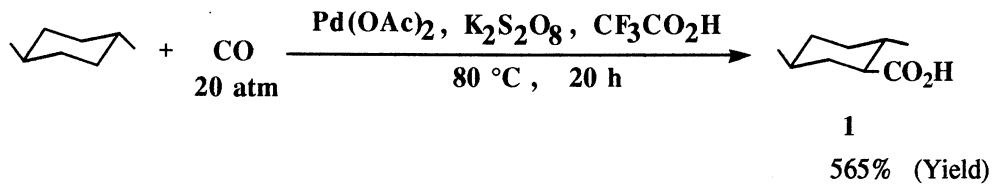


Pd-Catalyzed Regio- and Stereo-selective Carboxylation
of Cycloalkanes with CO

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The reactions of cycloalkanes with CO via the C-H bond activation by $\text{Pd}(\text{OAc})_2$ catalyst have been found to proceed regio- and stereo-selectively to give corresponding carboxylic acids. The reactivity of C-H bonds of cycloalkanes decreases in the order: tert- > sec- > prim-carbon, and the stereochemistry of the substituents on the main products is all equatorial.

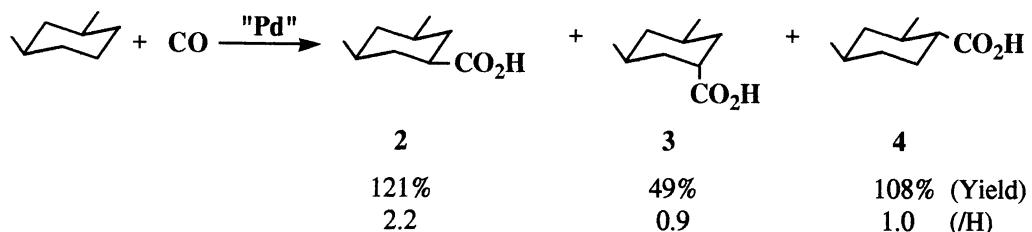
The selective functionalization of alkanes via C-H bond activation by transition metals is one of the most challenging and important subjects from both scientific and practical points of view.¹⁾ In previous paper, we reported our initial work on the carboxylation of cyclohexane with CO via the activation of alkane C-H bonds by palladium catalysts without irradiation.²⁾ In the present work, we carried out palladium-catalyzed reactions of a variety of cycloalkanes such as methyl-, tert-butyl-, cis-1,3-dimethyl-, trans-1,4-dimethylcyclohexanes and adamantane with CO, and investigated the regio- and stereo-selectivity of these reactions.



Scheme 1.

First, the reaction of *trans*-1,4-dimethylcyclohexane (5 ml) with 20 atm CO with $\text{Pd}(\text{OAc})_2$ (0.2 mmol) and $\text{K}_2\text{S}_2\text{O}_8$ (9 mmol) in CF_3COOH (3.3 ml) at 20 °C for 20 h in an autoclave gave *trans,cis*-2,5-dimethylcyclohexane-carboxylic acid (**1**) in 56.5% yield based on Pd with small amounts of 2,5-dimethylbenzoic acid (54%).³⁾ GC, GC-mass, and ^{13}C -NMR spectroscopic comparison with the authentic sample of **1**⁴⁾ revealed that three substituents (two CH_3 groups and one COOH group) in the acid (**1**) are all at the equatorial positions (Scheme 1). In this reaction, 1,4-dimethylcyclohexanecarboxylic acid and 4-methylcyclohexylacetic acid which seemed to be derived from attack of $\text{Pd}^{\text{t}}\text{OC}(\text{O})\text{CF}_3$ at the tert- and prim-carbons, respectively, were not formed. Hence, this reaction occurred quite regio- and stereo-selectively only on the less sterically hindered secondary C-2 position.

The reaction of *cis*-1,3-dimethylcyclohexane with CO under the same condition gave *cis,cis*-3,5-dimethylcyclohexanecarboxylic acid (**2**), its *trans,trans* isomer (**3**), and *trans,trans*-2,4-dimethylcyclohexanecarboxylic acid (**4**) in 121, 49, and 108% yields, respectively, together with small amounts of 2,4- and 3,5-dimethylbenzoic acids (44%). The result is summarized in Scheme 2 with the product ratio per one hydrogen. In the latter

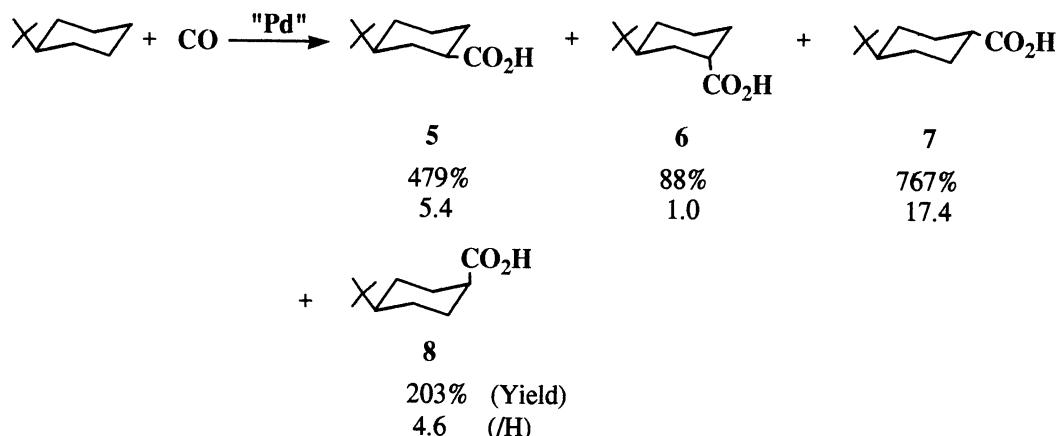


Scheme 2.

