cap) equipped with a magnetic stir bar was added **1** or **3** (0.2 mmol), $[RhCl(cod)]_2$ (4.9 mg, 0.01 mmol, 5 mol%), **L4** (9.3 mg, 0.02mol, 10 mol%) and dry *t*-BuOK (145.9 mg, 1.30 mmol, 6.5 equiv) (Note: *t*-BuOK should be dry). After taken out of the glove box, the tube was evacuated under vacuum and charged with CO_2 (1 atm, × 3). Then anhydrous solvent DMF (2.0 mL) was added along the inside wall of the tube under a flow of CO_2. Afterwards, the reaction tube was evacuated briefly under vacuum and charged with CO_2 (1 atm, × 3). The tube was capped and then placed into a preheated hotplate at 150 °C. The reaction was stirred vigorously (Note: good stirring is important!) for 24 h and cooled to room temperature. The reaction was diluted with EtOAc (20 mL) and filtered through a short pad of Celite. The tube and Celite pad were washed with an additional of 20 mL EtOAc. The filtrate was concentrated in vacuo, and purified by flash silica gel chromatography.

Data availability

The authors declare that all the relevant data supporting the findings of the study are available in this article and its Supplementary Information file, or from the corresponding author upon request.

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Author contributions

Y.G. performed the experiments and developed the reactions. Z.C started the initial reaction conditions development. S.L helped expanding the substrate scope. G.L. designed and directed the project, and wrote the manuscript with the feedback of Y.G., Z.C., and S.L.