Cp₂ZrCl₂-Mediated Three-Component Coupling Reactions of CO₂, Ethylene (or Alkynes), and Electrophiles Leading to Carboxylic Acid Derivatives

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Abstract: Zirconacycles **1** and **2** can be simply generated from Cp_2ZrCl_2 , EtMgBr, and an atmospheric pressure of CO_2 . The treatment of Cp_2ZrCl_2 with EtMgBr followed by exposure to CO_2 generates zirconacycle **1**, which can react with various electrophiles to give a variety of carboxylic acid derivatives. Unsaturated zirconacycles **2** can also generated from Cp_2ZrCl_2 , EtMgBr, alkynes, and CO_2 . Complexes **2** react with electrophiles to give α , β -unsaturated acids stereoselectively.

Key words: carbon dioxide, carboxylic acids, Grignard reactions, metallacycles, nucleophilic additions, alkynes

Carbon dioxide (CO₂) is an attractive C₁ building block in organic synthesis, because it is highly functional, abundant, inexpensive, nontoxic, and nonflammable. The fixation of CO₂ promoted by transition metal complexes has experienced particularly significant progress.¹ The hydrogenation of CO₂ to formic acid or related reactions catalyzed by ruthenium complexes has been the subject of extensive study.² Perhaps the most promising reactions involve the reaction of CO₂ and epoxides in preparing fivemembered cyclic carbonates^{3,4} or the copolymerization of CO₂ and epoxides leading to polycarbonates.⁵ The direct carboxylation of an aromatic ring (Kolbe–Schmitt reaction) is also of interest in this regard.⁶

Recently, the nickel-mediated or catalytic incorporation of CO₂ into unsaturated hydrocarbons, such as alkynes,⁷ allenes,8 1,3-butadienes,9 and diynes10 have been extensively studied. However, due to the relatively inert nature of CO₂, the number of efficient processes for chemical fixation remain limited, compared with gaseous CO.¹¹ Thus, a new type of transformation of CO_2 continues to pose a significant synthetic challenge. We wish to report here on a simple method for the generation of a zirconocene-CO2-ethylene complex 1 and new zirconocene-CO₂-alkyne complexes 2, and their use in the synthesis of unsaturated carboxylic acids (Scheme 1).¹² Zirconacycles, including zirconacyclopentadienes, zirconacyclopentenes, and zirconacyclopentanes, are recognized as useful intermediates in organic synthesis.¹³ Alt reported that the zirconacycle 1 can be prepared from $Cp_2Zr(C_2H_4)(PMe_3)$ and CO_2 .¹⁴ However, to the best of our knowledge, synthetic applications in which this complex is used have not been reported, although its high

SYNLETT 2005, No. 6, pp 0919–0922 Advanced online publication: 23.03.2005 DOI: 10.1055/s-2005-864807; Art ID: U02105ST © Georg Thieme Verlag Stuttgart · New York





potential as a β -metalocarboxylic acid or a homoenolate is self evident.¹⁵ We succeeded in generating the complex 1 in situ, directly from Cp₂ZrCl₂ by an improved method. Thus, the treatment of Cp₂ZrCl₂ with EtMgBr in THF at -78 °C followed by exposure to CO₂ at 0 °C gave complex 1, which was used in further reactions without isolation (Equation 1). It is noteworthy that complex 1 can be converted into various unsaturated carboxylic acid derivatives by coupling with a variety of electrophiles. Some representative examples are summarized in Scheme 1, and the results on the reaction with allylic electrophiles are shown in Table 1. Treatment of 1 with allyl bromide resulted in no reaction. However, the use of CuI (1.2 equiv) as the promoter gave 5-hexenoic acid (3) in 29% vield.^{16,17} The addition of DMPU (2 equiv) improved the yield to 76%. A reaction with cinnamyl bromide gave 6, indicating that the reaction proceeds by an S_N2' mechanism. The reaction at 20 °C slightly improved the yield of





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6. A reaction with propargyl bromide resulted in allenylation to give 8 in 65% yield. The reaction of cyclohexenone with 1 resulted in selectively 1,4-conjugate addition to give 9 in good yield.

