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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO_2 via Chelation-Assisted C−H Bond Activation

Hajime Mizuno, Jun Takaya, and Nobuharu Iwasawa*

Department of Chemistry, Tokyo Institute of Technology, O-Okayama, Meguro-ku, Tokyo 152-8551, Japan

Supporting Information

ABSTRACT: Rh-catalyzed direct carboxylation of unactivated aryl C−H bond under atmospheric pressure of carbon dioxide was realized via chelation-assisted C−H activation for the first time. Variously substituted and functionalized 2-arylpyridines and 1-arylpyrazoles underwent the carboxylation in the presence of the rhodium catalyst and a stoichiometric methylating reagent, $AlMe_2(OMe)$, to give carboxylated products in good yields. The catalysis is proposed to consist of methylrhodium(I) species as the key intermediate, which undergoes C−H activation to afford rhodium(III), followed by reductive elimination of methane to give nucleophilic arylrhodium(I). This approach demonstrates promising application of C−H bond activation strategy in the field of carbon dioxide fixation.

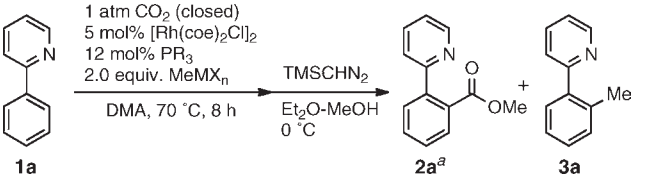
The catalytic nucleophilic carboxylation reaction using carbon dioxide as a one-carbon source through C−H bond activation of aromatic molecules is still a formidable challenge in the filed of synthetic chemistry.[1,2] Very recently, Boogaerts and Nolan reported the first example of such reaction, that is, the gold(I)-NHC catalyzed carboxylation reaction of sp^2 C−H bonds of electron-deficient arenes; however, this reaction was proposed to proceed via deprotonation by hydroxo−gold(I) complex and thus was limited to substrates which have rather acidic protons (pK_a of about 30).[3] In this paper, we report another approach for the direct carboxylation reaction of aromatic C−H bonds, that is, Rh(I)-catalyzed carboxylation of aromatic compounds via chelation-assisted ortho-metalation.

To realize such a reaction, we focused our attention on rhodium catalysts, as rhodium(I) complexes are well-known as a catalyst for C−H activation[4] and arylrhodium(I) species are expected to have sufficient nucleophilicity for carboxylation.[5,6] As for the key catalytic species, we have chosen methylrhodium(I), as there are several precedents where methylrhodium(I) activates aryl C−H bond to give Ar(Me)(H)Rh(III) species which undergoes reductive elimination of methane to give ArRh(I) species in stoichiometric reactions.[7] It was also expected that, by carrying out the reaction in the presence of an appropriate methylmetallic reagent, the key methylrhodium(I) would be regenerated by transmetalation with the rhodium(I) carboxylate.[8]

In the first place, 2-phenylpyridine was chosen as substrate and the reaction was examined using 5 mol % $[Rh(coe)_2Cl]_2$ (10 mol % based on Rh), 12 mol % trimesitylphosphine ($P(mes)_3$) in DMA (*N*,*N*-dimethylacetamide) at 70 °C under CO_2 atmosphere in a closed system in the presence of various methylmetallic reagents ($MeMX_n$). After extensive screening of the reagent, use of Me_3Al was found to give the desired *o*-carboxylated product **2** regioselectively in 41% yield along with *o*-methylated product **3a** in 16% yield (Table 1, entry 2). Furthermore, methylaluminum alkoxides were found to promote the carboxylation more efficiently (entries 3, 4). In particular, use of the aluminum reagent prepared from equimolar amounts of Me_3Al and MeOH before use gave the best result (entry 3).[9] Encouraged by these initial results, we further examined the effect of phosphine ligands. Although use of PPh_3 gave a low yield of carboxylation product, bulkier arylphosphines and alkylphosphines gave better results (entries 3, 5−7). Use of 20 mol % amount of monodentate phosphines suppressed the reaction and bidentate phosphine ligands such as dppm, dppp, and dppf did not give the desired product either. Among the ligands examined, PCy_3 was found to be the best ligand for this reaction (entry 7). Formation of dicarboxylated product was not observed under these reaction conditions.

