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Letter

Catalytic Carboxylation of Heteroaromatic Compounds: Double and Single Carboxylation with CO₂

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Abstract In the presence of PdCl₂[P(*n*-Bu)₃]₂ (10 mol%) and ZnEt₂, 2furyl and 2-pyrrolylmethyl acetate were carboxylated with CO₂ (1 atm), affording doubly carboxylated products in good yields. In this dearomative transformation, α , ε -dicarboxylic acids were obtained selectively, in contrast to our previous report in which α , γ -dicarboxylic acids were selectively produced from 2-indolylmethyl acetates. In contrast, 5-thiazolylmethyl acetate and naphthylmethyl acetates predominantly underwent single carboxylation.

Key words carboxylation, CO_2 , dearomatization, palladium, furan, pyrrole

Catalytic carboxylation of stable heteroaromatics with CO_2^{-1} is a powerful tool for the synthesis of heteroaromatic carboxylic acids.²⁻⁴ These carboxylic acids can be employed as synthetic precursors for many biologically active molecules because the carboxylic group is readily manipulated into pharmacologically important amidine, lactam, and lactone units. Among the reported routes for CO₂ fixation into heterocyclic compounds, one molecule of CO₂ is generally incorporated.²⁻⁴ However, we recently discovered that two CO₂ molecules could be incorporated into indole derivatives simultaneously;52-indolylmethyl acetates were doubly carboxylated at the α -and γ -positions via nucleophilic η^1 -allylpalladium and enamine species in the presence of the electron-rich palladium complex, PdCl₂[P(*n*-Bu)₃]₂, and ZnEt₂ (Scheme 1).⁵ Encouraged by this double carboxylation, we then considered that the extended ε-position might also be carboxylated when furan and pyrrole derivatives lacking the aryl moiety were employed. Given that catalytic double carboxylation using CO₂ has been very limited,⁶ a new type of catalytic double carboxylation of diverse substrates, without using highly nucleophilic arylmagnesium or lithium reagents, which are incompatible with several functional groups,⁷ is in high demand. We herein describe a catalytic double carboxylation of furan and pyrrole derivatives by using our established Pd/ZnEt₂ system^{5,8} through a dearomative process.⁹ In cases in which dearomatization did not proceed, which depended on the substrate employed, single carboxylation proceeded predominantly. We explain herein both catalytic transformations in detail.





We first investigated the carboxylation of furan derivatives (Table 1). 2-Furylmethyl acetate **1**, which can be readily prepared from the corresponding 2-furfuryl alcohol, was employed as a standard substrate. By following the previously established conditions,⁵ we utilized $PdCl_2[P(n-Bu)_3]_2$ (10 mol%), an air- and moisture-stable Pd complex, and $ZnEt_2$ (3.0 equiv) in DMF under 1 atm of CO₂ atmosphere. When the reaction was conducted at room temperature, doubly carboxylated compound **2** was obtained in 8% yield

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together with recovery of 1 in 23% yield (entry 1). The obtained product was the α,ε -dicarboxylate **2**, which highlighted the different reactivity compared with the double carboxylation of 2-indolylmethyl acetate, in which α,γ -dicarboxylates were selectively produced (see above).⁵ When the reaction temperature was raised to 40 °C, the yield increased to 44% (entry 2). However, further increasing the temperature did not give any improvement (entries 3 and 4). In addition, a shorter reaction time (4 h) gave a lower yield (entry 5). A higher pressure of CO_2 (10 atm) resulted in a similar yield (entry 6). Without the Pd catalyst, the carboxvlation did not proceed and 1 was recovered in 56% yield (entry 7). Changing the solvent from DMF to DMA increased the yield and 2 was obtained in 50% isolated yield (entry 8). Neither a higher temperature with DMA (60 °C) nor changing the solvent to THF was effective (entries 9 and 10).

Furans are known to react with electrophiles at the 5position rather than the 3-position through electrophilic substitution (i.e., Friedel–Crafts reaction). However, in our catalytic system, the first carboxylation was unlikely to be an electrophilic substitution because the carboxylation did not proceed without the Pd catalyst (Table 1, entry 7). Additionally, we believe that the reaction proceeded through a first carboxylation of η^1 -allylpalladium species followed by a second carboxylation of the resulting enol intermediate (see below) (Scheme 2). The first carboxylation has gained much interest because the unprecedented nucleophilic addition of η^1 -allylpalladium species takes place at the 5-position through π -conjugation.



