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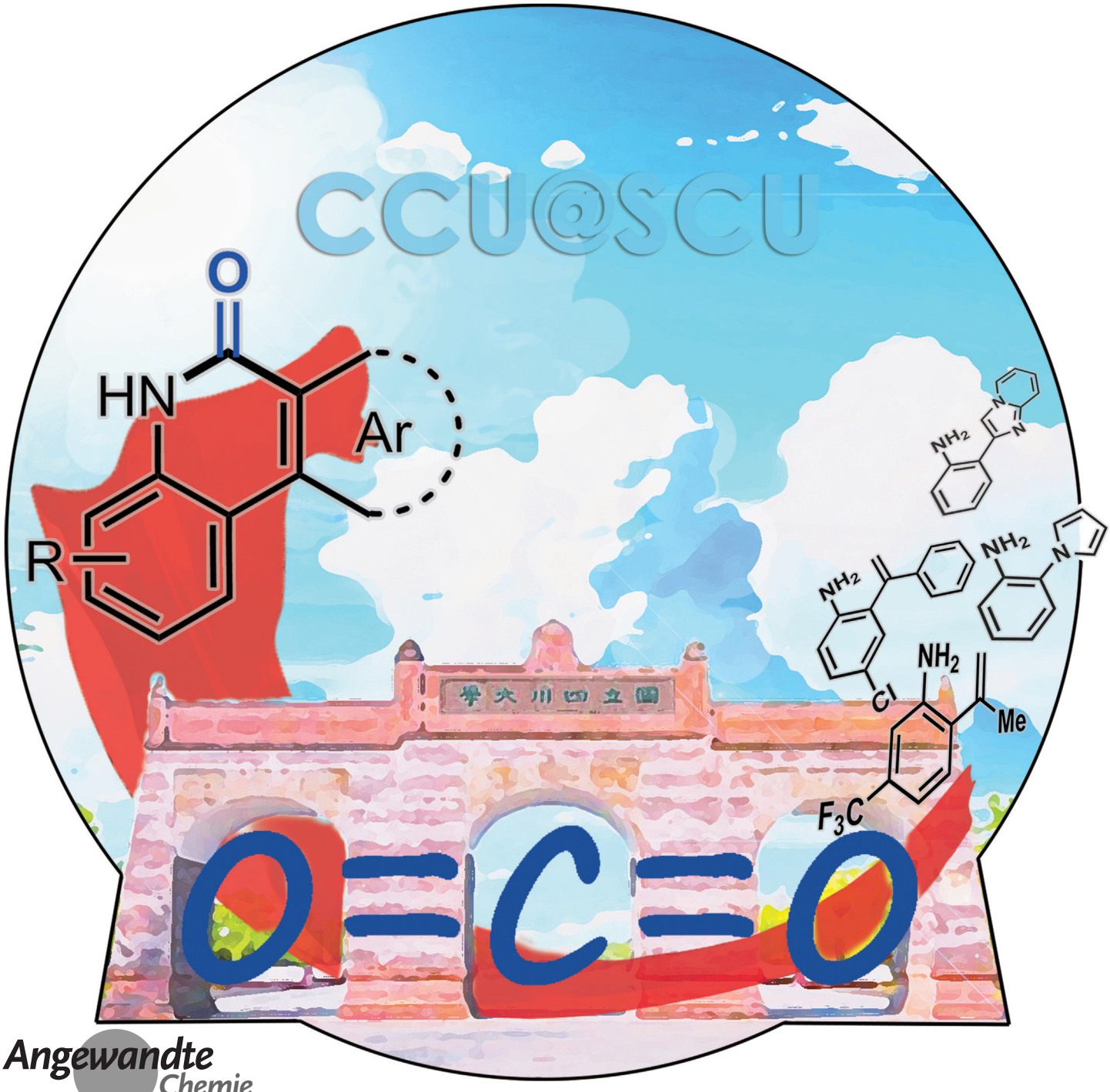
Lactamization of sp^2 C–H Bonds with CO_2: Transition-Metal-Free and Redox-Neutral