We next examined the generality of the reaction using several substituted phenylpyridines (Table 2). A wide range of substrates bearing an electron-donating or electron-withdrawing group at

Table 1. Screening of Reaction Conditions



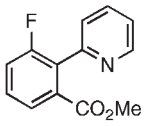
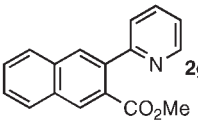
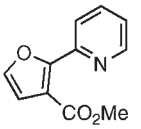
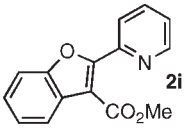
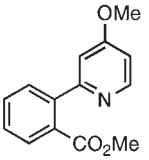
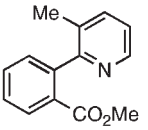
entry	$MeMX_n$	PR_3	**2a**/%	**3a**/%
1	$ZnMe_2$	$P(mes)_3$[b]	0	14
2	$AlMe_3$	$P(mes)_3$	41	16
3	$AlMe_2(OMe)$[c]	$P(mes)_3$	67	13
4	$AlMe(OMe)_2$[d]	$P(mes)_3$	48	22
5	$AlMe_2(OMe)$[c]	PPh_3	5	22
6	$AlMe_2(OMe)$[c]	$P(t\text{-}Bu)_3$	35	17
7	$AlMe_2(OMe)$[c]	PCy_3	73	21

[a] The product was obtained as its methyl ester after treatment of the crude mixture with $TMSCHN_2$. [b] $P(mes)_3$ = Tris(2,4,6-trimethylphenyl)-phosphine. [c] Prepared by adding an equimolar amount of MeOH to a toluene solution of $AlMe_3$ before use. [d] Prepared by adding two molar amounts of MeOH to a toluene solution of $AlMe_3$ before use.

Received: October 10, 2010
Published: December 30, 2010

dx.doi.org/10.1021/ja109097z | *J. Am. Chem. Soc.* 2011, 133, 1251–1253

Table 2. Generality of the Reaction Using Phenylpyridines[a]

entry	products	yield
1	R = H	**2a** 73 %
2	R = OMe	**2b** 75 %
3	R = Me	**2c** 65 %
4	R = $CH=CH_2$	**2d** 68 %
5	R = CO_2Me	**2e** 51 %
6		**2f** 58 %
7		**2g** 66 %
8		**2h** 69 %
9[b]		**2i** 88 %
10		**2j** 73 %
11[c]		**2k** 60 %

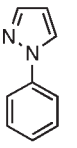
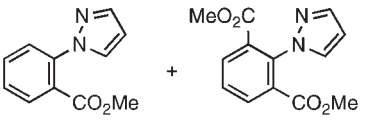
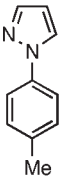
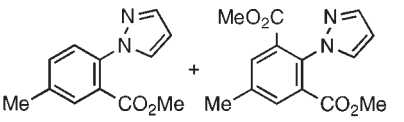
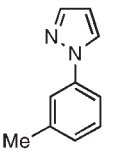
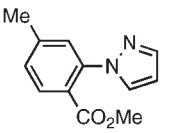
[a] The reaction was carried out according to the conditions of Table 1, entry 7. The products were obtained as their methyl esters after treatment of the crude mixture with $TMSCHN_2$. [b] $P(mes)_3$ was employed. [c] 10 mol % $[RhCl(coe)_2]_2$ and 24 mol % $P(mes)_3$ were employed.

the *p*-position smoothly underwent the carboxylation reaction in moderate to good yield by carrying out the reaction under the optimized conditions. It should be noted that styrene derivative gave the desired carboxylation product **2d** without affecting the alkene moiety (entry 4). Substitution of fluorine at ortho-position caused no problem (entry 6). The carboxylation of 2-(2-naphthyl)-pyridine occurred regioselectively at 3-position probably due to steric repulsion by peri-hydrogen (entry 7). Furthermore, heteroaromatic derivatives such as furan and benzofuran also gave the corresponding carboxylation products **2h** and **2i** in good yield. Introduction of an electron-donating substituent on the 4-position of the pyridine ring did not affect the efficiency of the reaction, while the reaction of sterically congested 3-methylpyridine derivative required increased loading of the catalyst (entries 10 and 11).[10] Thus, this protocol showed wide generality for preparation of functionalized pyridylarene carboxylic acids.

