# Palladium Acetate Catalyzed Synthesis of Cycloalkylacetic Acids by Regioselective Hydrocarboxylation of Methylenecycloalkanes with Formic Acid and 1,4-Bis(diphenylphosphino)butane

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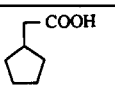
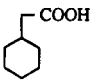
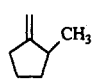
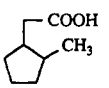
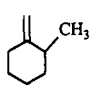
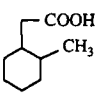
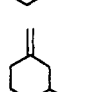
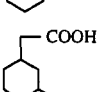
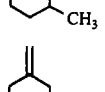
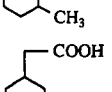
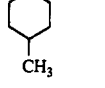
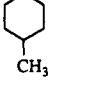
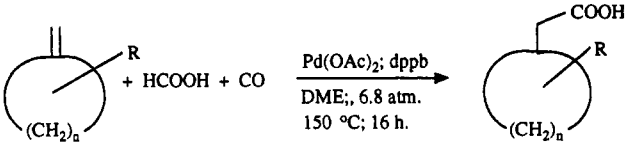
The selective hydrocarboxylation of alkenes and alkynes is of current interest,[1-3] and many catalysts have been successfully employed for such reactions.[4] However, they often lead to mixtures of products and unselective rearrangements. Recently, we found that palladium complexes in the presence of formic or oxalic acid and bidentate phosphine ligands are efficient catalysts for the selective hydrocarboxylation of alkenes and alkynes.[5,6] Herein, we describe new results on the selective hydrocarboxylation of methylenecycloalkanes to give cycloalkylacetic acids. (Several of the acids obtained by this reaction have antiinflammatory properties or are important intermediates in pharmaceutical chemistry.[7,8]) The synthesis of cyclohexylacetic acid, for example, was realized so far using Wittig–Horner reagents[9] followed by hydrogenation.[7] The yield of acid was low (30%) and unwanted by-products were formed. High yields and excellent selectivities for cycloalkylacetic acids were realized by direct hydrocarboxylation of the corresponding methylenecycloalkanes using catalytic amounts of palladium acetate ($Pd(OAc)_2$) and 1,4-bis(diphenylphosphino)butane (dppb), together with formic acid at a low pressure of carbon monoxide (6.8 atm.).

Methylenecyclohexane (R = H, $n$ = 5) reacts with 2 equiv of formic acid and a catalytic amount of palladium acetate and 1,4-bis(diphenylphosphino)butane (dppb) in 1,2-dimethoxyethane (DME) for 16 h at 150 °C and 6.8 atm of carbon monoxide to give cyclohexylacetic acid in 94% yield. No acids were formed in the absence of dppb or by the use of monodentate phosphine ligands such as triphenylphosphine. Low yields of acids (15–25%) were obtained using other bidentate phosphine ligands such as 1,2-bis(diphenylphosphino)ethane and 1,3-bis(diphenylphosphino)propane. Carbon monoxide is required for this reaction. Only reduction occurred (methylcyclohexane) when a nitrogen atmosphere was used. Repetition of the reaction in the presence of either water, water and hydrogen (6.8 atm), water and Lewis acid ($BF_3$·$Et_2O$), or acetic acid in place of formic acid does not result in the carbonylation of olefins.

**Table I. Hydrocarboxylation of Methylenecycloalkanes in the Presence of Formic Acid and Carbon Monoxide Catalyzed by $Pd(OAc)_2$–dppb[a]**

| entry | alkene[b] 1 | yield[c] (%) | product[d] 2 | trans:cis | ref |
|---|---|---|---|---|---|
| 1 |  | 86 |  | | |
| 2 |  | 94 |  | | |
| 3 |  | 65 |  | 82:18 | 15 |
| 4 |  | 70 |  | 72:28 | 7 |
| 5 |  | 90 |  | 15:85 | 14 |
| 6 |  | 95 |  | 80:20 | 7, 12 |
| 7 |  | 91 |  | 80:20 | 7, 13 |

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol); dppb (0.04 mmol); HCOOH (5.0 mmol); 1 (2.5 mmol); DME (5.0 mL); 150 °C; 16 h; 6.8 atm of CO. [b] Alkenes were prepared using methods described in the literature.[10,11] [c] Isolated yields. [d] Determined by NMR spectroscopy and by comparison with literature data[7,12-15] (entries 3–7) or by comparison with authentic materials (entries 1–2).




