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Pd-Catalyzed Dearomative Carboxylation of Indolylmethanol Derivatives

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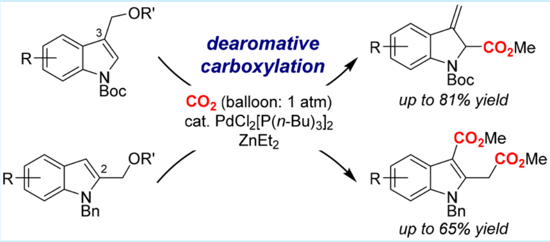
Supporting Information

ABSTRACT: By using a new catalytic system ($PdCl_2[P(n\text{-}Bu)_3]_2$ in combination with $ZnEt_2$), various 3-indolylmethanol derivatives were successfully carboxylated with CO_2 (1 atm) via dearomatization of the indole nucleus, affording 3-methyleneindoline-2-carboxylates. In contrast, carboxylation of 2-indolylmethanol derivatives afforded unexpected doubly carboxylated products, which are useful synthetic precursors for biologically active compounds.



Dearomative transformation of $(4n+2)\pi$ systems has received much attention because it allows for the direct construction of three-dimensional structures from stable, planar π-conjugated systems.[1] However, the difficulty involved in breaking the aromaticity often necessitates the use of harsh conditions, thus limiting the widespread application of this reaction to organic synthesis. Recently, transition-metal-catalyzed dearomative substitution of indole derivatives[2] under mild conditions has been developed by taking advantage of the dearomatization properties of the pyrrole moiety in the indole nucleus. In these dearomative techniques, however, the use of readily available indolylmethyl acetates and halides as substrates has been very limited. The reaction generally occurs at the α-position of the π-benzyl-Pd(II) (π-indolylmethylene-Pd(II)), which is expected to be formed by the oxidative addition of the substrate to Pd(0).[3] To realize an unusual dearomative process, we turned our attention to the nucleophilic allyl-Pd species, which generally reacts at the γ-position (Figure 1).[4]

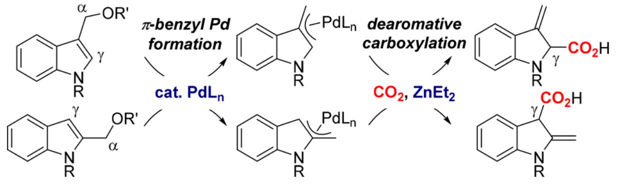


Figure 1. Pd-catalyzed dearomative transformations.

CO_2 is a fundamental C1 source because it is abundant, inexpensive, nontoxic, and renewable.[5] However, compared to other carbonyl compounds such as aldehydes and ketones, CO_2 is much less reactive toward various nucleophiles. Therefore, the introduction of CO_2 into an aromatic system by electrophilic dearomatization would be highly challenging in modern organic chemistry.[6] In this letter, we reveal a novel carboxylation of 3-indolylmethanol and 2-indolylmethanol derivatives by CO_2 via dearomatization of the indole nucleus in the presence of a Pd catalyst. Unexpectedly, carboxylation of the 2-indolylmethanol substrates afforded doubly carboxylated products.

First, *N*-Boc-3-indolylmethyl acetate **1a** was employed for the dearomative carboxylation using $PdCl_2$ (10 mol %) and $P(C_6H_4\text{-}p\text{-}CF_3)_3$ (20 mol %) in DMF at 40 °C for 16 h under a CO_2 (1 atm) atmosphere (Table 1, entry 1). Note that $P(C_6H_4\text{-}p\text{-}CF_3)_3$ was reported to be a suitable ligand for the arylative carboxylation of allenes.[7a] However, the carboxylation did not procced at all, and **1a** was recovered quantitatively. PPh_3 promoted the carboxylation slightly; however, the electron-donating phosphine $P(C_6H_4\text{-}p\text{-}OMe)_3$ promoted the dearomative carboxylation catalytically, affording 3-methyleneindoline-2-carboxylate **3a** in 22% yield along with 3-methylindole **4a** in 11% yield (entry 3). We next screened several trialkylphosphine ligands in an attempt to accelerate the oxidative addition of acetate **1a** to Pd(0). PMe_3, PEt_3, and $P(n\text{-}Bu)_3$ efficiently promoted the reaction to afford the product **3a** in around 70% yield together with **4a** in around 20% yield (entries 4−6), in which a trace amount of the aromatized compound **3a′** was also formed. The bulky trialkylphosphines $P(t\text{-}Bu)_3$ and PCy_3 completely suppressed the carboxylation (entries 7 and 8). Potential precursors of the Pd catalyst, such as $Pd(acac)_2$, $Pd(OAc)_2$, and $Pd(dba)_2$ exhibited similar reactivities (entries 9−11). The air-stable and readily available Pd complex $PdCl_2[P(n\text{-}Bu)_3]_2$[8] efficiently promoted the reaction, similar to the case of in situ generation of the catalyst (entry 12). Interestingly, the unprotected indolylmethanol **2a** also underwent the carboxylation in the presence of 3.5 equiv of $ZnEt_2$, affording **3a** in comparable yield (entry 13). The direct use of indolylmethanol without protection of the alcohol moiety would be highly attractive in terms of practical application as well as academic interest.

