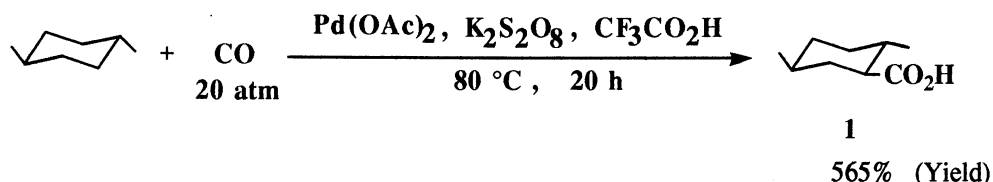


Pd-Catalyzed Regio- and Stereo-selective Carboxylation  
of Cycloalkanes with CO

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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.

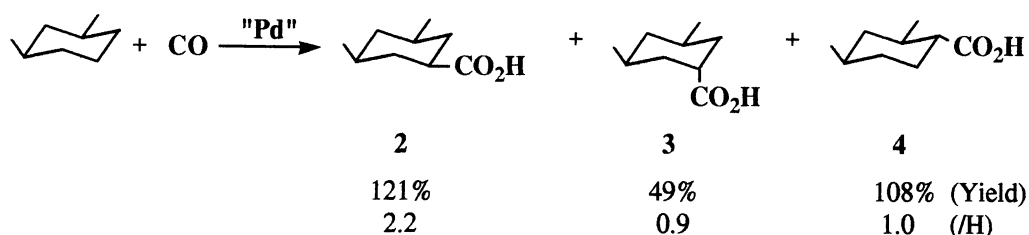
The selective functionalization of alkanes via C-H bond activation by transition metals is one of the most challenging and important subjects from both scientific and practical points of view.<sup>1)</sup> In previous paper, we reported our initial work on the carboxylation of cyclohexane with CO via the activation of alkane C-H bonds by palladium catalysts without irradiation.<sup>2)</sup> 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  $\text{CF}_3\text{COOH}$  (3.3 ml) at 20 °C for 20 h in an autoclave gave trans,cis-2,5-dimethylcyclohexanecarboxylic acid (**1**) in 565% yield based on Pd with small amounts of 2,5-dimethylbenzoic acid (54%).<sup>3)</sup> GC, GC-mass, and  $^{13}\text{C}$ -NMR spectroscopic comparison with the authentic sample of **1**<sup>4)</sup> revealed that three substituents (two  $\text{CH}_3$  groups and one  $\text{COOH}$  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  $\text{Pd}^+\text{OC}(\text{O})\text{CF}_3$  at the tert- and prim-carbons, respectively, were not formed. Hence, this reaction occurred quite regio- and stereoselectively 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

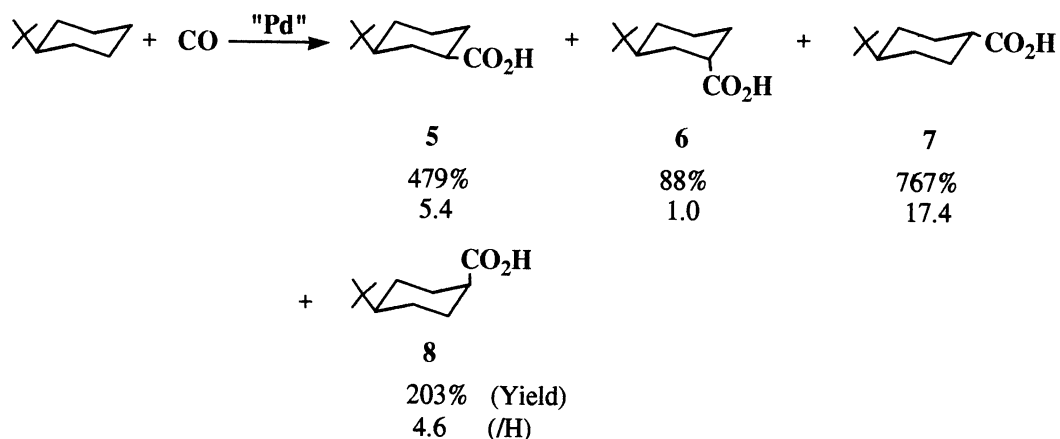


Scheme 2.

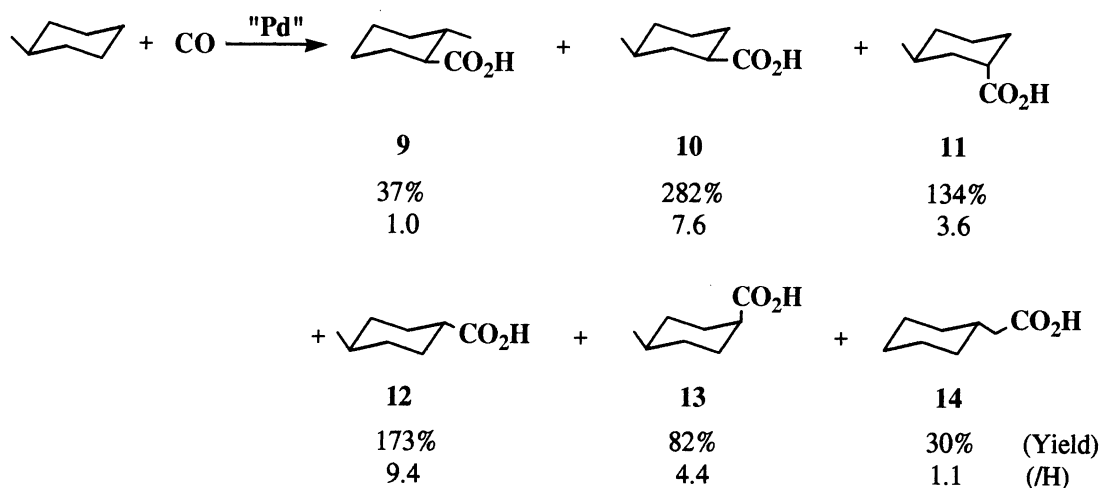
reaction, thermodynamically stable isomers **2** and **4** in which substituents are all at the equatorial positions were preferentially formed through attack at the sec-carbon. But only isomer derived from the reaction at the tert-carbon was not formed because of steric hindrance of the  $\text{CH}_3$  group. Thus, the reaction took place more preferentially at the position (C-3) far from the  $\text{CH}_3$  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-butylcyclohexanecarboxylic 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<sub>3</sub> (prim-carbon) were also formed.

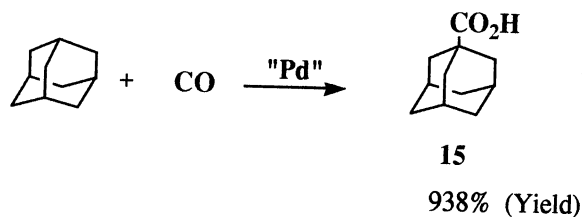


Scheme 3.



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 attack<sup>2)</sup> of Pd<sup>+</sup>OC(O)-CF<sub>3</sub> 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 stereoselectively. 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.

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#### 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.  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) of **1**:  $\delta$  20.3 ( $\text{CH}_3$ ), 22.2 ( $\text{CH}_3$ ), 31.9 ( $\text{CHMe}$ ), 33.8 ( $\text{CHMe}$ ), 34.3 ( $\text{CH}_2$ ), 34.6 ( $\text{CH}_2$ ), 38.2 ( $\text{CH}_2$ ), 51.3 ( $\text{CHCO}_2\text{H}$ ), and 182.8 ( $\text{CO}_2\text{H}$ ). Spectroscopic data of other products will be reported elsewhere.

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