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Ruthenium-catalyzed umpolung carboxylation of hydrazones with $\text{CO}_2 \dagger$

Si-Shun Yan,^a Lei Zhu,^b Jian-Heng Ye,^a Zhen Zhang,^a He Huang,^a Huiying Zeng, ^b^c Chao-Jun Li, ^b*^{cd} Yu Lan ^b*^b and Da-Gang Yu ^{*ae}

The first ruthenium-catalyzed umpolung carboxylation of hydrazones with CO_2 to generate important aryl acetic acids is reported. Besides aldehyde hydrazones, a variety of ketone hydrazones, which have not been successfully applied in previous umpolung reactions with other reactive electrophiles, also show high

reactivity and selectivity under mild conditions. Moreover, this operationally simple protocol features

good functional group tolerance, is readily scalable, and offers easy derivation of important structures,

including bioactive felbinac and adiphenine. Computational studies reveal that this umpolung reaction proceeds through the generation of a Ru-nitrenoid followed by concerted [4 + 2] cycloaddition with CO₂.

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Introduction

Carbon dioxide (CO_2) has attracted significant attention as an ideal C1 source due to its high abundance, low cost, low toxicity and renewability.¹ In numerous chemical transformations involving CO_2 ,² the synthesis of carboxylic acids through C–C bond formation is highly promising.^{3–5} Given that aryl acetic acids are present in myriad natural products, agrochemicals and drugs (Fig. 1),⁶ great effort has been devoted to the synthesis of this motif following various strategies.^{7,8} Notably, the transition metal-catalyzed reductive carboxylation of benzyl (pseudo)halides with CO_2 has been well documented by Martin



Fig. 1 Aryl acetic acid-containing drugs.

^aKey Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P. R. China. E-mail: dgyu@scu.edu.cn

- ^bSchool of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, P. R. China. E-mail: lanyu@cqu.edu.cn
- ^cThe State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China
- ^dDepartment of Chemistry and FQRNT Centre for Green Chemistry and Catalysis, McGill University, 801 Sherbrooke St. W., Montreal, Quebec H3A 0B8, Canada. E-mail: cj.li@mcgill.ca

^eState Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

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and He (Scheme 1a).⁸ However, the Ru-catalyzed carboxylation with CO_2 has rarely been investigated and very limited success has been achieved.⁹ Herein, we report a novel Ru-catalyzed umpolung carboxylation of hydrazones with CO_2 under mild conditions (Scheme 1b). This reaction features good functional group tolerance, high selectivity, broad substrate scope and facile scalability.

An umpolung strategy creates new reactivity by reversing the inherent polarity of common functional groups and consequently allowing for new reactions with distinct bond formations.¹⁰ Recently, transition-metal-free umpolung carboxylations of imines and derivatives with CO_2 have been well developed by Sato, Radosevich and Zhang to generate α -amino acids.¹¹ In 2015, an elegant base-promoted Shapiro-type carboxylation of *N*-tosylhydrazones to generate acrylic acids was reported by Cheng (Scheme 1b).¹² However, there is no report to generate important aryl acetic acids *via* the cleavage of C=N double bonds with a catalytic system. As part of our continuing interest in advancing sustainable organic synthesis with CO_2 ,¹³ we wondered whether transition metal-catalysis could resolve such



Scheme 1 Synthesis of aryl acetic acids with CO₂.

a challenge with different reaction mechanisms. Recently, one of us has developed Ru-catalyzed umpolung reactions with carbonyls as carbanion equivalents.¹⁴ Considering that hydrazones are easily prepared from carbonyl compounds, which widely exist in nature and industry, this new strategy promises to be more sustainable and efficient for the synthesis of phenylacetic acids, especially for complex examples. At the outset of our investigations, however, it was unclear whether such a procedure could ever be implemented, since Ru-assisted Wolff–Kishner reduction¹⁵ takes place smoothly under mild reaction conditions. The azine byproduct could also be easily generated from the hydrazones. Moreover, a possible side reaction of basepromoted Shapiro-type carboxylation of ketone hydrazones to acrylic acids may occur to compete with our designed reactions.¹²