Having established the optimal conditions using $PdCl_2[P(n\text{-}Bu)_3]_2$, we investigated the substrate scope of this trans-

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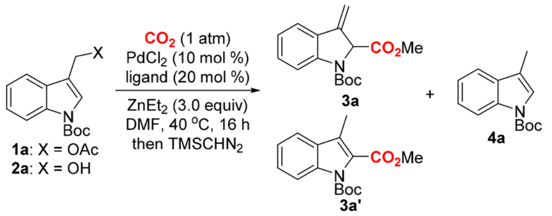
Table 1. Screening of Reaction Conditions



entry	substrate	Pd source	ligand	yield (%)[a] 3a + 3a′ (3a/3a′)	4a
1[b]	**1a**	$PdCl_2$	$P(C_6H_4\text{-}p\text{-}CF_3)_3$	0	0
2	**1a**	$PdCl_2$	PPh_3	6 (100:0)	2
3	**1a**	$PdCl_2$	$P(C_6H_4\text{-}p\text{-}OMe)_3$	22 (100:0)	11
4	**1a**	$PdCl_2$	PMe_3	74 (99:1)	12
5	**1a**	$PdCl_2$	PEt_3	78 (91:9)	24
6	**1a**	$PdCl_2$	$P(n\text{-}Bu)_3$	76 (96:4)	16
7[c]	**1a**	$PdCl_2$	$P(t\text{-}Bu)_3$	0	0
8[d]	**1a**	$PdCl_2$	PCy_3	0	0
9	**1a**	$Pd(acac)_2$	$P(n\text{-}Bu)_3$	68 (98:2)	24
10	**1a**	$Pd(OAc)_2$	$P(n\text{-}Bu)_3$	73 (98:2)	27
11	**1a**	$Pd(dba)_2$	$P(n\text{-}Bu)_3$	70 (98:2)	19
12	**1a**	$PdCl_2[P(n\text{-}Bu)_3]_2$ (10 mol %)		76 (97:3)	22
13[e]	**2a**	$PdCl_2[P(n\text{-}Bu)_3]_2$ (10 mol %)		77 (74[f]) (96:4)	23

[a]Yields and the **3**/**3′** ratios were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b]**1a** was recovered in 93% yield. [c]**1a** was recovered in 83% yield. [d]**1a** was recovered quantitatively. [e]3.5 equiv of $ZnEt_2$ was used. [f]Isolated yield.

formation (Figure 2). Compound **2a** could be carboxylated on a preparative scale (1 mmol) in a similar yield (69%). A variety of 3-indolylmethanol substrates bearing electron-withdrawing groups (Cl and CN) and electron-donating groups (Me and OMe) at the 5-position of the indole nucleus underwent the reaction with comparable efficiency (**2a**–**2e**). The highest yield (81% yield) was observed when using the 5-methyl derivative (**2d**). Furthermore, substituents at the 7- and 6-positions were well tolerated under the reaction conditions (**2f**–**2i**). Benzoindole **2j** also underwent this carboxylation effectively. The presence of acetate in the substrate was necessary; nevertheless, dearomative carboxylation also proceeded when Me or Ph was attached to the 2-position (**1k**, **1l**), leading to the formation of a quaternary carbon center adjacent to the nitrogen atom. Product **3a** could be further derivatized into synthetically useful compounds via versatile routes by taking advantage of the reactive *exo*-olefin at the 3-position (Scheme 1).[7a] Therefore, this dearomative carboxylation of simple 3-indolylmethanols would be a useful strategy for the functionalization of indoles.

