Quadri-Synergetic Effect for Highly Effective Carbon Dioxide Fixation and Its Application to Indologuinolinone

Suhua Li^a and Shengming Ma^{a,b,*}

^a State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China Fax: (+86)-21-6260-9305; e-mail: masm@sioc.ac.cn

^b Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai 200062, People's Republic of China

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Abstract: The first copper-catalyzed cyclic *anti*-nucleometallation–carboxylation of 2-alkynylanilines with carbon dioxide in the presence of dimethylzinc (ZnMe₂) and cesium fluoride (CsF) for the effective synthesis of indolyl-3-carboxylic acids and indolodihydropyran-2-one is described. Through a mechanistic study, it is unveiled that the metal ions Cu²⁺, Zn²⁺, Cs⁺ and F⁻ are working together for this CO₂based highly efficient carboxylation.

Keywords: alkynes; carbon dioxide; carboxylation; copper; nucleometalation

Much attention has been paid to the reactivity of CO₂ recently for the sake of environmental reasons and its abundant, inexpensive, and non-toxic features as a C₁ synthon.^[1] Challenges are its thermodynamic and kinetic stability. With more than ten years endeavor, there are mainly two types of transition metal-catalyzed carboxylation reactions by using CO₂ to form new carbon-carbon bonds: (i) the carboxylation of less reactive organometallic reagents $(Sn,^{[2]} B,^{[3]} Zn^{[4,5]})$, aryl bromides,^[6] arenes,^[7] and terminal C–H bonds of alkynes^[8] affording carboxylic acids [Scheme 1, Eq. (1)] and (ii) the carboxylation of carbon-carbon multiple bonds of alkenes,^[9] alkynes,^[10] and allenes^[11] [Scheme 1, Eq. (2)].^[12,13] On the other hand, anti-nucleometallation of carbon-carbon multiple bond is a key transformation in many transition metal-mediated syntheses.^[14,15] However, there is no report on reactions of this type involving in situ generated vinylic metallic intermediates with carbon dioxide.^[16] Here, we would like to report the first example on such a concept for the synthesis of indolecarboxylic acid derivatives.^[17]

$$R-M, R-X, R-H \longrightarrow R-COOH$$
(1)



Scheme 1. Carboxylation reactions with CO₂.

It is well known that the aza-metallation of o-(1-alkynyl)anilines would afford indoles.^[18-21] By taking the intermediate **B** formed from the cyclic anti-azametallation of alkynes as the starting point, its reaction with CO₂ under the reported protocols for the indole synthesis from 2-alkynylanilines was attempted (Table 1, entries 1–4).^[18–21] Unfortunately, no indolecarboxylic acid 2a was formed indicating the low reactivity of intermediate C (M=Rh, Hg) towards CO_2 . It is surprising that no carboxylation occurred even with $Cu(OAc)_2^{[21]}$ although the are many reports Cu-catalvzed CO₂-based carboxylation on reaction!^[3b-e,7b,c,8a,b,d,10c]

Thus, we started to identify such an intermediate C, which would have a much higher reactivity towards CO_2 . Recently, there are some reports on the carboxylation of zinc reagents with CO_2 producing related carboxylic acids under the catalysis of nickel or palladium or promoted by LiCl.^[4,5] Interestingly, when **1a** was reacted with 3 equivalents of $ZnEt_2$ in DMF under the atmosphere of CO_2 for 24 h, the expected product **2a** was indeed formed albeit in only 8% yield together with 65% of the aza-metallation-protonolysis product **3a**. The reaction was slightly improved by adding 1.5 equivalents of CsF. In the presence of

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Table 1. Attempted reactions of intermediate C with CO₂.



Entry	Catalyst	Solvent	Temperature [°C]	NMR yield [%]		Ref.
	2			2a	3 a	
1 ^[a,b]	_	toluene	reflux	0	53	[18]
2 ^[c,d]	Rh	toluene	100	0	92	[19]
3 ^[d]	$Hg(OTf)_{2}^{[e]}$	CH_2Cl_2	rt	0	100	[20]
4 ^[b]	$Cu(OAc)_2^{[f]}$	DCE	reflux	0	99	[21]

^[a] 1.2 equiv. of $ZnEt_2$ were used.

^[b] The reaction time was 24 h.

^[c] 5 mol% of Rh(CO)₂acac and 5.5 mol% of *rac*-BINAP were used. Toluene/H₂O = 10/1.

^[d] The reaction time was 17 h.

[e] 5 mol%.

^[f] 20 mol%.



^[a] No CsF was added.

Scheme 2. Effect of zinc reagent.

5 mol% of Cu(OAc)₂, the reaction afforded very similar results. Surprisingly, the selectivity of **2a** *vs.* **3a** was dramatically improved when $ZnMe_2$ was used instead of $ZnEt_2$ (Scheme 2)!