This catalytic system has been expanded to the double carboxylation of pyrrole derivatives that also have 6π electron systems (Scheme 3). According to our previous report,⁵ an electron-donating substituent at the nitrogen atom is expected to be preferred due to the enhancement of the nucleophilicity of the enamine intermediate. Thus, *N*-ben-







Entry	Solvent	Temp. (°C)	Time (h)	Yield (%) ^a		
				2	2'	Recovered 1
1	DMF	r.t.	16	8	trace	23
2	DMF	40	16	40 (44)	3 (5)	0
3	DMF	60	17	21	0	0
4	DMF	80	18	0	0	0
5	DMF	40	4	19	trace	trace
6 ^b	DMF	40	16	44	trace	2
7 ^c	DMF	40	16	0	0	56
8	DMA	40	18	49 (50)	trace	0
9	DMA	60	16	39	2	0
10	THF	40	18	9	0	0

^a Yields were determined by ¹H NMR analysis by using 1,1,2,2-tetrachlo-

roethane as an internal standard. Isolated yields are given in parentheses. ^b The reaction was conducted under 10 atm of CO₂.

^c Without PdCl₂[P(*n*-Bu)₃]₂.

zylpyrrole derivative **3** was initially employed as a substrate. However, product **4** was obtained in only 2% yield, even at longer reaction times, without recovery of **3**, which was probably due to its instability, and this promoted the elimination of the acetate moiety.

Therefore, different protecting groups with electronwithdrawing ability were investigated under the optimal conditions (Scheme 4). Fortunately, the carbamate protection with C(O)Ot-Bu (Boc) and C(O)OMe increased the yield of **6** up to 43% with α , ϵ -selectivity, but these protecting groups were partially eliminated under the purification





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process using basic silica gel column chromatography (NH silica gel). Even though the yields were moderate, we successfully demonstrated a new type of double carboxylation of nitrogen-containing heteroaromatics.

We next examined other heteroaromatics in this carboxylation with CO_2 . The use of 2-thiophenylmethyl acetate afforded the doubly carboxylated product in only 2% yield (data not shown), whereas carboxylation of 5-thiazolylmethyl acetate **7** afforded the singly carboxylated product in 38% yield at slightly higher temperature (60 °C) without generation of the doubly carboxylated product **9** (Scheme 5).



The observed mono-selectivity was attributed to the difficulty of breaking the aromaticity of the thiazole ring. The terminal η^1 -allylpalladium species did not react at either the ε - or γ -position through a dearomative process. In fact, 1- and 2-naphthalenemethyl acetates, which are stable aromatics but susceptible to the initial oxidative addition to Pd(0), underwent single carboxylation predominantly, affording α -carboxylated products **11a** and **11b** in 51% and 44% yield, respectively, without forming the dearomative product **11a'** (Scheme 6). Although the yields were moderate due to the generation of methylnaphthalenes **12a** and **12b**, this is the first example of palladium-catalyzed carboxylation of benzylic carboxylates.^{10,11}



We next propose two reasonable catalytic cycles (Scheme 7). In the carboxylation of 2-furylmethyl acetate **1** and 2-pyrrolylmethyl acetate **5**, initially, the oxidative addition of **1** or **5** to Pd(0)L_n would result in the formation of η^3 -allylpalladium **I**. Transmetalation between **I** and ZnEt₂ gives the nucleophilic η^1 -allylethylpalladium **II**,¹² which reacts with CO₂ at the ε -position through dearomatization of the furan or the pyrrole ring, giving palladium carboxylate **III**, bearing either an enol or an enamine moiety. The nucleo-

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philic enol or the enamine can then undergo the second carboxylation with CO_2 after transmetalation with $ZnEt_2$,¹³ giving oxocarbenium or iminium intermediate **V**, which could undergo rearomatization followed by protonation by acidic work-up and methyl esterification to afford **2** or **6**.



Scheme 7 Proposed catalytic cycle

In a similar manner, 5-thiazolylmethyl acetate **7** can oxidatively add to Pd(0)L_n to afford **VI**, which is transmetalated with ZnEt₂, affording **VII**. Intermediate **VII** would be in equilibrium with **VII'** through η^3 -allylpalladium **VII'**. Of two η^1 -allylethylpalladium intermediates (**VII** and **VII'**), terminal **VII** seemed to be more stable than internal **VII'**, but ε - or γ -carboxylation would not proceed from **VII** because braking the aromaticity of the thiazole nucleus would be difficult. Therefore, η^1 -allylethylpalladium **VII'**, stabilized by two double bonds (alkene and imine), would attack CO₂ at the γ -position to give palladium carboxylate **VIII**, which is reduced by ZnEt₂ to regenerate Pd(0)L_n together with release of zinc carboxylate **IX**. It would then be hydrolyzed, affording singly carboxylated compound **8**.

In summary, we have developed a catalytic carboxylation of heteroaromatic compounds with CO₂. Double or single carboxylation occurred, depending on the substrate

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employed. Even though yields were moderate due to the competing β -hydride elimination, this methodology could open new routes to the synthesis of carboxylated heterocycles from CO₂.

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Supporting Information

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