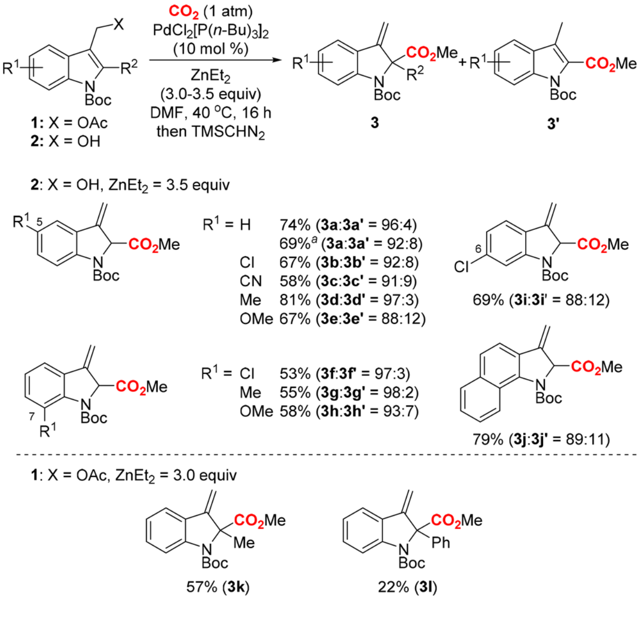
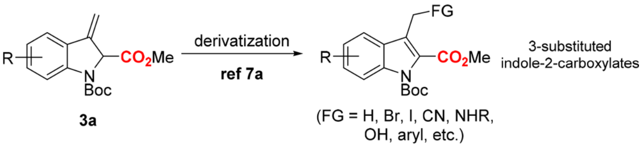


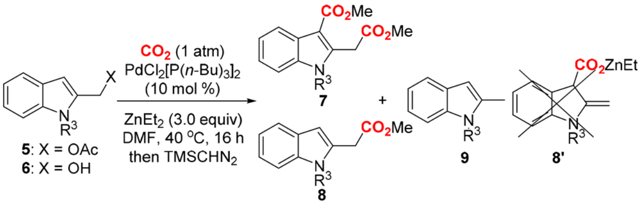
Figure 2. Substrate scope for dearomative carboxylation. Isolated yields are shown. The **3**/**3′** ratios were determined by ^{1}H NMR analysis. [a]Preparative-scale synthesis (1 mmol).

Scheme 1. Derivatization to 3-Substituted Indoles



We next investigated the carboxylation of 2-indolylmethanol derivatives. When Boc-protected substrate **5a** was subjected to the optimal reaction conditions listed in Table 1, an unexpected doubly carboxylated product **7**[9] was obtained in 27% yield, rather than the 2-methylene-3-carboxylate **8′** (Table 2). As the expected intermediate **8′** has an enamine structure, we considered that the second carboxylation of a nucleophilic enamine would proceed rapidly to furnish a doubly carboxylated compound **7** (vide infra). Therefore, the protecting group on the indole nitrogen was replaced with an electron-donating substituent in order to enhance the second carboxylation (entries 2–5). Among Me, MOM, PMB, and Bn, Bn was found to be the most promising protecting group, affording **7e** in 63% yield (58% isolated yield). In all of these cases, a small amount of

Table 2. Screening of Double Carboxylation Conditions



entry	R^3	substrate	yield (%)[a] 7	8	9	rec 5 or 6
1	Boc	**5a**	27	0	1	0
2	Me	**5b**	41	34	6	6
3	MOM	**5c**	60	<1	4	0
4	PMB	**5d**	58	16	15	0
5	Bn	**5e**	63 (58)	14	16	0
6[b]	Bn	**5e**	62	9	14	0
7[c]	Bn	**5e**	0	0	0	99
8[d,e]	Bn	**6e**	42	6	20	21
9[d,e,f]	Bn	**6e**	32	2	30	32