Furthermore, it was found that the pyrazolyl group was also an effective directing-group of this reaction (Table 3). In this case, double carboxylation at both ortho-positions partially proceeded using nonsubstituted and *p*-substituted benzene derivatives to give 2-mono- and 2,6-dicarboxylated products **4** and **4′** in the combined yield of 80% (entries 1 and 2),[11] while *m*-substituted derivative gave the corresponding monocarboxylated product **4c** selectively in good yield (entry 3).

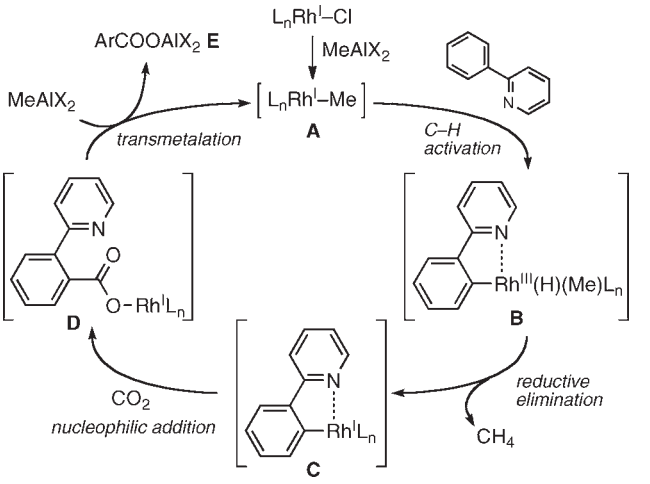
Although further studies were required to clarify the detailed mechanism of the reaction, we currently believe the reaction proceeds as follows (Scheme 1). First the methylrhodium(I) **A** would be produced by the reaction of rhodium(I) chloride and methylaluminum reagent, and then this would give the key arylrhodium(I) **C** via arylrhodium(III) species **B** generated by chelation-assisted C−H bond activation (oxidative addition), followed by reductive elimination of methane. Subsequently, nucleophilic carboxylation of arylrhodium(I) **C** would afford rhodium carboxylate **D** which would undergo transmetalation with methylaluminum reagent to give aluminum carboxylate **E** with regeneration of methylrhoduim(I) **A**. *o*-Methylated product **3** would be produced via C−C bond forming reductive elimination from the arylrhodium(III) intermediate **B**.[12]

Table 3. Generality of the Reaction Using Phenylpyrazoles[a]

entry	substrate	products
1		 **4a** 57% **4′a** 23%
2		 **4b** 44% **4′b** 35%
3		 **4c** 67%

[a] The reaction was carried out according to the conditions of Table 1, entry 7. The products were obtained as their methyl esters after treatment of the crude mixture with $TMSCHN_2$.

Scheme 1. Proposed Catalytic Cycle



In summary, we have succeeded in developing a catalytic direct carboxylation of aromatic compounds via chelation-assisted C−H bond activation. By carrying out the reaction in the presence of methylaluminum reagent, nucleophilic C−C bond formation was achieved with C−H bond activation. This concept will find abundant applications in C−H bond activation chemistry.

■ ASSOCIATED CONTENT

Supporting Information. Preparative methods and spectral and analytical data of compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ja109097z |*J. Am. Chem. Soc.* 2011, 133, 1251–1253

AUTHOR INFORMATION

Corresponding Author
niwasawa@chem.titech.ac.jp

ACKNOWLEDGMENT

This research was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (No. 22105006), a Grant-in-Aid for Scientific Research (A) (No. 21245024) and a Grant-in-Aid for Scientific Research on Innovative Areas (No. 20200049) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

REFERENCES

(1) Reviews on transition metal-promoted CO_2-fixation reactions, see (a) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988,** *88*, 747. (b) Yin, X.; Moss, J. R. *Coord. Chem. Rev.* **1999,** *181*, 27. (c) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007,** *107*, 2365.(d) *Carbon Dioxide as Chemical Feedstock*; Aresta, M., Ed.; Wiley-VCH: Weinheim, 2010. (e) Correa, A.; Martín, R. *Angew. Chem., Int. Ed.* **2009,** *48*, 6201. (f) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010,** *39*, 3347.