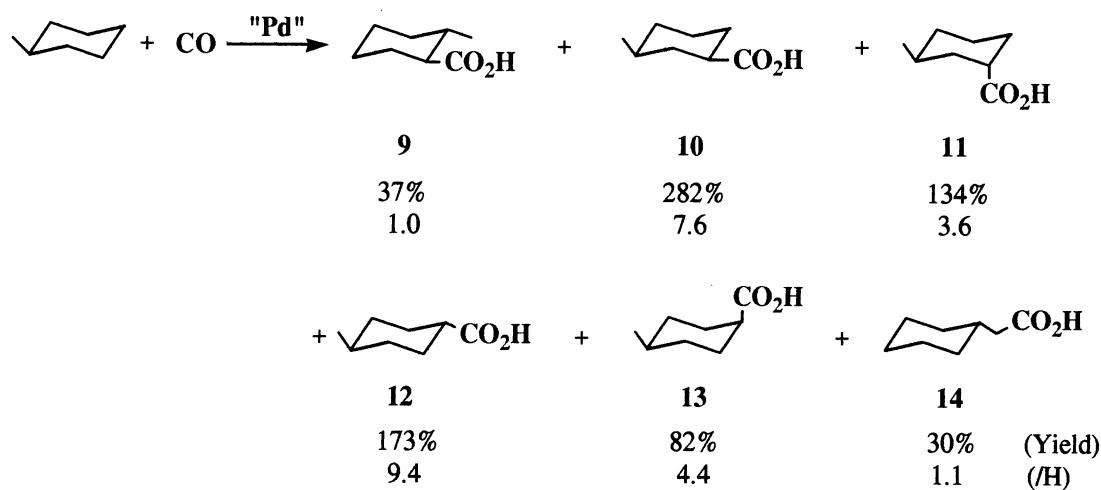
reaction, thermodynamically stable isomers **2** and **4** in which substituents are all at the equatorial positions were preferentially formed through attack at the sec-carbon. But only isomer derived from the reaction at the tert-carbon was not formed because of steric hindrance of the CH_3 group. Thus, the reaction took place more preferentially at the position (C-3) far from the CH_3 group than at the adjacent C-2 position (**2** + **3** vs. **4**).

Similar results were obtained in the reactions of tert-butyl- and methylcyclohexanes. The product ratios for *trans*-4-tert-butylcyclohexane-carboxylic acid (**7**) and *trans*-4-methylcyclohexanecarboxylic acid (**12**) whose substituents are all at the equatorial positions were the highest in the respective cases. No isomer derived from the reaction at tert-carbon was not formed (Schemes 3 and 4). In the case of methylcyclohexane, small amounts (30%) of cyclohexylacetic acid (**14**) derived from the reaction at

CH_3 (prim-carbon) were also formed.

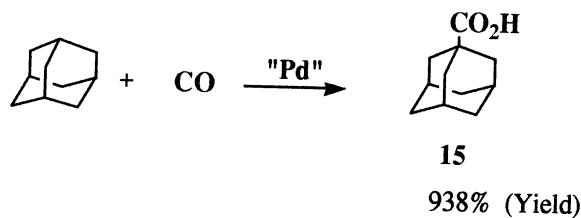


Scheme 3.



Scheme 4.

In the reactions of substituted cyclohexanes described above, no products derived from the reaction at tert-carbon were formed because of steric hindrance of the substituents. However, the reaction of adamantane with CO gave 1-adamantanecarboxylic acid (**15**) in 565% yield as a sole product (Scheme 5). This result indicates that electrophilic attack²⁾ of $\text{Pd}^{\text{+}}\text{OC(O)-CF}_3$ species at the tert-carbon (C-1) is most favorable, since there is no



Scheme 5.

steric hindrance at the bridge-head position of this compound.

From these results we conclude that the present Pd-catalyzed electrophilic carboxylation of cycloalkanes with CO proceeds regio- and stereo-selectively. The reactivity of C-H bonds of cycloalkanes decreases in the order: tert- > sec- > prim-carbon. And the COOH groups in main products were all at the stable equatorial positions.

This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (No. 02453093).

References

- 1) K. Takaki and Y. Fujiwara, *Kagaku*, **46**, 80 (1991); "Activation and Functionalization of Alkanes," ed by C. L. Hill, Wiley, New York (1989).
- 2) Y. Fujiwara, K. Takaki, J. Watanabe, Y. Uchida, and H. Taniguchi, *Chem. Lett.*, 1989, 1687.
- 3) All reactions were carried out as described in Ref. 2.
- 4) Authentic carboxylic acid (**1**) was prepared by two methods: one by the Raney-Ni reduction of 2,5-dimethylbenzoic acid, and the other by the Diels-Alder reaction of methyl crotonate with isoprene. Other acids were also prepared by similar methods except for the acids **7**, **8**, and **14** which are commercially available. ^{13}C -NMR (CDCl_3) of **1**: δ 20.3 (CH_3), 22.2 (CH_3), 31.9 (CHMe), 33.8 (CHMe), 34.3 (CH_2), 34.6 (CH_2), 38.2 (CH_2), 51.3 (CHCO_2H), and 182.8 (CO_2H). Spectroscopic data of other products will be reported elsewhere.

(Received June 1, 1991)