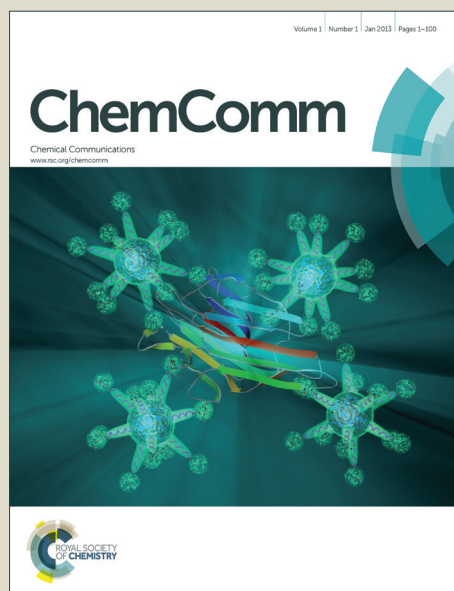


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COMMUNICATION

Direct Carboxylation of Simple Arenes with CO₂ through a Rhodium-Catalyzed C–H Bond Activation

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Takuya Suga, Hajime Mizuno, Jun Takaya and Nobuharu Iwasawa*

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A direct carboxylation of simple arenes under atmospheric pressure of CO₂ is achieved through a rhodium-catalyzed C–H bond activation without the assistance of a directing group. Various arenes such as benzene, toluene, xylene, electron rich or electron deficient benzene derivatives, and heteroaromatics are directly carboxylated with high TON.

The direct carboxylation reaction of simple arenes with carbon dioxide (CO₂), which is an abundant and potentially renewable carbon source, has still remained a great challenge due to low reactivity of CO₂.^{1–3} Recently several groups developed the gold(I) or copper(I) hydroxide-catalyzed carboxylation of arenes without a directing group, however, the substrates are limited to electron deficient arenes having a rather acidic C–H bond since the key arylmetal intermediates are generated through deprotonation by the basic metal hydroxides.⁴ On the other hand, we reported rhodium(I)-catalyzed direct carboxylation of phenylpyridine derivatives via chelation-assisted C–H bond activation. Although this reaction showed no limitation concerning the acidity of the C–H bond, the pyridine moiety was required to promote the reaction effectively.⁵ Additionally, the two representative stoichiometric reactions for carboxylation of simple arenes with CO₂, that is, the base-promoted Kolbe-Schmitt reaction of phenol derivatives and the aluminum-promoted Friedel-Crafts type carboxylation, also have some drawbacks of substrate limitation and necessity of high pressure of CO₂.^{6–8} Therefore, development of a new direct carboxylation reaction of simple arenes with wide generality is highly desired. Herein we report a direct carboxylation of simple arenes under atmospheric pressure of CO₂ through a rhodium-catalyzed C–H bond activation without the assistance of a directing group.⁹ The reaction is applicable to both electron

rich and deficient arenes, demonstrating promising utility as a new CO₂-fixation reaction.

To realize the direct carboxylation of simple arenes, we started investigations utilizing the combination of a rhodium catalyst and a methylaluminum reagent as a stoichiometric reductant based on our previous success in the chelation-assisted carboxylation of phenylpyridine derivatives.⁹ However, the rhodium catalyst with a bulky monodentate phosphine ligand, which is the active catalyst in our previous report, was totally ineffective for the direct carboxylation of benzene under various conditions. Extensive screening of the ligand and reaction conditions revealed that isolated 1,2-bis(dialkylphosphino)ethane-rhodium(I) chloride complexes **1** showed catalytic activity for the carboxylation of benzene in the presence of AlMe₃ as a stoichiometric reductant. A small amount of benzoic acid was obtained with a catalyst turnover number (TON) of 2.8 by treatment of the rhodium complex **1c** bearing 1,2-bis(dicyclohexylphosphino)ethane (dcype) with an excess amount of AlMe₃ (100 equiv. to Rh) in a mixture of benzene and DMA (*N,N*-dimethylacetamide) (20:1) as solvent at 85 °C for 6 h (entry 3, Table 1). The TON decreased when analogous complexes **1a** and **1b** bearing 1,2-bis(diethyl- or diisopropylphosphino)ethane (depe or dippe) were employed as a catalyst (entries 1 and 2), suggesting critical effect of bulkiness of alkyl substituents probably on stabilization of catalytically active, coordinatively unsaturated rhodium species. The bidentate structure was also essential as two molar amounts of bulky monodentate phosphine, PCy₃, was not effective at all (entry 4). Furthermore, use of AlMe_{1.5}(OEt)_{1.5} instead of AlMe₃ dramatically improved efficiency of the reaction,¹⁰ achieving the TON of 29 in benzene-DMA and of 40 by further addition of TMU (1,1,3,3-tetramethylurea), which is believed to

stabilize coordinatively unsaturated Rh(I) species through coordination, as a second cosolvent (entries 5 and 6).¹¹ AlMe₂(OEt) was slightly less effective than AlMe_{1.5}(OEt)_{1.5} (entry 7). It should be noted that the reaction in the absence of DMA gave poor result (TON=3.2, entry 8), indicating polar cosolvents play important roles.¹²