Results and discussion

 Table 1
 Optimization of the reaction conditions^a

With these challenges in mind, we began our study by evaluating the reaction of benzaldehyde hydrazone **1a** with CO₂ (Table 1). To our delight, we found that many diphosphine ligands could promote this reaction (entries 1–3) and dppf gave the best result (entry 3), which might arise from higher nucleophilicity of the *in situ* generated Ru-complex. We also tested a variety of bases and found that inorganic bases were superior to organic bases in this reaction (entries 3–6). Increasing or decreasing the amount of base gave a lower yield (entries 7 and 8). CsF served as an efficient additive to enhance the yield (entry **11**), which might arise from enhanced nucleophilicity with the fluoride anion as a strong hydrogen bond acceptor. Control experiments demonstrated that the Ru-catalyst was vital to this

With the optimized reaction conditions in hand, we then tested the scope of aldehyde hydrazones (Table 2), most of which were prepared from the corresponding aldehyde in one step and used without further purification, thus representing a significant advantage from a practical standpoint. Both electron-donating and electron-withdrawing groups on the phenyl ring were compatible. Different substituents at various positions on the arenes, including a bulky trifluoromethyl group at the ortho position (2r), did not hamper the reaction. Remarkably, a variety of functional groups, such as fluoro (2b), chloro (2c and 2l), bromo (2d, 2m and 2p), iodo (2e and 2q), ether (2g, 2j and 2k), ester (2i), nitro (2n), and cyano (20), were all tolerated, providing a possibility for further transformations. Moreover, different kinds of fused rings (2s, 2t and 2u) and heterocycles, such as thiophene, benzothiophene and indole (2v, 2w and 2x), were compatible in this reaction. It is worth noting that a pharmaceutical agent felbinac (2f) and a known plant growth stimulant (2w) were both prepared readily and in a good yield with our strategy.

Given that α -substituted phenylacetic acids are present in a large collection of bioactive molecules, we wondered whether our procedure could be extended to ketone hydrazones, which have not been successfully applied in previous umpolung reactions with other reactive electrophiles.¹⁴ Although Wolff– Kishner reduction was anticipated, we were delighted to discover that benzophenone hydrazone reacted smoothly to give the diphenylacetic acid **4a** in 72% or 86% yield with minor modification of the reaction conditions (Table 3). Furthermore, the substrates with different substituents, including fluoro, chloro, and methoxyl, afforded the desired products in

N ^{NH2} H 1a	+ CO ₂ (1 atm, closed)	[Ru(<i>p</i> - <i>cy</i> mene)Cl ₂] ₂ (2 mol%) ligand (4 mol%) base (1.3 equiv), CsF (0.4 equiv) DMF (2 mL), 80 °C, 24 h then HCl (aq.)	Соон 2а
Entry	Ligand	Base	Yield ^b (%)
1	dppp	Cs_2CO_3	44
2	dppe	Cs_2CO_3	19
3	dppf	Cs ₂ CO ₃	85 (83)
4	dppf	K_3PO_4	51
5	dppf	KO ^t Bu	80
6	dppf	DBU	27
7 ^c	dppf	Cs_2CO_3	73
8^d	dppf	Cs_2CO_3	72
9	No	Cs_2CO_3	13
10	dppf	No	31
11^e	dppf	Cs_2CO_3	78
12^{f}	dppf	Cs_2CO_3	N.D.
13^g	dppf	Cs_2CO_3	N.D.

^{*a*} Reaction conditions: **1a** (0.4 mmol). ^{*b*} Yields were determined by crude ¹H NMR using dibromomethane as an internal standard, and the isolated yields are given in parentheses. ^{*c*} Base (0.4 mmol). ^{*d*} Base (0.6 mmol). ^{*e*} No CsF. ^{*f*} No [Ru(*p*-cymene)Cl₂]₂. ^{*g*} N₂ instead of CO₂. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. N.D. = not detected.





^{*a*} Reaction conditions: 1 (0.4 mmol), 1 atm of CO_2 , $[Ru(p-cymene)Cl_2]_2$ (0.008 mol), dppf (0.016 mmol), Cs_2CO_3 (0.52 mmol), CsF (0.16 mmol), DMF (2 mL), 80 °C, and 24 h; isolated yields.

