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Direct C-2 carboxylation of 3-substituted-indoles using a combined Brønsted base consisting of LiO-*t*-Bu/CsF/18-crown-6

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Abstract: Herein, we report that a combination of LiO-*t*-Bu, CsF, and 18-crown-6 can be used to carry out the carboxylation of indole derivatives at the C-2 position under an ambient CO_2 atmosphere. Substrates bearing an electrophilic substituent (i.e., cyano, formyl, benzoyl, phenylsulfonyl, phenylsulfinyl, and chloride) at the C-3 position are smoothly converted into their corresponding carboxylated products with high functional group compatibility.

Indoles constitute the core motif of a wide range of natural compounds, pharmaceuticals, and functional organic materials.¹ Indole 2-carboxylic acid derivatives are a particularly important family among them, which find widespread use in biologically active compounds and as synthetic precursors for their synthesis.² Accordingly, the development of competent synthetic methodology is highly desirable. C-H bond carboxylation of indoles at the C-2 position using CO2 as a low-cost, abundant, and non-toxic C1 unit has been used for this purpose.³ Conventionally, strong Brønsted bases such as BuLi, i-Pr₂NLi, and (i-Pr₂N)₂Mg have been used in the reaction, which consists of a two-step protocol including the deprotonation of the C-H bond at the C-2 position and subsequent carboxylation of the resulting 2-lithioand 2-magnesio-indole intermediates (Table 1a).⁴ However, the functional group tolerance of this reaction is rather limited, owing to the use of these strong bases and the preparation of the reactive carbanion intermediates. Transition metal catalysis has been employed for direct carboxylation using a one-step reaction (Table 1b). Takaya, Iwasawa, et al. have reported that rhodium catalyzes the carboxylation of 1-methylindole in the presence of AIMe_{1.5}(OEt)_{1.5}, however, the scope of the indole substrate used in the reaction was not demonstrated.⁵ Thus, further development of an efficient and practical carboxylation reaction with high functional group compatibility is of great interest in organic chemistry.6-9

Recently, the direct carboxylation of (hetero)aromatic substances using Brønsted bases, wherein the (hetero)aromatic carbanion species generated via deprotonation is trapped in situ with CO_2 , has been thoroughly investigated (Figure 1c).^{10–12} This methodology is attractive in terms of its potential to expand the substrate scope and functional group tolerance, and also benefits from its operational simplicity. Among these reactions, Kobayashi et al. demonstrated that the carboxylation of NH-indoles takes place at the C-3 position in the presence of LiO-*t*-Bu via deprotonation of the N–H bond (Figure 1, i).¹¹ However, no reports have described the application of this system to the carboxylation



(b) Direct carboxylation using transition-metal catalysis Takaya & Iwasawa's work





(c) Direct carboxylation using Brønsted bases

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$$\begin{array}{c} H \\ Ar \end{array} \xrightarrow{\text{Brønsted base}} CO_2 H \\ \hline Ar \end{array}$$

(i) Heteroaromatic substrates used in previous reports



(ii) This work: LiO-t-Bu/CsF/18-crown-6 mediated carboxylation of 3-substituted-indoles



Figure 1. C–H carboxylation of indoles at the C-2 position and those related to this study.

of indoles at the C-2 position.

We previously reported that a combined Brønsted base system consisting of LiO-*t*-Bu/CsF/18-crown-6 can be successfully used for the carboxylation of electron-rich heteroarenes, such as benzothiophene and benzofuran derivatives (Figure 1, i).¹² Herein, we found that this system can efficiently carry out the C-2 carboxylation of indole substrates bearing an electron-withdrawing group (i.e., cyano, aldehyde, ketone, sulfonyl, sulfinyl, and chloride) at the C-3 position (Figure 1, ii). Substituents on the benzene ring of the indole are

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compatible in the reaction, which include methyl, methoxy, methylthio, fluorine, chlorine, bromine, iodine, and nitro groups.

This study began by optimizing the carboxylation conditions using 3-cyano-1-methylindole **1a** as a model substrate (Table 1). A mixture of **1a** (0.30 mmol), alkoxide base (0.90 mmol), and additive(s) (0.90 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI) (1.5 mL) was stirred at 100 °C under an ambient CO₂ atmosphere. After 15 h, the reaction mixture was treated with methyl iodide at 60 °C. A standard extractive work-up afforded the crude product, which was used to determine the yield of the target carboxylated product **2a** using NMR spectroscopy. The use of LiO-*t*-Bu afforded **2a**, albeit in 7% yield (entry 1). The addition of CsF improved the product yield to 28% (entry 2). Furthermore, employing 18-crown-6 in the reaction provided **2a** in 82% yield (entries 3–5). The use of LiO-*t*-Bu/CsF/18-crown-6 was essential in the reaction (entries 6 and 7). Moreover, decreasing the amount

Table 1. Optimization of the reaction conditions used in the carboxylation of 1a.^{a,}

1. Alkoxide base (3.0 equiv.) Additive(s) (3.0 equiv.)

DMI, 100 °C, 15 h

co.

of these reactants (2 equiv.) reduced the product yield (entry 8), while the use of other alkoxide bases (NaO-*t*-Bu, KO-*t*-Bu, and LiOMe) or alkali-metal halides (RbF, CsCl, and CsI) was not as effective (entries 9–14).¹³ Finally, when the reaction temperature was increased to 120 °C, product **2a** was isolated in 97% yield (entry 15). When the reaction was scaled up to 1.0 mmol, a high yield of **2a** was still observed (entry 16).