Such a reaction in DMSO, THF, or MeCN afforded the carboxylation product 2a in 75–79% yield together with 5–20% of cycloisomerization product 3a (entries 1–3, Table 2). Other copper salts, such as Cu(OTf)₂, CuI, CuBr, CuCl, were tested and no better result was observed (entries 4–7). Reducing the amount of ZnMe₂, CsF and catalyst loading resulted in diminished yields (entries 8–10). Other protecting groups were also been examined: when Boc was used, 44% of carboxylic acid was produced. The substrates with an Ac or a trifluoroacetyl group produced a complicated mixture.

Next, the scope of the reaction was studied under the standard conditions (Table 3). Various substituted groups \mathbf{R}^1 at the terminal position of the alkynes moiety such as aryl (entries 1 and 2), thienyl (entry 3), alkenyl (entry 4), benzyl (entry 5), and alkyl (entries 6-10) were tested producing excellent yields of the corresponding indole-3-carboxylic acids. When R^2 is the electron-donating methoxy group, carboxylic acid 2q could also be produced in 92% yield (entry 15). 2-Alkynylanilines with a ketonic carbonyl group in \mathbb{R}^1 (entry 6), halogen (entries 11, 12, and 14) and ester (entry 13) functionality in \mathbb{R}^2 or \mathbb{R}^3 of the aryl group could also work very well in this reaction, leaving further opportunity for elaboration without protection and deprotection. The reaction can be conducted using 3 mmol (1.1 g) of **1h** to produce **2h** in

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	NHTs 1a	cat. (5 mol%), CsF (1.5 equiv.) ZnMe ₂ (3 equiv), CO ₂ balloon, solvent, 55 °C, 3 h	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \\ \end{array} $	—Ph
Entry	Cat.	Solvent	Yield [%] of 2a ^[b]	Yield [%] of 3a ^[b]
1	$Cu(OAc)_2$	DMSO	79	5
2	$Cu(OAc)_2$	THF	78	9
3	$Cu(OAc)_2$	CH ₃ CN	75	20
4	$Cu(OTf)_2$	DMF	83	13
5	CuÌ	DMF	85	11
6	CuBr	DMF	79	16
7	CuCl	DMF	83	14
8 ^[c]	$Cu(OAc)_2$	DMF	76	5
9 ^[d]	$Cu(OAc)_2$	DMF	83	12
10 ^[e]	$Cu(OAc)_2$	DMF	82	8

Table 2. Optimization of reaction conditions.^[a]

^[a] The reaction was carried out with 0.5 mmol of **1a**, Cu (5 mol%), CsF (1.5 equiv.), ZnMe₂ (1.2 M in toluene, 1.25 mL, 1.5 mmol), and a balloon of CO₂ (about 1 L) in 3 mL of the indicated solvent at the indicated temperature.

^[b] NMR yield.

^[c] 2 equiv. of ZnMe₂ were used instead of 3 equiv. of ZnMe₂.

^[d] 1 equiv. of CsF was used.

[e] $3 \mod \%$ of Cu(OAc)₂ were used.

Table 3. Synthesis of indolyl-3-carboxylic acid from 2-alkynylanilines.^[a]



Entry		Yield [%] of 2 ^[b]		
	\mathbf{R}^1	\mathbf{R}^2	R^3	
1	Ph	Н	H (1a)	94 (2a)
2	p-MeOC ₆ H ₄	Н	H (1b)	90 (2b)
3	2-thienyl	Н	H (1c)	91 (2c)
4	1-cyclohexenyl	Н	H (1d)	96 (2d)
5	Bn	Н	H (1e)	94 (2e)
6	CH_2CH_2Ac	Н	$H(\mathbf{1f})$	87 (2f)
7	<i>n</i> -Bu	Н	H (1 g)	92 (2 g)
8	CH ₂ OBn	Н	$H(1\mathbf{h})$	90 (2h)
9 ^[c]	CH ₂ OBn	Н	H (1h)	86 (2h)
10	CH_2Cy	Н	H (1i)	94 (2i)
11	<i>n</i> -Bu	F	$H(\mathbf{1j})$	93 (2j)
12	<i>n</i> -Bu	Cl	$H(1\mathbf{k})$	97 (2k)
13	<i>n</i> -Bu	CO_2Me	H(1)	92 (2I)
14	<i>n</i> -Bu	Cl	F (1m)	95 (2m)
15	<i>n</i> -Bu	OMe	H (1q)	92 (2q)

[a] The reaction was carried out with 0.5 mmol of 1, Cu(OAc)₂ (5 mol%), CsF (1.5 equiv.), ZnMe₂ (1.2M in toluene, 1.25 mL), and a balloon of CO₂ (about 1 L) in 3 mL of DMF at 55 °C.

^[b] Isolated yield.