Table 3 Substrate scope of ketone hydrazones⁴



^{*a*} The same reaction conditions as given in Table 2; isolated yields. ^{*b*} Using KO'Bu (1.5 equiv.) instead of Cs_2CO_3 (1.3 equiv.) as a base.

moderate to good yields (**4b–4h**). Besides the benzophenone hydrazones, readily-available ketone hydrazones **3i** and **3j** furnished the corresponding α -alkylphenylacetic acid products in synthetically useful yields, showing the further utility of this process.

To further demonstrate the utility of this umpolung carboxylation, we conducted a gram-scale synthesis of 3-bromophenylacetic acid 2m in 83% yield (Scheme 2). An antihyperlipidemic drug, fenofibrate 3k', could be subjected to this method to produce the acid 4k in 60% isolated yield. Moreover, the product 4a was readily converted in one step to adiphenine (5), an inhibitor of the nicotinic receptor.^{16a} The antiproliferative agent 6 and the known histone deacetylase inhibitor 7 were efficiently accessed by respective amidations in good yields (see the ESI† for details).^{16b-d}

On the basis of preliminary mechanistic studies and previous reports,¹⁴ a plausible mechanism is proposed to



Scheme 2 Gram-scale synthesis and transformations.

account for this transformation. As shown in Fig. 2, catalyst **A** could be generated (see the ESI[†] for details) which undergoes ligand exchange with hydrazone and Cs_2CO_3 to give complex **B**, which then undergoes two step deprotonation to generate a Runitrenoid complex **D**.¹⁷ After a concerted hetero-[4 + 2] cycloaddition with CO₂, a six-membered Ru-cycle **E** can be formed. Then the release of N₂, a driving force for this reaction, and the following protonation-ligand exchange provide the desired product and regenerate the active catalyst **B**. Alternatively, the intermediate **F** could also be generated from **D** *via* sequential isomerization, carbenation, and CO₂ insertion (Path-B).

To further identify the proposed mechanism, a density functional theory (DFT) method M06-L was employed to investigate this reaction.¹⁸ The reactant **1a** coordinated Ru carbonate species **B** was considered as a starting complex (see the Fig. S1† for details). The first N–H bond cleavage proceeds *via* a transition state **8-ts** (Fig. S2†), with a free energy barrier of 23.9 kcal mol⁻¹, to generate the amino-Ru intermediate **C**. Subsequently, the second step deprotonation occurs rapidly with the assistance of Cs₂CO₃, leading to the formation of the Ru-nitrenoid intermediate **D**.

After the formation of Ru-nitrenoid **D**, in Path-A (Fig. 3), the six-membered Ru-cycle complex **E** was obtained through an intermolecular hetero-[4 + 2] cycloaddition with CO₂, with a free energy barrier of 22.4 kcal mol⁻¹.¹⁹ The subsequent C–N bond cleavage leads to the generation of the benzylruthenium intermediate **F**, which is exergonic by 34.1 kcal mol⁻¹ as a result of N₂ release. The phenylacetate **14** was then released after the following protonation-ligand exchange, and the active catalyst **B** was also concomitantly regenerated. Meanwhile, the calculation of activation free energy of Path-B has also been conducted. The



Fig. 2 Proposed mechanism.

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Fig. 3 Free energy profiles of Path-A (plain) and Path-B (dashed) for ruthenium-catalyzed carboxylation. The distances are represented in angstroms.

isomerization of the Ru-nitrenoid intermediate **D** could afford the diazoalkane-coordinated Ru complex **G**, which is endergonic by 13.0 kcal mol⁻¹. The subsequent carbenation could proceed rapidly to afford the Ru-carbenoid **H** with an energy barrier of 1.8 kcal mol⁻¹. CO₂ insertion *via* a transition state **17ts** then generates the common benzylruthenium intermediate **F**. The overall activation free energy of Path-B is determined to be 26.6 kcal mol⁻¹, which is 4.2 kcal mol⁻¹ higher than that of the [4 + 2] cycloaddition step in Path-A. Therefore, the carbenation pathway (Path-B) turns out to be unfavorable in comparison with Path-A.