[a]Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. [b]The reaction was conducted under 10 atm of CO_2. [c]Without $PdCl_2[P(n\text{-}Bu)_3]_2$. [d]3.5 equiv of $ZnEt_2$ was used. [e]Reaction time: 60 h. [f]Reaction temp: 60 °C.

monocarboxylated product **8** was obtained as the side product. Even under 10 atm pressure, the yield of the doubly carboxylated product was not improved (entry 6). In the absence of the Pd catalyst, the reaction did not proceed at all, indicating the exclusion of the Friedel−Crafts-type carboxylation of the indole nucleus (entry 7).[10] In this system, the unprotected 2-indolylmethanol **6e** was somewhat inferior (entry 8), even though the reaction temperature was increased to 60 °C (entry 9).

The substrate scope of 2-substituted indolylmethanol derivatives was then investigated (Figure 3). The reaction time depended on the substrate structure. Carboxylation of all the substrates except **5l** depicted in Figure 3 proceeded to completion within 4 h. Preparative-scale synthesis could also be successfully applied, and product **7e** was obtained in comparable yield (54%). Several substrates bearing electron-donating and electron-withdrawing substituents underwent the double carboxylation to afford the corresponding products in moderate yields (**5f**−**5k**). Regardless of the location of the chloro substituent (5-, 6-, and 7-positions), the products were obtained in similar yields (**5f**, **5g**, and **5i**). When a methyl group was introduced at the 3-position, the monocarboxylated product **8l** was exclusively obtained in moderate yield.

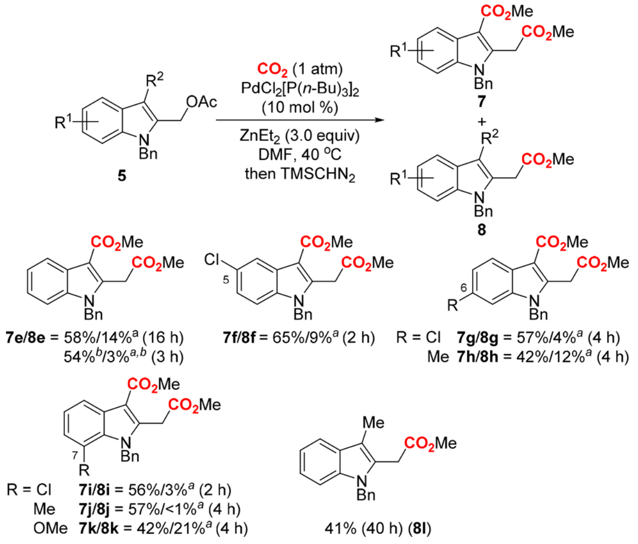


Figure 3. Substrate scope for dearomative double carboxylation. Isolated yields are shown. [a]Yields of **8** were determined by ^{1}H NMR analysis. [b]Preparative-scale synthesis (1 mmol).

A plausible catalytic cycle is depicted in Figure 4. In the carboxylation of 3-indolylmethanols, initially, the oxidative addition of **2a** to Pd(0)L$_n$ results in the formation of η^3-allylpalladium **I**. Transmetalation between **I** and ZnEt$_2$ would give the nucleophilic η^1-allylethylpalladium **II**,[4] which reacts with CO$_2$ at the 2-position of the indole through dearomatization. The resulting palladium carboxylate **III** is reduced by ZnEt$_2$ to regenerate Pd(0)L$_n$, together with release of zinc carboxylate **IV**. It would then be protonated upon acidic workup and methylated with TMSCHN$_2$, affording the desired compound **3a**. 3-Methylindole **4a** would be generated from intermediate **II** via β-hydride elimination, followed by reductive elimination.

Similarly, 2-indolylmethyl acetate **5e** oxidatively adds to Pd(0)L$_n$ to afford **V**, which is transmetalated with ZnEt$_2$, affording **VI** and **VI′**. The former is carboxylated at the 3-position of the indole to afford 2-methyleneindoline-3-carboxylate **VII** having an enamine structure. After transmetalation with ZnEt$_2$, the enamine of **VIII** would undergo the second carboxylation with CO$_2$,[11] giving iminium intermediate **IX**, which undergoes rearomatization, followed by hydrolysis to give **7e**. On the other hand, η^1-allylethylpalladium **VI′**, which is in equilibrium with another π-benzyl intermediate **VI″**, is carboxylated with CO$_2$ at the γ-position to afford the monocarboxylated byproduct **8e**.