*Zhen Zhang, Li-Li Liao, Si-Shun Yan, Lei Wang, Yun-Qi He, Jian-Heng Ye, Jing Li, Yong-Gang Zhi, and Da-Gang Yu**

Dedicated to Professor Peter Kündig and Professor Gerhard Erker on the occasion of their 70th birthdays



Abstract: *The first direct use of carbon dioxide in the lactamization of alkenyl and heteroaryl C–H bonds to synthesize important 2-quinolinones and polyheterocycles in moderate to excellent yields is reported. Carbon dioxide, a nontoxic, inexpensive, and readily available greenhouse gas, acts as an ideal carbonyl source. Importantly, this transition-metal-free and redox-neutral process is eco-friendly and desirable for the pharmaceutical industry. Moreover, these reactions feature a broad substrate scope, good functional group tolerance, facile scalability, and easy product derivatization.*

Carbon dioxide (CO_2) is an important and ideal one-carbon (C1) source and it shows great potential in organic synthesis owing to its nontoxicity, abundance, availability, and recyclability.[1] Transformations of CO_2 to useful chemicals have been attracting increasing attention for a long time. Although it is challenging to activate and utilize CO_2 owing to its thermodynamic stability and kinetical inertness, a variety of efficient CO_2 transformations have been discovered in the past decades.[2] In addition to transformations in the presence of reductants,[3] various kinds of non-reductive processes have been realized to generate organic carboxylates,[4a–c] (poly)-carbonates,[4d,e] carbamates/oxazolidinones,[4f] ureas,[4g] and lactones.[4h] Notably, the leading groups of Nolan and Cazin,[5a–c] Hou,[5d–f] and Iwasawa,[4h,5g,h] as well as others,[5i–l] have reported elegant progress toward the direct carboxylation and lactonization of sp^2 C–H bonds, which are highly attractive owing to the high step- and atom-economy. However, the challenging lactamization of sp^2 C–H bonds with CO_2 remains unresolved.

2-Quinolinones and polyheterocycles containing a free (NH)-lactam are common motifs in drugs, bioactive natural products, photoelectric materials, and important intermediates in organic synthesis (Figure 1).[6] Multiple methods to generate such structures have been disclosed.[7] One of the most efficient methods is the transition-metal-catalyzed oxidative carbonylation of *ortho*-alkenyl or -aryl anilines with CO by direct sp^2 C–H bond transformation (Scheme 1).[8] For example, the Alper group developed the efficient Pd-catalyzed synthesis of 2-quinolinones using substoichiometric copper acetate and air as the terminal oxidant (Scheme 1 A).[8a] Meanwhile, the groups of Zhu,[8b] Chuang,[8c] and Zhang[8d] independently reported the oxidative carbonylation of *ortho*-aryl anilines with CO using stoichiometric copper or silver salts as the oxidants (Scheme 1 B). Although these methods are step-efficient, atom-economic, and display a good substrate scope, the use of highly toxic CO and high-valence transition metals as the oxidants causes safety issues, high cost, and risk for heavy metal residues, all of which hamper industrial applications, especially in the pharmaceutical sector. Therefore, developing a method that avoids toxic CO or heavy metal salts is highly desirable.[9] In principle, CO_2, with its higher oxidation state than CO, might act similarly to the combination of CO and oxidants. Herein, we report the first lactamization of sp^2 C–H bonds with CO_2 to generate diverse 2-quinolinones and polyheterocycles under transition-metal-free and redox-neutral conditions (Scheme 1 C). Our process is scalable and green, with broad substrate scope and good functional group tolerance. Moreover, the products readily can be transformed into diverse derivatives and important drugs.