Moreover, Fig. 4 shows the variation of the natural bond orbital (NBO)²⁰ atomic charges on benzylic carbon during the catalytic cycle. It demonstrates that the increasing of the electron density on benzylic carbon is accompanied by the two step N–H cleavage, which clearly indicates the umpolung of the reactants. Thus, the Ru-nitrenoid **D** exhibits enhanced reactivity with CO₂.

Conclusions

In summary, we have realized the first Ru-catalyzed umpolung carboxylation of hydrazones with CO_2 for synthesizing important aryl acetic acids under mild conditions. The only byproduct in this reaction is N_2 while overall a high atom efficiency is realized displaying significant advantages in carboxylations. Besides aldehyde hydrazones, a variety of ketone hydrazones, which have not been successfully applied in previous umpolung reactions with other reactive electrophiles, also show high reactivity and selectivity in this reaction. This methodology displays a broad substrate scope, functional group tolerance, scalability and easy derivation of important structures. With a deeper understanding of this reaction, DFT calculations reveal the fundamental of this transformation with the generation of a Ru-nitrenoid and intermolecular [4 + 2] cycloaddition with CO₂.



Fig. 4 Calculated NBO atomic charges on benzylic carbon during the catalytic cycle.

Conflicts of interest

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Notes and references

- 1 (a) M. Aresta, Carbon Dioxide as Chemical Feedstock, Wiley-VCH, Weinheim, 2010; (b) L. Ackermann, Angew. Chem., Int. Ed., 2011, **50**, 3842.
- 2 (a) T. Sakakura, J.-C. Choi and H. Yasuda, Chem. Rev., 2007, 107, 2365; (b) K. Huang, C.-L. Sun and Z.-J. Shi, Chem. Soc. Rev., 2011, 40, 2435; (c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann and F. E. Kühn, Angew. Chem., Int. Ed., 2011, 50, 8510; (d) Y. Tsuji and T. Fujihara, Chem. Commun., 2012, 48, 9956; (e) M. He, Y. Sun and B. Han, Angew. Chem., Int. Ed., 2013, 52, 9620; (f) L. Zhang and Z. Hou, Chem. Sci., 2013, 4, 3395; (g) M. Aresta, A. Dibenedetto and A. Angelini, Chem. Rev., 2014, 114, 1709; (h) C. Maeda, Y. Miyazaki and T. Ema, Catal. Sci. Technol., 2014, 4, 1482; (i) C. S. Yeung and V. M. Dong, Top. Catal., 2014, 57, 1342; (j) Q. Liu, L. Wu, R. Jackstell and M. Beller, Nat. Commun., 2015, 6, 5933; (k) Z. Zhang, T. Ju, J.-H. Ye and D.-G. Yu, Synlett, 2017, 28, 741.
- 3 For reviews, see: (a) M. Börjesson, T. Moragas, D. Gallego and R. Martin, ACS Catal., 2016, 6, 6739; (b) S. Wang, G. Du and C. Xi, Org. Biomol. Chem., 2016, 14, 3666; (c) Q. Zhu, L. Wang, C. Xia and C. Liu, Chin. J. Org. Chem., 2016, 36, 2813; (d) Q.-W. Song, Z.-H. Zhou and L.-N. He, Green Chem., 2017, 19, 3707; (e) W. Zhang, N. Zhang, C. Guo and X. Lu, Chin. J. Org. Chem., 2017, 37, 1309; (f) X.-F. Wu and F. Zheng, Top. Curr. Chem., 2017, 375, 4; (g) J. Luo and I. Larrosa, ChemSusChem, 2017, 10, 3317; (h) Y.-Y. Gui, W.-J. Zhou, J.-H. Ye and D.-G. Yu, ChemSusChem, 2017, 10, 1337; (i) A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas and R. Martin, Angew. Chem., Int. Ed., 2018, DOI: 10.1002/ anie.201803186.
- 4 For selected examples of carboxylation of electrophiles with CO₂, see: (a) A. Correa and R. Martin, J. Am. Chem. Soc., 2009, 131, 15974; (b) T. Fujihara, K. Nogi, T. Xu, J. Terao and Y. Tsuji, J. Am. Chem. Soc., 2012, 134, 9106; (c) H. Tran-Vu and O. Daugulis, ACS Catal., 2013, 3, 2417; (d) T. Moragas, J. Cornella and R. Martin, J. Am. Chem. Soc., 2014, 136, 17702; (e) Y. Liu, J. Cornella and R. Martin, J. Am. Chem. Soc., 2014, 136, 11212; (f) K. Nogi, T. Fujihara, J. Terao and Y. Tsuji, Chem. Commun., 2014, 50, 13052; (g) X. Wang, Y. Liu and R. Martin, J. Am. Chem. Soc., 2015, 137, 6476; (h) K. Nogi, T. Fujihara, J. Terao and Y. Tsuji, J. Org. Chem., 2015, 80, 11618; (i) T. Mita, Y. Higuchi and Y. Sato, Chem.-Eur. J., 2015, 21, 16391; (j) M. Börjesson, T. Moragas and R. Martin, J. Am. Chem. Soc., 2016, 138, 7504; (k) F. Juliá-Hernández, T. Moragas, J. Cornella and R. Martin, Nature, 2017, 545, 84; (l) K. Shimomaki, K. Murata, R. Martin and N. Iwasawa, J. Am. Chem. Soc., 2017, 139, 9467; (m) Q.-Y. Meng, S. Wang and B. König, Angew. Chem., Int. Ed., 2017, 56, 13426.
- 5 For selected examples of carboxylation of nucleophiles with CO₂, see: (a) M. Shi and K. M. Nicholas, J. Am. Chem. Soc., 1997, **119**, 5057; (b) K. Ukai, M. Aoki, J. Takaya and N. Iwasawa, J. Am. Chem. Soc., 2006, **128**, 8706; (c) T. Ohishi, M. Nishiura and Z. Hou, Angew. Chem., Int. Ed.,