With the optimized conditions for the carboxylation reaction in hand, we next examined the substrate scope using 3-cyanoindoles (Figure 2). Substrates **1b-d** bearing electron-donating methyl, methoxy, and methylthio groups, were used in the reaction and their corresponding carboxylated products were prepared in 85, 95, and 87% yields, respectively. Halogen-substituted indoles **1e-h** with F, Cl, Br, and I in the 5-position also yielded their corresponding carboxylated products in excellent yields (90, 92, 99, and 96%, respectively). The reactions of **1i** and **1j**, which contain a chloride atom at the 6- and 7-positions, respectively, also proceeded in high yields. Substrates **1k-n** containing benzyl, methoxymethyl, phenyl, and 2-pyridyl groups on the nitrogen atom were investigated in the reaction and afforded the desired products in high yields (91, 94, 90, and 88%, respectively).

N N	2. Me	el (3.0 equiv.)	N - N		,	
Me 1a Entry	(1 atm)	Additive(s)	Za Yield of 2a		CN	CN 1. LiO- <i>t</i> -Bu (3.0 equiv.) CsF (3.0 equiv.) 18-crown-6 (3.0 equiv.) Divide 100 900 400
	AIRONIGE DOSE	Additive(3)	(%) ^b		$R' + M + CO_2$	$R' + H + CO_2$ DMI, 120 °C, 15 h 2. Mel (3.0 equiv.) 60 °C, 2 h
1	LiO- <i>t</i> -Bu	_	7		1 (1 atm	1 (1 atm)
2	LiO- <i>t</i> -Bu	CsF	28		CN	CN CN CN
3	LiO- <i>t</i> -Bu	CsF, 12-crown-4	21		Me CO ₂ Me	
4	LiO- <i>t</i> -Bu	CsF, 15-crown-5	51		Me 2b 85%	Me Me 2b 85% 2c 95%
5	LiO- <i>t</i> -Bu	CsF, 18-crown-6	82		, 00 %	
6	LiO- <i>t</i> -Bu	18-crown-6	6		CO ₂ Me	
7	-	CsF, 18-crown-6	0		Me 2e 90%	Me Me 2e 90% 2f 92%
8	LiO- <i>t</i> -Bu (2 equiv.)	CsF (2 equiv.), 18- crowp-6 (2 equiv.)	65	1	CN	CNCN
q	NaO- <i>t</i> -Bu	CsE 18-crown-6	38		CO ₂ Me	
10	KO-t-Bu	CsE 18-crown-6	43		We Me	Me Me
10	LiOMa		45		2h, 96%	2h, 96% 2i, 94%
10			V 67		CN	CN CN
12			07		N N	CO ₂ Me CO ₂ Me
13	LIO- <i>t</i> -Bu	CsCi, 18-crown-6	8		Bn 2k 91%	Bn MOM
14	LiO- <i>t</i> -Bu	Csl, 18-crown-6	1		ÇN	CN
15	LiO- <i>t</i> -Bu	CsF, 18-crown-6	quant. (97) ^{c,d}		CO ₂ Me	CO ₂ Me
16	LiO- <i>t</i> -Bu	CsF, 18-crown-6	(95) ^{d,e}			N N

CO₂Me

^aCarboxylation: **1a** (0.30 mmol), CO₂ (1 atm), alkoxide base (0.90 mmol), additive(s) (0.90 mmol), DMI (1.5 mL), 100 °C, 15 h. Methyl esterification: MeI (0.90 mmol), 60 °C, 2 h. ^bThe yield of **2a** was determined using ¹H NMR spectroscopy with 1,1,2-trichloroethane as an internal standard. The reaction was conducted at 120 °C. ^cThe yield reported in the parenthesis denotes the isolated yield. ^eCarboxylation: **1a** (1.0 mmol), CO₂ (1 atm), LiO-*t*-Bu (3.0 mmol), CSF (3.0 mmol), 18-crown-6 (3.0 mmol), DMI (5.0 mL), 120 °C, 15 h. Methyl esterification: MeI (3.0 mmol), 60 °C, 2 h.

2n, 88%^d

Figure 2. Scope of 3-cyanoindoles used in the carboxylation reaction.^{*a, b a*}The reactions were conducted on a 0.3 mmol scale. ^{*b*}The isolated yields are reported. ^cThe reaction was conducted at 140 °C. ^{*d*}The reaction was conducted at 130 °C.