^[c] The reaction was conducted using 3.0 mmol (1.174 g) of 1 h.

86% yield (entry 9), which showed the practicality of this reaction. The structure of **2d** was confirmed by its X-ray diffraction study (Figure 1, *left*).^[22]

Six-membered lactones are widely present as structural subunits in a large number of natural compounds showing important biological activities.^[23]

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Figure 1. ORTEP plot of 2d (left) and 4o (right) shown with ellipsoids at the 30% probability level.

From the structure of **2**, we envisioned that if there is a hydroxy group in \mathbb{R}^1 , lactones may be formed after *anti*-amino carboxylation followed by lactonization from **1n–p**. To our delight, when the substrate **1n** was used in this reaction, indolodihydropyran-2-one **4n** could be produced efficiently by this method. Substituents in the α -position of hydroxy group in 2-alkynylanilines **10** and **1p** such as methyl and phenyl (Scheme 3) were examined yielding **40** and **4p** in good to excellent yields. The structure of **40** was confirmed by an X-ray diffraction study (Figure 1, *right*).^[24] With the combination of indole and lactone, this type of compounds will be potentially useful in medicinal chemistry.

In order to show the potential of this protocol, an indoloquinolinone exhibiting cytotoxic activity^[25] was selected as our target (Scheme 4).^[26] Symmetric diamide **6** was synthesized from 2-iodoaniline and 2-ethynylaniline *via* Sonogashira coupling followed by double tosylation. The cyclizative carboxylation of **6** (5.17 g, 10 mmol) was then conducted under the standard reaction conditions which was followed by treatment with EDCI and detosylation with Na/naphthalene to afford 1.4 g (61% yield for the three steps) of indoloquinolinone with a single run, indicating the practicality of this method.

After addition of two equivalents of $ZnMe_2$ (1.2M in toluene) to the solution of **1a** in DMF- d_7 at room temperature, the signal at 10 ppm for NH disappeared, indicating that that the proton on the nitrogen was deprotonated by ZnMe₂ rapidly. To further probe the mechanism of this reaction, three experiments were conducted in the absence of CO_2 (Scheme 5). The reaction of 1a with ZnMe₂ in the presence of 5 mol% Cu(OAc)₂ and 1.5 equivalents of CsF in DMF for 5 min followed by quenching with D₂O provided the protonolysis product 3a-d in 34% with D incorporation of 58% while the same reaction in the absence of $Cu(OAc)_2$ afforded **3a**-d in 32% yield with 97% of D incorporation after 3 h (Scheme 5), indicating that the reactivity of such intermediate C with Cu is much higher: The low D incorporation in the presence of $5 \mod Cu(OAc)_2$ must be caused by the faster protonation of this highly reactive intermediate C with DMF. This was confirmed by running the reaction in DMF- d_7 affording **3a**-d with 89% D incorporation.

In addition, several control experiments were conducted as shown in Table 4. The reaction could not work well if any one reagent, $Cu(OAc)_2$, CsF, and ZnMe₂, was removed from the catalytic system (Table 4, entries 1–3). In addition, it was observed



Scheme 3. Synthesis of indolodihydropyran-2-ones.

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Scheme 4. Synthesis of indoloquinolinone.



Scheme 5. Studies on the formation and reactivity of the indolyl intermediate C.

that CsF or ZnMe₂ may both alone promote the formation of **2a**, albeit in very low yields (5-9%)(Table 4, entries 5 and 6) while with Cu(OAc)₂ (5 mol%) alone, the formation of **2a** was not observed, however, intermediate **C** was formed highly efficiently: the reaction afforded the cycloisomerization product **3a** in 98% yield (entry 4), indicating that indolyl metal intermediates **C-Cs** and **C-Zn** react very slowly with CO₂ and intermediate **C-Cu** shows no reactivity (Scheme 6). In addition, it should be noted that the combined reagent of copper and zinc **C-Zn-Cu** is more reactive than **C-Zn** or **C-Cu**, which is consistent with the observation by Knochel et al.^[27] that copper-zinc reagents demonstrate higher reactivity towards electrophiles such as aldehydes, acid chlorides, enones, allylic bromides as compared to the corresponding zinc reagents. However, it is still not very effective towards CO_2 in this reaction (Table 4, entry 3).