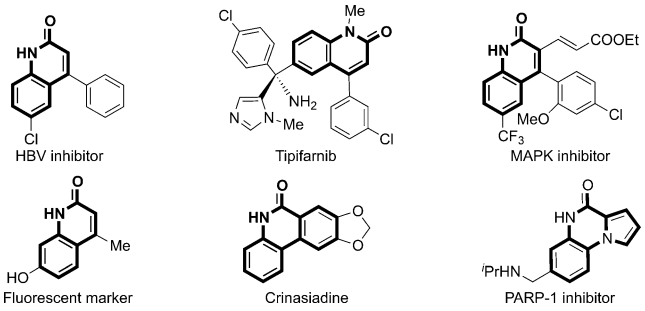
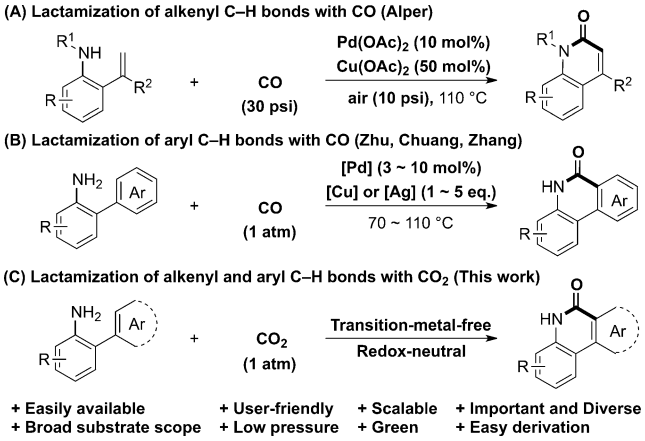


Figure 1. Selected biologically active 2-quinolinones and polyheterocycles containing a lactam moiety.



Scheme 1. Lactamization of alkenyl and aryl C–H bonds.

It is well known that anilines can react with CO_2 under basic conditions by nucleophilic attack/C–N bond formation to generate carbamates/carbamic acids.[4g,10] We envisioned that the electron-rich alkene at the *ortho* position of an aniline might undergo an intramolecular nucleophilic attack on the in situ generated carbamates/carbamic acids to provide the corresponding lactams. Based on this hypothesis, we first tested the direct lactamization of 2-(prop-1-en-2-yl)aniline **1a** to generate 2-quinolinone **2a** in the presence of 1 atm of CO_2 (Supporting Information, Table S1). We explored a variety of

[*] Z. Zhang, L.-L. Liao, S.-S. Yan, L. Wang, Y.-Q. He, J.-H. Ye, Dr. J. Li, Prof. Dr. D.-G. Yu
Key Laboratory of Green Chemistry & Technology
Ministry of Education
College of Chemistry, Sichuan University
29 Wangjiang Road, Chengdu 610064 (P. R. China)
E-mail: dgyu@scu.edu.cn
Z. Zhang, Prof. Dr. Y.-G. Zhi
Chengdu Institute of Organic Chemistry
Chinese Academy of Sciences
Chengdu, Sichuan, 610041 (P. R. China)
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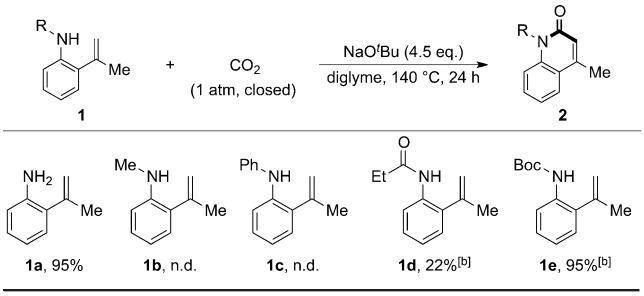
bases using 1,4-dioxane as the solvent. Although many kinds of bases elicited no reactivity (Table S1, entries 1–3), several alkali metal *tert*-butoxides promoted the reaction to generate **2a** in moderate to good yields (Table S1, entries 4–6). Many other solvents, including tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and diglyme, were tested to generate **2a** with KO^{t}Bu as the base (Table S1, entries 7–11). Meanwhile, NaO^{t}Bu also promoted the reaction to give **2a** in 82% yield when diglyme was applied as the solvent (Table S1, entry 12). Excess of base and high temperature are important for high efficiency. For example, no conversion was observed when no or 1 equivalent of NaO^{t}Bu was used, demonstrating the critical role of the base (Table S1, entries 12–15). The yield improved to 95% when 4.5 equivalent of NaO^{t}Bu was used at 140°C (Table S1, entry 17). Under these conditions, good conversion was observed in just 2.5 hours (Table S1, entry 18). Importantly, the inductively coupled plasma atomic emission spectrometer (ICP-AES) detection of transition metal sources demonstrated that this reaction is free of transition metals (see the Supporting Information for details).