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The reaction system was then extended to the reaction of 3substituted-indoles bearing an electron-withdrawing group other than a cyano group (Figure 3). 1-Methyl-3-formylindole 3a was used in the carboxylation and furnished the target product 4a with the formyl moiety tolerated in the reaction. Its derivatives 3b-f, which comprise methoxy, chloro, bromo, iodo, and nitro groups, underwent the carboxylation reaction to give their corresponding products in good yields (91, 94, 97, 94, and 93%, respectively). 3-Formyl-7-azaindole 3g was also used in the reaction and produced its corresponding carboxylated product in 82% yield. In these reactions, side reaction of self-condensation, wherein the deprotonatively formed indoyl carbanion species adds onto the formyl moiety of another molecule, was not observed. This is presumably ascribed to the relatively low reactivity (electrophilicity) of the formyl group compared to that of CO₂, owing to the presence of the electron-rich indoyl substituent,¹⁴ and/or ascribed to the protection of the formyl moiety as a hemiacetal form in the reaction with the *tert*-butoxide base.¹⁵ Then. the reaction of 3-benzovl-1-methylindole 3h was carried out and afforded product 4h in 66% yield. When substrates 3i and 3j bearing phenylsulfonyl and phenylsulfinyl groups were examined. the target products were obtained in 77 and 91% yields, respectively. 3-Chloro-substituted indole 3k also furnished the carboxylated product in 81% yield.16



Figure 3. Scope of 3-substituted indoles bearing an electron-withdrawing group used in the carboxylation reaction.^{*a, b*} ^aThe reactions were conducted on a 0.3 mmol scale. ^{*b*}The isolated yields are reported. ^cThe reaction was conducted at 150 °C. ^{*a*}The reaction was conducted at 160 °C. ^{*b*}The reaction was conducted at 180 °C.

Carboxylations of 3-formyl-substitued-heteroaromatic substrates, other than the indole, were also tested (Figure 4). Thus, when benzothiophene, benzofuran, and pyrrole derivatives

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Figure 4. Carboxylations of 3-formyl-substitued-heteroarenes other than the indole.^{*a, b a*}The reactions were conducted on a 0.3 mmol scale. *b*The isolated yields are reported. *c*The reaction was conducted at 80 °C. *d*The reaction was conducted at 130 °C.

5a-c were employed in the reactions, the desired carboxylated products were produced in 93, 86, and 52% yields, respectively.

The reaction was confirmed to proceed via the formation of a *tert*-butyl carbonate species (Scheme 1). When the reaction of **1a** was carried out in the presence of [LiOCO₂-*t*-Bu], CsF, and 18-crown-6 under an Ar atmosphere, the carboxylated product **2a** was obtained in 92% yield. The compatibility of the weak aromatic carbon–halogen bonds (i.e., C–Br and C–I)¹⁷ in substrates **1g**, **1h**, **3d**, and **3e** was a result of the in situ generation of the weaker Brønsted base of the carbonate base derived from *tert*-butoxide.¹⁸



Scheme 1. Carboxylation of **1a** using [LiOCO₂-*t*-Bu], CsF, and 18-crown-6 under an Ar atmosphere.^{*a*, *b*, *a*}The reaction was conducted on a 0.3 mmol scale. *b*Isolated yield.

The proposed mechanism for the carboxylation reaction is depicted in Scheme 2. The carbonate base $[MOCO_2-t-Bu]$ (M = Cs coordinated by 18-crown-6) or *tert*-butoxide [MO-t-Bu], which are in the equilibrium under a CO₂ atmosphere, deprotonates **1a** at the C-2 position to form indoyl carbanion species **A**.^{18, 19} Subsequent reaction of **A** with CO₂ occurs to furnish carboxylated product **B**.



Scheme 2. Proposed mechanism for the carboxylation reaction.

In summary, direct carboxylation of a variety of indole derivatives efficiently takes place at the C-2 position using a combined Brønsted base consisting of LiO-*t*-Bu, CsF, and 18-crown-6. An electron-withdrawing substituent at the C-3 position,

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such as a cyano, formyl, benzoyl, phenylsulfonyl, phenylsulfinyl, and chloride group, facilitates the reaction. The system displays high functional group tolerance on the benzene ring of the indole (i.e., Me, MeO, MeS, F, Cl, Br, I, and NO₂).

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Keywords: • Indoles • Carbon dioxide fixation • C1 building blocks • Brønsted base • C–H functionalization

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Entry for the Table of Contents

Key Topic: Indole carboxylation



A combination of LiO-*t*-Bu, CsF, and 18-crown-6 can be used to carry out the carboxylation of indole derivatives at the C-2 position under an ambient CO₂ atmosphere. Substrates bearing an electrophilic substituent (i.e. CN, formyl, benzoyl, phenylsulfonyl, phenylsulfinyl, and chloride) at the C-3 position are smoothly converted into their corresponding carboxylated products with high functional group compatibility.