2008, 47, 5792; (d) H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu and K. Oshima, Org. Lett., 2008, 10, 2681; (e) C. S. Yeung and V. M. Dong, J. Am. Chem. Soc., 2008, 130, 7826; (f) L. Zhang, J. Cheng, T. Ohishi and Z. Hou, Angew. Chem., Int. Ed., 2010, 49, 8670; (g) I. I. F. Boogaerts and S. P. Nolan, J. Am. Chem. Soc., 2010, 132, 8858; (h) O. Vechorkin, N. Hirt and X. Hu, Org. Lett., 2010, 12, 3567; (i) K. Nemoto, H. Yoshida, N. Egusa, N. Morohashi and T. Hattori, J. Org. Chem., 2010, 75, 7855; (j) H. Mizuno, J. Takaya and N. Iwasawa, J. Am. Chem. Soc., 2011, 133, 1251; (k) Z. Xin, C. Lescot, S. D. Friis, K. Daasbjerg and T. Skrydstrup, Angew. Chem., Int. Ed., 2015, 54, 6862; (l) W.-Y. Gao, H. Wu, K. Leng, Y. Sun and S. Ma, Angew. Chem., Int. Ed., 2016, 55, 5472; (m) A. Banerjee, G. R. Dick, T. Yoshino and M. W. Kanan, Nature, 2016, 531, 215; (n) S. Fenner and L. Ackermann, Green Chem., 2016, 18, 3804; (o) J. Luo, S. Preciado, P. Xie and I. Larrosa, Chem.-Eur. J., 2016, 22, 6798; (p) K. Michigami, T. Mita and Y. Sato, J. Am. Chem. Soc., 2017, 139, 6094.