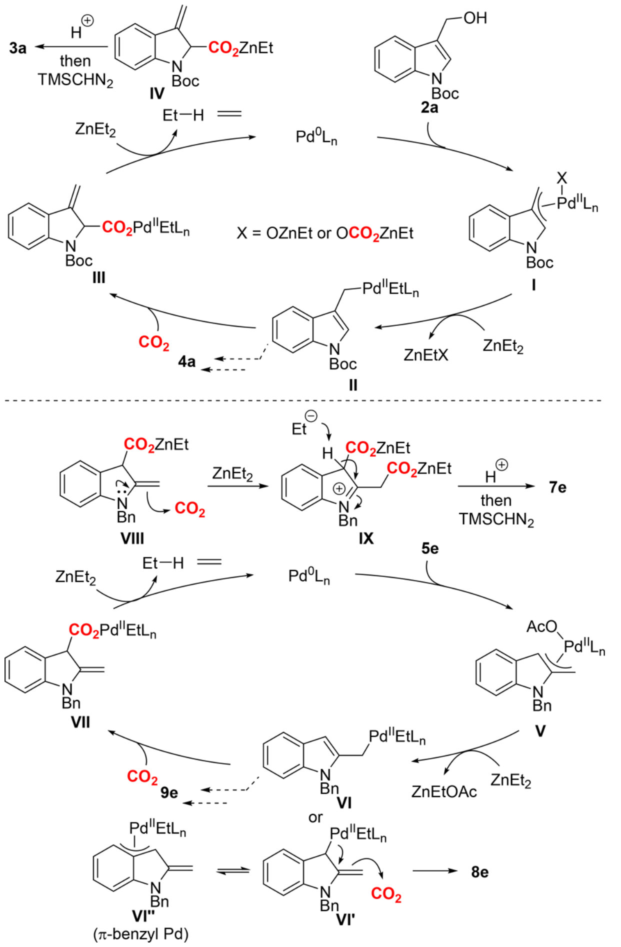
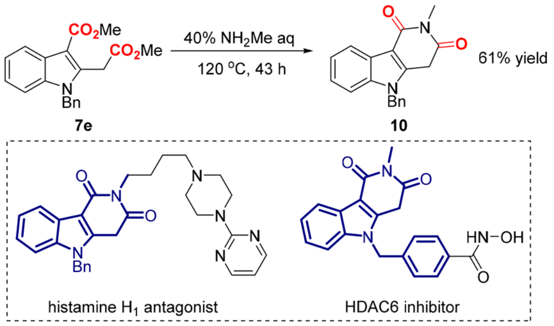


Figure 4. Proposed catalytic cycle.

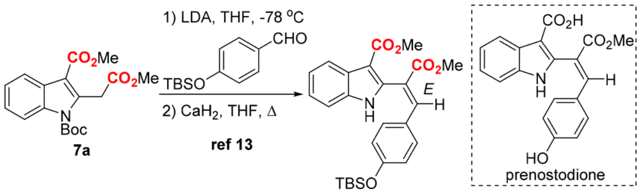
To demonstrate the synthetic utility of the doubly carboxylated compound **7**, we investigated the transformation of **7e** to a tricyclic compound (Scheme 2). Cyclic imide **10** was obtained in 61% yield by treatment with aqueous NH$_2$Me solution (40%) in a sealed tube. This unique structure can be found in some biologically active compounds that exhibit

Scheme 2. Derivatization to Cyclic Imide



histamine H_1 and HDAC6 inhibitory activities.[12] In addition, **7a** is known to be converted to the UV-absorbing prenostodione core by aldol condensation, followed by *E* selective E1cB elimination (Scheme 3).[13]

Scheme 3. Aldol Condensation with Aldehyde



In conclusion, we have successfully developed the first Pd-catalyzed dearomative carboxylation of indole derivatives with CO_2. Carboxylation of 3-indolylmethanol with an unprotected alcohol moiety afforded 3-methyleneindoline-2-carboxylates in high yields. On the other hand, 2-indolylmethyl acetates were converted into doubly carboxylated products. Extensive efforts are now being undertaken toward the double carboxylation of various other heterocycles, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03337.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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