(2) For recent examples of transition metal-catalyzed carboxylation under CO_2 atmosphere, see (a) Mori, M. *Eur. J. Org. Chem.* **2007,** 4981. (b) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006,** *128*, 8706. (c) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008,** *10*, 2697. (d) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008,** *47*, 5792. (e) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008,** *10*, 2681. (f) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2008,** *130*, 7826. (g) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008,** *130*, 14936. (h) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008,** *130*, 15254. (i) Correa, A.; Martín, R. *J. Am. Chem. Soc.* **2009,** *131*, 15974. (j) Johnson, M. T.; Johansson, R.; Kondrashov, M. V.; Steyl, G.; Ahlquist, M. S. G.; Roodt, A.; Wendt, O. F. *Organometallics* **2010,** *29*, 3521, and references cited therein.

(3) (a) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010,** *132*, 8858. During preparation of this manuscript, Cu(I)-catalyzed similar reactions were reported by the same group and Hou's group. (b) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010,** *49*, 8674. (c) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010,** *49*, 8670. See also (d) Vechorkin, O.; Hirt, N.; Hu, X. *Org. Lett.* **2010,** *12*, 3567.

(4) For a review of Rh-catalyzed functionalization via C−H activation, see Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010,** *110*, 624.

(5) See ref 2b. See also, (a) Kolomnikov, I. S.; Gusev, A. O.; Belopotapova, T. S.; Grigoryan, M. K.; Lysyak, T. V.; Struchkov, Yu. T.; Vol'pin, M. E. *J. Organomet. Chem.* **1974,** *69*, C10. (b) Albano, P.; Aresta, M.; Manassero, M. *Inorg. Chem.* **1980,** *19*, 1069. (c) Darensbourg, D. J.; Grötsch, G.; Wiegreffe, P.; Rheingold, A. L. *Inorg. Chem.* **1987,** *26*, 3827.

(6) For examples of addition of arylmetallic species generated by C−H bond activation to polar C═X bond: To ketene; (a) Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978,** 535. To aldehydes; (b) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007,** *46*, 6518. (c) Kuninobu, Y.; Matsuki, T.; Takai, K. *Org. Lett.* **2010,** *12*, 2948, and references cited therein. (d) Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010,** *352*, 1145. (e) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009,** *11*, 3120. To isocyanate; (f) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008,** *64*, 5974. (g) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006,** *128*, 202. To ketone; (h) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009,** *351*, 2850. To chlorocarbonyl compounds; it is proposed that the reaction proceeds via oxidative addition of a C−Cl bond of the chlorocarbonyl group. (i) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009,** *131*, 2792. To diethyl azodicarboxylate; it is proposed that the reaction proceeds via the ethoxycarbonyl radicals. (j) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008,** *130*, 3304. To formic acid (k) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004,** *6*, 2437. To nitriles; (l) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006,** *71*, 3551. (m) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004,** *126*, 2302.

(7) (a) Price, R. T.; Anderson, R. A.; Muetterties, E. L. *J. Organomet. Chem.* **1989,** *376*, 407. (b) Boyd, S. E.; Field, L. D; Hambley, T. W.; Partridge, M. G. *Organometallics* **1993,** *12*, 1720. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003,** *103*, 169.

(8) For examples of catalyst regeneration from metal carboxylates using organoaluminum or zinc reagents, see refs 2a, 2g−2j.

(9) No carboxylation product was obtained without rhodium catalyst under the reaction conditions, and therefore, the possibility of Al-promoted carboxylation of arenes was ruled out. For example of Al-promoted carboxylation of arenes, see Olah, G. A.; Török, B.; Joschek, J. P.; Bucsi, I.; Esteves, P. M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2002,** *124*, 11379.

(10) In all cases except for the reaction of furan-derivative **2i** (Table 2, entry 9), formation of *o*-methylated products was observed in about 4−15% yield.

(11) Small amounts of *o*-methylated products (4−7%) were observed.

(12) C−H activation by rhodium carboxylate complex **D** followed by transmetalation and reductive elimination should be considered as another possible pathway to give arylrhodium(**I**) complex **B**. Preliminary mechanistic studies showed that the transmetalation of a rhodium carboxylate complex with $AlMe_2(OMe)$ is very fast and proceeded even at room temperature, whereas the C−H activation of phenylpyridine by a rhodium carboxylate complex did not occur under the reaction conditions. Therefore, we currently believe that the transmetalation precedes the C−H activation as in Scheme 1. Details will be reported in due course.