- 6 (a) A. L. Blobaum and L. J. Marnett, *J. Biol. Chem.*, 2007, 282, 16379; (b) J. E. Milne, T. Storz, J. T. Colyer, O. R. Thiel, M. Dilmeghani Seran, R. D. Larsen and J. A. Murry, *J. Org. Chem.*, 2011, 76, 9519; (c) R. D. Grigg, J. W. Rigoli, R. Van Hoveln, S. Neale and J. M. Schomaker, *Chem.-Eur. J.*, 2012, 18, 9391.
- 7 For selected examples, see: (a) H. L. Finkbeiner and G. D. Cooper, J. Org. Chem., 1962, 27, 3395; (b) C. M. Williams, J. B. Johnson and T. Rovis, J. Am. Chem. Soc., 2008, 130, 14936; (c) M. D. Greenhalgh and S. P. Thomas, J. Am. Chem. Soc., 2012, 134, 11900; (d) P. Shao, S. Wang, C. Chen and C. Xi, Org. Lett., 2016, 18, 2050; (e) S. Kawashima, K. Aikawa and K. Mikami, Eur. J. Org. Chem., 2016, 2016, 3166; (f) K. Murata, N. Numasawa, K. Shimomaki, J. Takaya and N. Iwasawa, Chem. Commun., 2017, 53, 3098; (g) V. R. Yatham, Y. Shen and R. Martin, Angew. Chem., Int. Ed., 2017, 56, 10915; (h) M. Gaydou, T. Moragas, F. Juliá-Hernández and R. Martin, J. Am. Chem. Soc., 2017, 139, 12161.
- 8 (a) T. León, A. Correa and R. Martin, J. Am. Chem. Soc., 2013, 135, 1221; (b) A. Correa, T. León and R. Martin, J. Am. Chem. Soc., 2014, 136, 1062; (c) S. Zhang, W.-Q. Chen, A. Yu and L.-N. He, ChemCatChem, 2015, 7, 3972; (d) T. Moragas, M. Gaydou and R. Martin, Angew. Chem., Int. Ed., 2016, 55, 5053.
- 9 L. Wu, Q. Liu, I. Fleischer, R. Jackstell and M. Beller, *Nat. Commun.*, 2014, 5, 3091.
- 10 (a) D. Seebach, Angew. Chem., Int. Ed., 1979, 18, 239; (b)
 N. Marion, S. Díez-González and S. P. Nolan, Angew. Chem., Int. Ed., 2007, 46, 2988; (c) X. Bugaut and F. Glorius, Chem. Soc. Rev., 2012, 41, 3511; (d) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, Chem. Rev., 2015, 115, 9307.
- 11 (a) T. Mita, J. Chen, M. Sugawara and Y. Sato, Angew. Chem., Int. Ed., 2011, 50, 1393; (b) T. Mita, J. Chen, M. Sugawara and Y. Sato, Org. Lett., 2012, 14, 6202; (c) T. Mita, M. Sugawara, H. Hasegawa and Y. Sato, J. Org. Chem., 2012, 77, 2159; (d) T. Mita, Y. Higuchi and Y. Sato, Chem.-Eur. J., 2013, 19,

1123; (e) A. A. Sathe, D. R. Hartline and A. T. Radosevich, *Chem. Commun.*, 2013, **49**, 5040; (f) T. Mita, Y. Higuchi and Y. Sato, *Org. Lett.*, 2014, **16**, 14; (g) T. Mita, J. Chen and Y. Sato, *Org. Lett.*, 2014, **16**, 2200; (h) T. Mita, M. Sugawara, K. Saito and Y. Sato, *Org. Lett.*, 2014, **16**, 3028; (i) C.-X. Guo, W.-Z. Zhang, H. Zhou, N. Zhang and X.-B. Lu, *Chem.-Eur. J.*, 2016, **22**, 17156.