1 2

R = H, $CH_3$, Ph.

n = 4,5.

dppb= $Ph_2P$-$(CH_2)_4$-$PPh_2$.

The results of the application of the $Pb(OAc)_2$–dppb–HCOOH catalytic system[5] for the regio- and stereoselective hydrocarboxylation to other methylenecycloalkanes are given in Table I. In all cases, good yields of acids were obtained (65–95%). Methylenecyclopentane gives the corresponding carboxylic acid in 86% yield (entry 2). The hydrocarboxylation of substituted methylenecycloalkanes is also stereoselective. The 2-, 3-, and 4-methylmethylenecycloalkanes (entries 3–6) afford the corresponding

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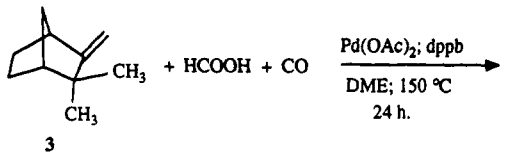
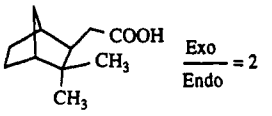
methylcycloalkylacetic acids, in which the thermodynamically more stable isomer was the major product. Similarly, 4-phenylmethylenecyclohexane (entry 7) gave 4-phenylcyclohexylacetic acid in 91% yield, where the trans isomer was formed as a major product (80%).

Camphene, 3, can also react under the described conditions, but the best yield (65%) of the corresponding acid[16] was obtained at 40 atm (30% at 6.8 atm). In both cases the ratio of exo to endo isomer was 2.




3




4

30% (using 6.8 atm CO)
65% (using 40 atm CO)

The mechanism is likely analogous to that proposed previously for reactions of simple olefins.[5a]

In conclusion, the simple catalytic system $Pd(OAc)_2$–dppb–HCOOH is useful for the synthesis of cycloalkylacetic acids, some of which have antiinflammatory properties.

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## Experimental Section

**General Considerations.** $^1H$ NMR spectral data were obtained using Varian Gemini 200 and/or XL-300 spectrometers. Mass spectral determinations were made using a VG 7070E instrument.

All methylenecycloalkanes were prepared using methods described in the literature.[10,11] Triphenylphosphine, 1,4-bis(diphenylphosphino)butane, 1,3-bis(diphenylphosphino)propane, 1,2-bis(diphenylphosphophino)ethane, palladium acetate, HCOOH, and DME were purchased from Aldrich Chemical Co. and were used as received.

**General Procedure for the Hydrocarboxylation of Methylenecycloalkanes.** In a 45-mL autoclave were placed $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), dppb (17 mg, 0.04 mmol), and 5.0 mmol of formic acid in 5.0 mL of DME. To this mixture was added 2.5 mmol of cycloalkene. The autoclave was purged with carbon monoxide and then pressurized to 6.8 atm. CO. The reaction mixture was stirred at 150 °C. After reaction was complete (16–24 h), the reaction was cooled to room temperature and the autoclave was opened. The solvent was removed by rotary evaporation, and 1–2 N NaOH (15 mL) was added to the resulting oil or solid. The NaOH solution was washed with ether (3 × 50 mL), neutralized to pH ~7 with concnd HCl, and then extracted with ether (3 × 50 mL). The ether was washed with $H_2O$ (3 × 50 mL), dried ($MgSO_4$), and concentrated to give the acid. Further purification, if necessary, was effected by distillation.

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