A nickel complex also promotes the coupling reactions.¹⁸ The reaction of **1** with cinnamyl bromide in the presence of Ni(cod)₂ (0.5 equiv) resulted in α -allylation to give product **10**, in contrast to CuI, where γ -allylation took place. Palladium complexes also led to the selective formation of α -allylation product **10**, but the efficiency was lower than when the nickel catalyst was used (17%).

The use of PrMgBr in place of EtMgBr, followed by treatment with allyl bromide gave the expected carboxylic acids in low yield and the ratio of the normal and branched

isomers was low. Our attention was next focused on the generation of an unsaturated zirconium– CO_2 complex, such as **2**. It is well known that ethylene, on a zirconium complex can be replaced by other molecules, such as alkynes, aldehydes, nitriles, and isocyanates, to generate other zirconacycles.¹⁹ Thus, complex **2** was obtained simply by the treatment of Cp₂ZrCl₂ with EtMgBr, the addition of an alkyne, and exposure of the reaction mixture to CO_2 , as shown in Scheme 2.²⁰ The use of 3-hexyne gave 2-ethyl-2-pentenoic acid (**12a**) in 70% isolated yield upon acidic treatment. A terminal alkyne gave the corresponding unsaturated carboxylic acid **12d** regioselectively in good yield.

 Table 1
 The Reaction of 1 with Various Electrophiles^a

| Electrophile | Promoter ^b | Product | Yield (%) ^{c,d} |
|--------------|-----------------------|-------------------|-------------------------------------|
| Br | CuI, DMPU | СООН | 76 |
| Br Br | CuI, DMPUCuI | 3 Br COOH | 44 70 |
| e Br | CuI | 4 Me | 67 (57:43) |
| Ph | CuI | 5 COOH Ph | 43 (92:8) 51 (93:7) ^f |
| | CuI | 6 но СООН 7 | 24 ^f |
| ≡ Br | CuI | Соон | 65 |
| | CuI | 8 Ц соон | 57 |
| Br | Ni(cod) ₂ | 9 Соон | 66 |
| Ph | Ni(cod) ₂ | 3 РhСООН 10 | 45 (2:>98) |
| | | | |
| PhI | Ni(cod) ₂ | Ррссоон | 37 |
| | | 11 | |

^a Reaction conditions: Cp₂ZrCl₂ (1 mmol), 3.0 M EtMgBr in Et₂O (2.2 mmol), electrophile (1.2 mmol), 60 °C, 12 h.

^b CuI (1.2 mmol), DMPU (2 mmol), Ni(cod)₂ (0.5 mmol).

^c Isolated yield.

^d The number in parenthesis is the ratio of γ -allylation and α -allylation product.

e A 86:14 mixture of crotyl bromide and 3-bromo-but-1-ene was used.

^f The reaction was carried out at 20 °C.



Scheme 2

The use of allyl bromide as an electrophile gave 2,3-diethylhexa-2,5-dienoic acid (13) in 61% yield (Scheme 3).²¹ The treatment of 2 with NBS/CuI and I₂ underwent halogenation to give 14 and 15, respectively in good yields.²²



Scheme 3

In summary, we report on the development of some new transformations of CO_2 with EtMgBr (as an ethylene source) and electrophiles mediated by Cp_2ZrCl_2 .²³ A variety of carboxylic acid derivatives can be obtained from **1** and electrophiles. Related unsaturated complexes **2** are also easily generated and lead to α , β -unsaturated carboxylic acids stereoselectively. The reaction employs CO, at atmospheric pressure and mild reaction conditions.

Acknowledgment

This work was supported, in part, by grants from Monbusho (The Ministry of Education, Science, Sports, and Culture) and Japan Society for the Promotion of Science. N.C. wishes to thank to The Kansai Electronic Power Co. Inc. for financial support.