- 12 S. Sun, J. T. Yu, Y. Jiang and J. Cheng, *J. Org. Chem.*, 2015, **80**, 2855.
- 13 (a) W.-J. Yoo and C.-J. Li, Adv. Synth. Catal., 2008, 350, 1503; (b) Z. Zhang, L.-L. Liao, S.-S. Yan, L. Wang, Y.-Q. He, J.-H. Ye, J. Li, Y.-G. Zhi and D.-G. Yu, Angew. Chem., Int. Ed., 2016, 55, 7068; (c) J.-H. Ye, L. Song, W.-J. Zhou, T. Ju, Z.-B. Yin, S.-S. Yan, Z. Zhang, J. Li and D.-G. Yu, Angew. Chem., Int. Ed., 2016, 55, 10022; (d) Z. Zhang, T. Ju, M. Miao, J.-L. Han, Y.-H. Zhang, X.-Y. Zhu, J.-H. Ye, D.-G. Yu and Y.-G. Zhi, Org. Lett., 2017, 19, 396; (e) Y.-Y. Gui, N. Hu, X.-W. Chen, L.-L. Liao, T. Ju, J.-H. Ye, Z. Zhang, J. Li and D.-G. Yu, J. Am. Chem. Soc., 2017, 139, 17011; (f) J.-H. Ye, M. Miao, H. Huang, S.-S. Yan, Z.-B. Yin, W.-J. Zhou and D.-G. Yu, Angew. Chem., Int. Ed., 2017, 56, 15416; (g) J.-H. Ye, L. Zhu, S.-S. Yan, M. Miao, X.-C. Zhang, W.-J. Zhou, J. Li, Y. Lan and D.-G. Yu, ACS Catal., 2017, 7, 8324; (h) Z.-B. Yin, J.-H. Ye, W.-J. Zhou, Y.-H. Zhang, L. Ding, Y.-Y. Gui, S.-S. Yan, J. Li and D.-G. Yu, Org. Lett., 2018, 20, 190; (i) L. Zhu, J.-H. Ye, M. Duan, X. Qi, D.-G. Yu, R. Bai and Y. Lan, Org. Chem. Front., 2018, 5, 633; (j) Z. Zhang, C.-J. Zhu, M. Miao, J.-L. Han, T. Ju, L. Song, J.-H. Ye, J. Li and D.-G. Yu, Chin. J. Chem., 2018, 36, 430; (k) L. Sun, J.-H. Ye, W.-J. Zhou, X. Zeng and D.-G. Yu, Org. Lett., 2018, DOI: 10.1021/acs.orglett.8b01079; (l) G. Shen,

W.-J. Zhou, X.-B. Zhang, G.-M. Cao, Z. Zhang, J.-H. Ye, L.-L. Liao, J. Li and D.-G. Yu, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC03039A.

- 14 (a) H. Wang, X.-J. Dai and C.-J. Li, *Nat. Chem.*, 2016, 9, 374;
 (b) N. Chen, X.-J. Dai, H. Wang and C.-J. Li, *Angew. Chem.*, *Int. Ed.*, 2017, 56, 6260; (c) X.-J. Dai, H. Wang and C.-J. Li, *Angew. Chem.*, *Int. Ed.*, 2017, 56, 6302; (d) W. Wei, X.-J. Dai, H. Wang, C. Li, X. Yang and C.-J. Li, *Chem. Sci.*, 2017, 8, 8193.
- 15 M. E. Furrow and A. G. Myers, *J. Am. Chem. Soc.*, 2004, **126**, 5436 and references therein.
- 16 (a) G. Spitzmaul, F. Gumilar, J. P. Dilger and C. Bouzat, Br. J. Pharmacol., 2009, 157, 804; (b) P. Urbani, M. G. Cascio, A. Ramunno, T. Bisogno, C. Saturnino and V. D. Marzo, Bioorg. Med. Chem., 2008, 16, 7510; (c) G. Autore, A. Caruso, S. Marzocco, B. Nicolaus, C. Palladino, A. Pinto, A. Popolo, M. S. Sinicropi, G. Tommonaro and C. Saturnino, Molecules, 2010, 15, 2028; (d) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu and J. Zhang, Angew. Chem., Int. Ed., 2017, 56, 2749.
- 17 (a) J. L. Jat, M. P. Paudyal, H. Gao, Q.-L. Xu, M. Yousufuddin,
 D. Devarajan, D. H. Ess, L. Kurti and J. R. Falck, *Science*,
 2014, 343, 61; (b) V. Bizet, L. Buglioni and C. Bolm, *Angew. Chem., Int. Ed.*, 2014, 53, 5639; (c) Y. Lin, L. Zhu, Y. Lan
 and Y. Rao, *Chem.-Eur. J.*, 2015, 21, 14937.
- 18 The activation free energy of cycloaddition between aminoruthenium C and CO_2 is up to 38.1 kcal mol⁻¹ (Fig. S3†), which suggests that the second N–H bond cleavage would be preferentially occur from amino-ruthenium C.
- 19 For more computational details, please see in ESI.†
- 20 A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, 88, 899.