With the best reaction conditions in hand, we investigated the effect of substituents on the aniline nitrogen (Table 1). Neither alkyl (**1b**) nor aryl (**1c**) substituted anilines afforded the desired products. When amide **1d** and carbamate **1e** were applied as substrates, **2a** was obtained in 22% and 95% yield, respectively. This might arise from in situ generation of free aniline **1a** or the intermediates under the reaction conditions (see the Supporting Information).

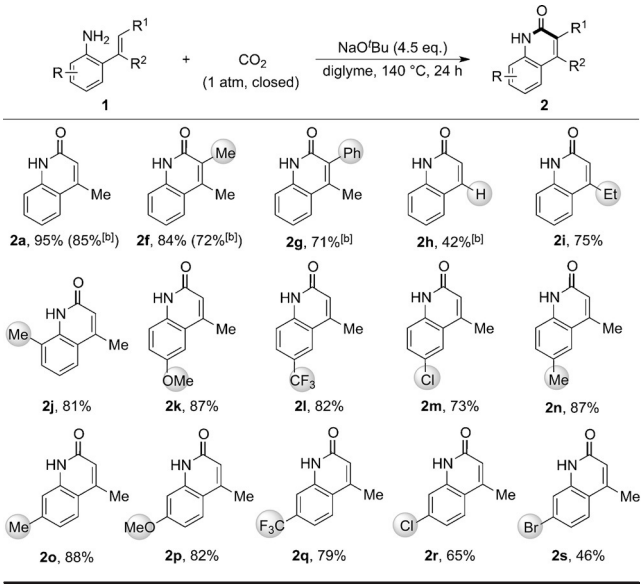
Table 1: Test of different substituents on nitrogen of anilines.[a]



[a] Reaction conditions: **1** (0.2 mmol), NaO^{t}Bu (4.5 equiv.), 1 atm of CO_2, 2 mL of diglyme, 24 h, 140°C. The yields are isolated yields. [b] **2a** was obtained as the product. n.d. = not detected.

Based on these results, we further investigated the reactivities of free anilines with *ortho*-alkenyl substitution (Table 2). First, varying the substitution on the alkene moiety was tested. We found that both terminal alkenes (**1a**) and internal alkenes (**1f** and **1g**) could be applied in the reaction to give the products in good yields. Moreover, the substrate with a methyl group on the alkene (**1a**) showed better reactivity than those with a hydrogen (**1h**) or an ethyl group (**1i**). Secondly, we tested various kinds of substituents on the arene. It was found that the steric hindrance did not hamper the reaction, forming **2j** in 81% yield. The anilines with electron-donating groups (EDGs; **1k** and **1p**) showed similar reactivity to those with electron-withdrawing groups (EWGs; **1l** and **1q**). Many kinds of functional groups, including OMe

Table 2: Lactamization of 2-alkenylanilines with CO_2.[a]