Table 1. Optimization of Reaction Conditions

entry	[Rh]	[Al]	cosolvent	TON ^d
1	1a	AlMe ₃	DMA ^b	0
2	1b	AlMe ₃	DMA ^b	1.0
3	1c	AlMe ₃	DMA ^b	2.8
4	2	AlMe ₃	DMA ^b	0
5	1c	AlMe _{1.5} (OEt) _{1.5} ^a	DMA ^b	29
6	1c	AlMe _{1.5} (OEt) _{1.5} ^a	DMA + TMU ^c	40
7	1c	AlMe ₂ (OEt)	DMA + TMU ^c	34
8	1c	AlMe _{1.5} (OEt) _{1.5} ^a	-	3.2

^a 1.1 mmol of the Al reagent was used. See also ref. 10. ^b 0.1 mL. ^c 0.1 mL DMA + 6 μ L TMU. ^d Calculated based on NMR yield. Effects of other factors (other co-solvents, concentrations) were summarized in Supporting Information.

Direct carboxylation of various simple arenes proceeded successfully under the optimized reaction conditions (Table 2). Simple monosubstituted arenes such as toluene **3b** and cumene **3c** were carboxylated to give toluic acids **4b** and cumic acids **4c** as a mixture of regioisomers with good TON (TON=18 for **4b** and 22 for **4c**) at 120 and 145 °C (entries 2 and 3). The steric repulsion of the bulky isopropyl group suppressed the carboxylation at the *ortho*-position. Among three isomers of xylene, the TON of *o*-xylene **3d** was the highest (TON=46) while that of *m*- and *p*-xylenes decreased to 33 and 22, also indicating the importance of steric accessibility for efficient C–H activation (entries 4–6). The regioselectivity in these reactions are clearly different from those in aluminum-mediated Friedel-Crafts type carboxylation of arenes (e.g. α : β : γ = 7:3:90 for **3b** and 0:100:0 for **3e** by Olah's report^{7a}), ruling out the possibility of electrophilic substitution pathway promoted by aluminum species. Importantly, the reaction was also applicable to a solid arene such as naphthalene **3h** by using cyclooctane as an inert solvent to give a mixture of 1- and 2-naphthoic acids **4h** with TON of 16 (entry 8).

Furthermore, good compatibility of this reaction with various functional groups was demonstrated. Arenes having fluorine (**3i**), chlorine (**3p**), silicon (**3k**), and trifluoromethyl (**3j** and **3n**) substituents were successfully carboxylated to afford corresponding benzoic acid derivatives with high TON of up to 48 (entries 9–11, 14, and 16).¹³ Regioselective formation of 3,5-bis(trifluoromethyl)benzoic acid **4n** with high TON is noteworthy in the reaction of **3n** (entry 14). The reactions of electron rich arenes such as anisole **3l**, *N,N*-dimethylaniline **3m**, and benzo-1,4-dioxane **3o** also proceeded (entries 12, 13, and 15) although the TON slightly decreased probably due to partial inhibition by coordination of the oxygen and nitrogen atoms to the catalyst.¹⁴ Moreover, this reaction is applicable not only to benzene derivatives but also to heteroaromatic compounds. Carboxylation of benzofuran **3q** and 1-methylindole **3r** proceeded at 2-positions selectively, which are hardly carboxylated by Lewis acid or base-promoted carboxylation protocols (entries 17 and 18).^{7,8,15} Interestingly, ferrocene **3s** showed exceptionally high reactivity, and the TON reached 60 (entry 19). These results clearly demonstrate several advantages and characteristic of this reaction as follows. 1) The reaction is applicable to both electron rich and deficient arenes whereas previously reported acid- or base-promoted reactions are limited to either one of them. 2) Preferential carboxylation with different regioselectivities from those of previous reports is possible. 3) The reaction proceeds under atmospheric pressure of CO₂ whereas Al-mediated electrophilic carboxylation requires high pressure. Therefore, this rhodium-catalyzed protocol demonstrates a new approach toward direct carboxylation of simple arenes utilizing CO₂ as a C1 source.