Furthermore, it was observed that CsF may be replaced with KF affording **2a** in a lower yield of 82%, showing that Cs⁺ also plays an important role ensuring a better reactivity of intermediate **C** towards CO₂ (compare Scheme 2 with entry 7 in Table 4); when CsF was replaced with Cs₂CO₃, the yield of **2a** is also lower [85% *vs.* 96%, (compare Scheme 2 with entry 8 in Table 4)], indicating the effect of F⁻ for CO₂ activation *via* its reaction with CO₂ forming FCO₂⁻ to increase the reactivity of the C=O bond in CO₂.^[3a,b,10d,e,28]

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	NHTs 1a	Cu(OAc) ₂ (8 CsF (1.5 eq ZnMe ₂ (3 e DMF, 58 CO ₂ ballo	5 mol%), uiv.) HCl equiv.), 5 °C pon, <i>t</i>	COOH N Ts 2a	H N Ts 3a	
Entry	Cu(OAc) ₂	CsF	ZnMe ₂	Time t [h]	NMR Yield 2a	d [%] 3a
1	××		\checkmark	24	20	49
2	\checkmark		×	24	5	83
3		×		24	23	50
4		×	×	24	0	98
5	×		×	28	5	34
6	×	×		24	9	64
7	\checkmark	KF ^[a]	, V	24	82	7
8		$Cs_2CO_3^{[b]}$, V	24	85	5
9	×	$KF^{[a]}$		24	18	43
10	×	$Cs_2CO_3^{[b]}$		24	14	42

Table 4. Control experiments for mechanistic study.

^[a] 1.5 equiv. of KF were used instead of CsF.

^[b] 1.5 equiv. of Cs₂CO₃ were used instead of CsF.



Scheme 6. Reactivities of different indolyl metal intermediates towards CO₂

Thus, it is concluded that the three metals Cu, Cs and Zn are working together for the efficient formation as well as smooth reaction of intermediate C towards CO₂ in the current high-yielding carboxylation reaction with the additional help from F⁻ activating CO_2 (Scheme 7).



Scheme 7. A plausible mechanism.

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this laboratory.

In conclusion, we have developed an efficient

Cu(OAc)₂-catalyzed synthesis of indole-3-carboxylic acid and indolodihydropyran-2-one from the readily

available2-alkynylanilines with CO₂ in the presence of ZnMe₂ and CsF. It is the first example of an anti-nu-

cleometallation of carbon-carbon triple bonds-carboxylation reaction based on CO₂ activation. This concept may be applied to other nucleometallation reactions. Although the structural nature of the in-situ generated highly reactive intermediate C surely needs

further attention, the formation and reactivity infor-

mation of metallic reagents unveiled here may be useful for the design of new reactions of carbon diox-

ide. Further studies in this area are being pursued in

Note added in proof: Very recently, Inamoto et al. reported the synthesis of indolyl-3-carboxylic acids from o-(1-alkynyl)anilines by using 10 equivalents of K₂CO₃ under 10 atm CO₂ without any transition metal catalyst, see: K. Inamoto, N. Asano, Y. Nakamura, M. Yonemoto, Y. Kondo, *Org. Lett.* **2012**, *14*, 2622–2625.

Experimental Section

Typical Procedure for the Preparation of 2-Phenyl-1tosyl-1*H*-indole-3-carboxylic Acid (2a, Table 3, entry 1)

To an oven-dried Schlenk tube were added 2-alkynylaniline **1a** (173.8 mg, 0.500 mmol), Cu(OAc)₂ (4.5 mg, 0.025 mmol), CsF (114.1 mg, 0.751 mmol), and 3 mL of DMF under an argon atmosphere. The mixture was immediately frozen with a liquid nitrogen bath and the argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L). Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added ZnMe₂ (1.2 M in toluene, 1.25 mL, 1.5 mmol) with a syringe. Then the resulting mixture was stirred at 55°C with a preheated oil bath for 3 h as monitored by TLC. After that, the resulting mixture was quenched with 3M HCl. The aqueous layer was extracted with EtOAc $(5 \text{ mL} \times 5)$ and the combined organic layer was washed with water (5 mL×2) and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to $DCM/CH_3OH = 20/1$) to afford **2a** as a white solid; yield: 183.5 mg (94%); mp 230-231 °C (petroleum ether/ethyl acetate); ¹H NMR (300 MHz, DMSO- d_6): $\delta = 12.62$ (bs, 1 H, CO_2H), 8.22 (d, J=8.1 Hz, 1H, ArH), 8.11–8.07 (m, 1H, ArH), 7.54–7.29 (m, 11 H, ArH), 2.32 (s, 3 H, Me); ¹³C NMR (75 MHz, DMSO- d_6): $\delta = 164.4$, 145.8, 144.5, 135.5, 134.4, 131.0, 130.5, 130.1, 129.0, 127.5, 127.0, 126.6, 125.6, 124.7, 121.8, 114.9, 114.1, 21.0; MS: m/z = 391 (M⁺, 1.18), 91 (100); IR (neat): v = 3400-2300 (br), 1669, 1598, 1549, 1479, 1445, 1374, 1302, 1264, 1241, 1214, 1188, 1170, 1120, 1106, 1088, 1051, 1028 cm⁻¹; anal. calcd. for C₂₂H₁₇NO₄S: C 67.50, H 4.38, N 3.58; found: C 67.56, H 4.50, N 3.36.

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