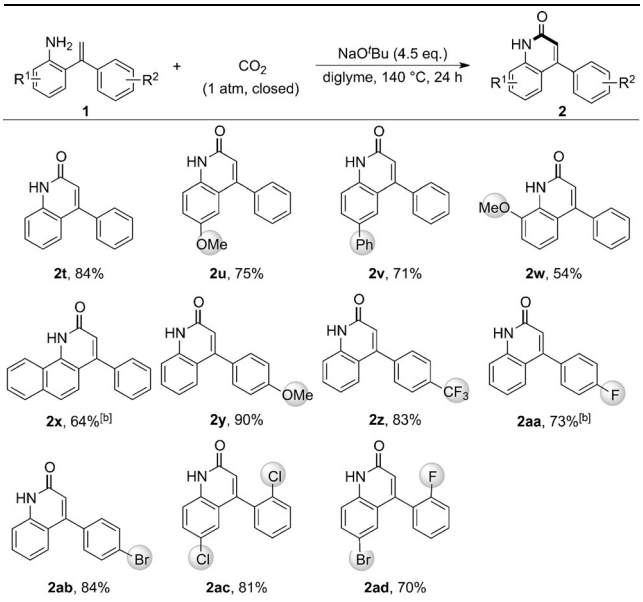


[a] Reaction conditions: the same as Table 1. [b] **1** (0.3 mmol), NaO^{t}Bu (3.0 equiv.).

(**2k** and **2p**), CF_3 (**2l** and **2q**), Cl (**2m** and **2r**), and Br (**2s**), were well tolerated, providing great opportunities for drug synthesis[6c,11] and further functionalization.[12]

Considering the high importance of 4-aryl-2-quinolinones, we further tested the reactivities of *ortho* α-styrenyl-substituted anilines (Table 3), which can be easily synthesized from simple anilines with alkynes.[13] We found that most of the 2-(1-arylvinyl)anilines could undergo the reaction to generate the corresponding 4-aryl-2-quinolinones in moderate to excellent yields. Similarly, many kinds of functional groups

Table 3: Lactamization of 2-alkenylanilines with CO_2.[a]

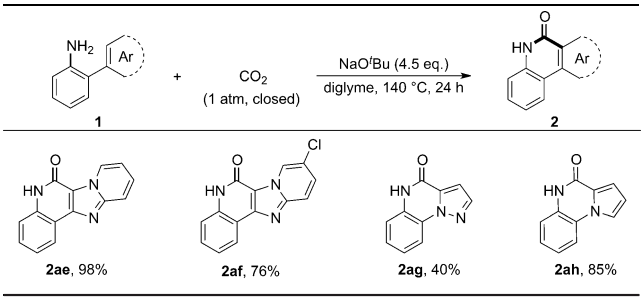


[a] Reaction conditions: the same as Table 1. [b] **1** (0.3 mmol), NaO^{t}Bu (3.0 equiv.).

did not affect the reaction. The aniline motifs with *para* substituents (**2u**) showed higher yields than those with *ortho* functionality (**2w**). Naphthylamine **1x** also successfully underwent this transformation. The electron-rich aryl groups on the alkenes (**2y**) showed higher reactivity than the electron-poor ones (**2z**, **2aa**, and **2ad**), which might be a result of the different alkene nucleophilicities. Moreover, the substrates with two carbon–halide bonds, either with the same (**2ac**) or different (**2ad**) halogen, also afforded the desired products in good yields.

Based on the success of *ortho*-alkenyl anilines in this reaction and the similar reactivity in many kinds of sp^2 C–H transformations, we further investigated the reactions of *ortho*-aryl anilines **1** (Table 4) with CO_2 to generate poly-