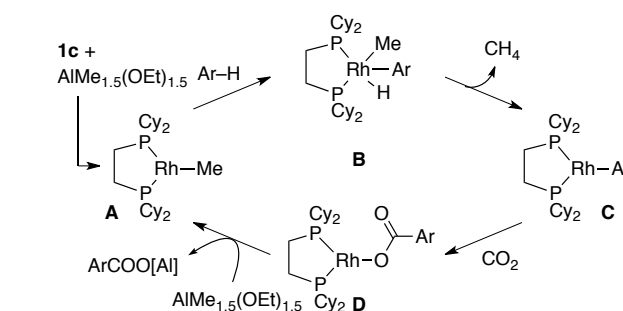
Table 2. Carboxylation of benzene derivatives

entry	arene	temp. /°C	TON ^a	regio ^b (α : β : γ)
1		85	4a 37	–
2		120	4b 18	17:57:26
3		145	4c 22	0.67:33
4		145	4d 46	12:88:–
5		145	4e 33	0:33:67
6		145	4f 22	–

7		3g	145	4g 25	23:77:–
8 ^c		3h	145	4h 16	46:54:–
9		R = F 3i	85	4i 39	59:29:12
10		R = CF ₃ 3j	120	4j 44	0.77:23
11		R = SiMe ₃ 3k	145	4k 39	0.64:36
12		R = OMe 3l	145	4l 15	23:54:23
13		R = NMe ₂ 3m	145	4m 9	0.56:44
14		3n	145	4n 48	0.0:100
15 ^d		3o	145	5o 22	55:45:–
16		3p	145	4p 15	49:51:–
17 ^d		3q	145	5q 12	100:0:–
18 ^d		3r	145	5r 21 ^e	86:14:–
19 ^{c,d}		3s	145	5s 60 ^f	–

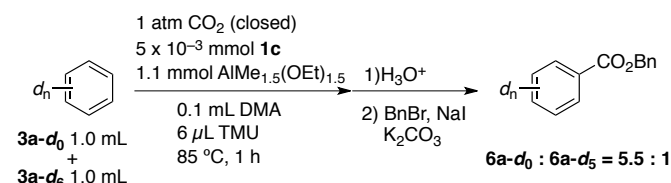
^a Calculated based on the isolated yield of products. ^b Determined by ¹H NMR. ^c 5.0 mmol of an arene was used in 2.0 mL of cyclooctane. ^d Isolated after Me-esterification. ^e Small amounts of other regioisomers were detected by GC-MS. The TON was calculated based on the yield of α - and β -isomers. ^f Small amounts of dicarboxylated products were detected.

A tentatively proposed reaction mechanism is shown in Scheme 1. The reaction starts with generation of a methylrhodium(I) complex **A** from **1c** and AlMe_{1.5}(OEt)_{1.5} followed by oxidative addition of an sp² C–H bond of a simple arene to **A**, giving an aryl(hydride)(methyl)rhodium(III) intermediate **B**. Reductive elimination of methane from **B** affords a highly reactive arylrhodium(I) complex **C**.¹⁶ Nucleophilic addition of **C** to CO₂ gives a rhodium(I) benzoate complex **D**,¹⁷ which is converted to the methylrhodium(I) **A** through transmetalation with AlMe_{1.5}(OEt)_{1.5}.¹⁸



Scheme 1. Proposed Mechanism.

To obtain mechanistic insights, the competitive reaction of C₆H₆ and C₆D₆ was examined in the same vessel. After esterification with benzyl bromide, the KIE value ($[\mathbf{6a-d}_0]/[\mathbf{6a-d}_5]$) at the point of 1 h reaction time was estimated to be 5.5, which suggests that the C–H bond activation step is the rate-determining step.¹⁹



Scheme 2. KIE Experiment.

In conclusion, we have developed a novel method for direct carboxylation of simple arenes with 1 atm CO₂ through a rhodium-catalyzed C–H bond activation without the assistance of a directing group. This reaction demonstrates wide generality, intriguing regioselectivity, that are not achieved by previous acid- or base-promoted protocols. These findings are highly promising to expand synthetic utility of the direct carboxylation of simple arenes even though a stoichiometric amount of aluminum reagent is required at present. Further improvement of the efficiency of the reaction and investigations on the reaction mechanism are in progress.

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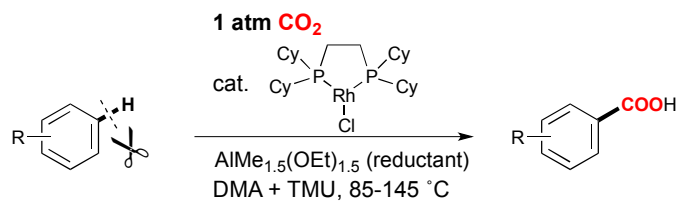
Notes and References

Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551 Japan. E-mail: niwasawa@chem.titech.ac.jp

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of all new compounds. See DOI: [10.1039/c000000x/](https://doi.org/10.1039/c000000x/)

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- TON up to 60
- applicable to benzene, toluene, electron-rich/deficient arenes, heteroaromatics, ferrocene

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