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- (17) The reaction was carried out in a 20 mL two-necked flask equipped with a condenser and an inlet tube. To a solution of Cp₂ZrCl₂ (1 mmol, 292 mg) in THF (10 mL) under an atmosphere of dry nitrogen was added EtMgBr (3.0 M solution in Et₂O, 2.2 mmol, 740 µL) at -78 °C. After the mixture was stirred for 1 h at the same temperature, carbon dioxide was bubbled from CO₂ balloon and the reaction mixture was allowed to warm to 0 °C. After the mixture was stirred for 30 min, CuI (1.2 mmol, 228.6 mg) and allyl bromide (1.2 mmol) was added to the reaction mixture, which was stirred at 60 °C for 12 h. Then, the reaction mixture was quenched with 1 N HCl and extracted with Et₂O. The organic layer was extracted with 4 N NaOH aq and the aqueous layer was neutralized with 6 N HCl, washed with Et₂O and brine, dried over MgSO₄. A crude product was obtained after evaporation of the residue in vacuo. 5-Bromohex-5-enoic Acid (4): colorless oil. ¹H NMR

Synlett 2005, No. 6, 919-922 © Thieme Stuttgart · New York

- $(CDCl_3): \delta = 1.91 (tt, J = 7.3, 7.3 Hz, 2 H, CH_2), 2.39 (t, J = 7.3 Hz, 2 H, CH_2CO), 2.49 (t, J = 7.3 Hz, 2 H, CH_2C=), 5.44 (d, J = 1.9 Hz, 1 H, CH=), 5.60–5.61 (m, 1 H, CH=). {}^{13}C NMR (CDCl_3): \delta = 22.6 (CH_2), 32.3 (CH_2CO), 40.3 (CH_2C=), 117.6 (CH_2=), 133.1 (C=), 179.6 (CO). IR (neat): 2944 (s), 2913 (s), 2753 (m), 2670 (m), 1720 (s), 1704 (s), 1629 (s), 1452 (s), 1430 (s), 1411 (s), 1245 (s), 1201 (s), 1180 (s), 1118 (s), 1060 (w), 1035 (w), 1002 (w), 925 (s), 890 (s), 779 (m), 644 (w), 605 (w), 555 (w), 532 (m). MS:$ *m*/z calcd for C₆H₁₀81BrO₂: 194.9844; found: 194.9859.
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- (21) The reaction was carried out in a 20 mL two-necked flask equipped with a condenser and a three-way cock. To a solution of Cp_2ZrCl_2 (1 mmol, 292.3 mg) in THF (10 mL) under an atmosphere of dry nitrogen was added EtMgBr (3.0 M solution in Et₂O, 2.2 mmol, 740 µL) at -78 °C. After the mixture was stirred for 1 h at the same temperature reaction mixture was allowed to warm to 0 °C, and alkyne (1.0 mmol) was added. After the mixture was stirred, the flask was changed with CO₂ and warmed to 50 °C. After the mixture

was stirred for 1 h, the reaction mixture was quenched with 1 N HCl and extracted with Et_2O . The organic layer was extracted with 4 N NaOH aq and aqueous layer was neutralized with 6 N HCl, washed with Et_2O and brine, dried over MgSO₄. The solvent was evaporated in vacuo and afforded products.

- 2,3-Diethylhexa-2,5-dienoic Acid (13): colorless oil. ¹H NMR (CDCl₃): $\delta = 1.05$ (t, J = 7.6 Hz, 3 H, CH₃), 1.06 (t, J = 7.6 Hz, 3 H, CH₃), 2.16 (q, J = 7.6 Hz, 2 H, CH₂), 2.35 (q, J = 7.6 Hz, 2 H, CH₂), 3.17 (d, J = 6.6 Hz, 1 H, =CCH₂C=), 5.01 (dd, J = 8.5, 1.9 Hz, 1 H, CH₂=), 5.06 (dd, J = 15.4, 1.9 Hz, 1 H, CH₂=), 5.75–5.90 (m, 1 H, CH=). ¹³C NMR (CDCl₃): $\delta = 12.8$ (CH₃), 14.1 (CH₃), 22.8 (CH₂), 26.3 (CH₂), 38.4 (=CCH₂C=), 115.8 (CH₂=), 129.2 (COC=), 136.1 (CH=), 151.6 (C=), 174.5 (CO). IR (neat): 3077 (s), 2971 (s), 2935 (s), 2877 (s), 1681 (s), 1637 (s), 1617 (s), 1455 (m), 1403 (s), 1376 (m), 1301 (s), 1251 (s), 1191 (s), 1122 (w), 1049 (w), 997 (m), 948 (m), 912 (s), 788 (m), 746 (w) cm⁻¹. MS: m/z calcd for C₁₀H₁₆O₂: 168.1150; found: 168.1157.
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