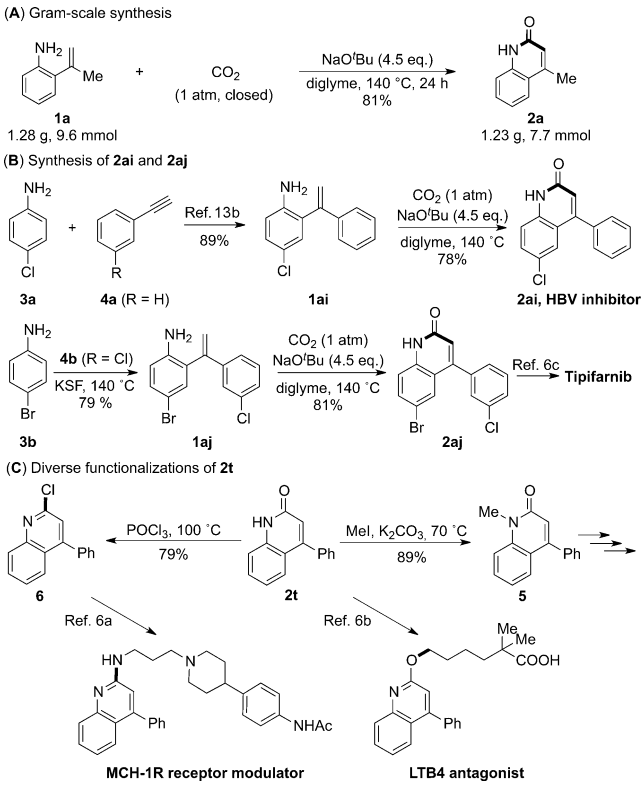
Table 4: Lactamization of 2-heteroarylanilines with CO_2.[a]



[a] Reaction conditions: the same as Table 1.

heterocycles containing a free (NH)-lactam and their derivatives, which are also common motifs in bioactive compounds. To our delight, anilines with many kinds of *ortho*-heteroarenes, including imidazo[1,2-a]pyridine (**1ae** and **1af**), pyrazole (**1ag**), and pyrole (**1ah**), could undergo the base-mediated lactamization to give the desired products in moderate to excellent yields. Notably, **2ah** is the core structure of PARP-1 inhibitors (Figure 1).[6e]

After developing the methodology, we further demonstrated its utility by applying it toward the synthesis of some valuable intermediates and biologically active compounds. First, we found that the reaction with aniline **1a** is amenable to scale-up to gram quantities with comparable yield and efficiency (Scheme 2A). Second, the important 4-aryl-2-quinolinones **2ai** (HBV inhibitor)[6d] and **2aj** (a key intermediate to Tipifarnib)[6c] were both rapidly accessed in good yields by application of the appropriate 2-(1-arylvinyl)anilines **1ai**[13b] and **1aj**,[13a] readily obtained from the heterogeneously catalyzed reactions between a *para*-haloaniline **3** and a simple arylalkyne **4**, to our reaction conditions (Scheme 2B). Moreover, 4-phenyl-2-quinolinones **2t** was selected as a model substrate for scaffold diversification (Scheme 2C). For example, selective methylation of nitrogen[14] was realized to give **5** in good yield, which provides opportunities for the selective bromination of the alkenyl C–H bond and further transformations.[12a,15] Meanwhile, **2t** could be transformed easily to 2-alkoxyquinolines (such as a known LTB4 antagonist),[6b] 2-chloroquinolines **6**, as well as 2-aminoquinolines (such as a known MCH-1R receptor modulator).[6a] This



Scheme 2. Large scale reaction and synthetic applications. KSF = Montmorillonite KSF.

versatility demonstrates that the products rapidly obtained from our method are highly useful and attractive in synthetic and medicinal chemistry.

Furthermore, a series of experiments were performed to investigate the mechanism. Based on the results, we propose that both **1e** and urea **7** may be the intermediate to the highly reactive isocyanate **8**,[16a] which undergoes irreversible cyclization to generate the product **2a** (see the Supporting Information for details).[16b]

In conclusion, we have developed a lactamization of sp^2 C–H bonds to synthesize important 2-quinolinones and polyheterocycles containing a free (NH)-lactam motif in moderate to excellent yields with CO_2 as the ideal carbonyl source. Importantly, this transition-metal-free and redox-neutral process is efficient and eco-friendly, making it an attractive method for the pharmaceutical industry. Finally, these reactions feature a broad substrate scope, good functional group tolerance, facile scalability, and easy derivatization of the products to drugs and bioactive compounds.

Acknowledgements

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