

The reaction of dialkoxytitanacyclopropanes and dialkoxytitanacyclopropenes with carbon dioxide

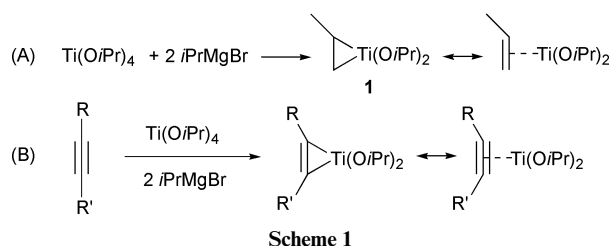
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Dialkoxytitanacyclopropanes and dialkoxytitanacyclopropenes react with one molecule of carbon dioxide to afford diversely substituted carboxylic acids after hydrolysis.

Dialkoxytitanacyclopropanes are putative intermediates in the Kulinkovich cyclopropanation reaction.¹ They are most conveniently generated from titanium alkoxides² and Grignard reagents (Scheme 1, A). When this procedure is run in the

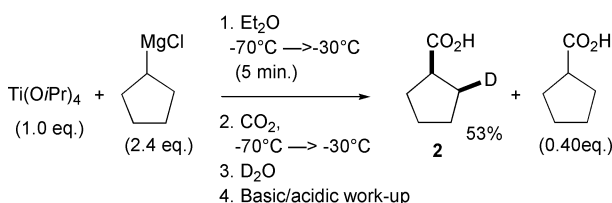


presence of internal alkynes, dialkoxytitanacyclopropenes are formed³ (Scheme 1, B). The chemistry of both types of complex is very rich.^{1,4} However, to the best of our knowledge, their reaction with carbon dioxide has not been investigated so far, although examples involving bis(cyclopentadienyl)titanacyclopropenes are known.⁵

Dialkoxytitanacyclopropanes are normally generated in the presence of the requisite electrophilic trap, a carboxylic ester (in the original Kulinkovich reaction) or amide (in the extension discovered by de Meijere *et al.*). Because of the well-known reaction of Grignard reagents with CO₂,⁶ this standard procedure could not be applied, and a pre-formed solution of titanacyclopropane was required.

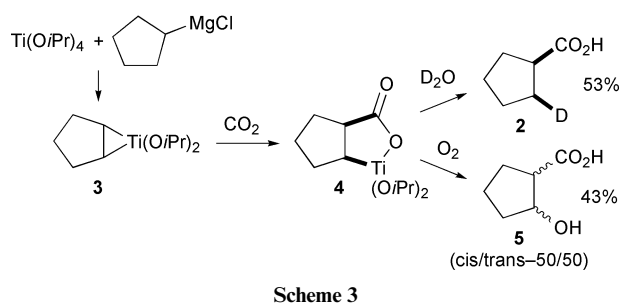
Marek *et al.*⁷ have already reported the preparation of diisopropoxy(η²-propene)titanium **1** in diethyl ether at -50 °C,⁸ albeit with unsatisfactory reproducibility. We chose to work with the cyclopentylmagnesium chloride–titanium tetraisopropoxide system⁹ because we thought side-reactions might be slower than in the case of **1**.

When a mixture of cyclopentylmagnesium chloride and titanium tetraisopropoxide in diethyl ether was rapidly warmed from -70 °C to -30 °C, then treated with carbon dioxide followed by D₂O, β-deuterated cyclopentylcarboxylic acid **2** was produced (Scheme 2). Best results were obtained with 2.4 equivalents of Grignard reagent. Working at -40 °C instead



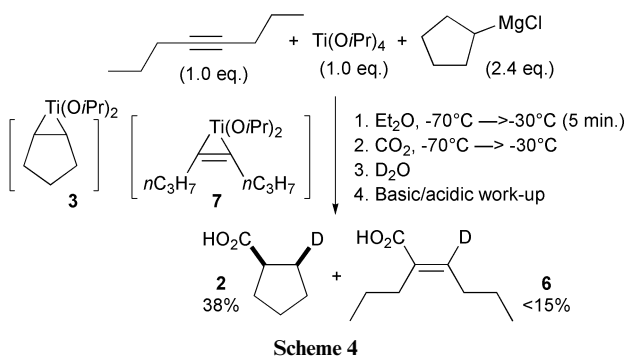
of -30 °C did not improve the yield, but made the reaction slower. The presence of non-deuterated cyclopentylcarboxylic acid probably stemmed from the reaction of remaining cyclopentylmagnesium chloride with CO₂.

Intermediate complex **3** probably reacts with one molecule of carbon dioxide to yield the new species **4**, which delivers **2** upon hydrolysis or alternatively, the β-hydroxy acid **5** when oxygen is added as the second reagent (Scheme 3).



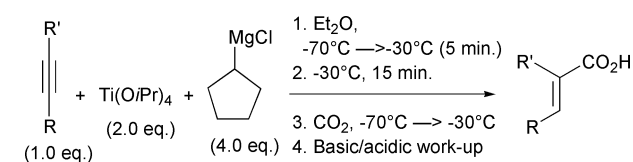
Solutions of complex **3** can thus be prepared in about 50% yield by simply mixing cyclopentylmagnesium chloride and titanium tetraisopropoxide in diethyl ether at -70 °C, warming to -30 °C in 5 minutes, then cooling again to -70 °C.† We believe that the formation of **3** is faster than its decomposition at -30 °C if the concentration of Grignard reagent is sufficient, although both processes seem to occur simultaneously. The choice of diethyl ether as the solvent proved to be essential: in diisopropyl ether, the process was much less efficient, while in THF it did not proceed.¹⁰

The reaction was repeated in the presence of oct-4-yne under otherwise identical conditions. The major product was still deuterated acid **2**, while vinyl carboxylic acid **6** arising from the reaction of diisopropoxy(η²-octyne)titanium **7** with CO₂ was produced in low yield (Scheme 4).



The ligand exchange reaction appeared to be slower than the formation of intermediate **3** at -30 °C, and the reaction time was thus extended to 15 minutes. Using 2.0 equivalents of cyclopentylmagnesium chloride instead of 2.4 relative to Ti(OiPr)₄, the reaction was found to be much cleaner, and best

Table 1



Alkyne	Isolated product(s)	Yield (%)
1. $n\text{-C}_3\text{H}_7\text{-C}\equiv\text{C}-n\text{-C}_3\text{H}_7$	$n\text{-C}_3\text{H}_7\text{-CH=CH-CO}_2\text{H}$	83%
2. $\text{Ph-C}\equiv\text{C}-n\text{-C}_3\text{H}_7$	$\text{Ph-CH=CH-CO}_2\text{H}$	43% ^{b,c}
3. $\text{Ph-C}\equiv\text{C}-n\text{-C}_3\text{H}_7$	$\text{Ph-CH=CH-CO}_2\text{H}$ $\text{Ph-CH=CH-CO}_2\text{H}$ (deuterated)	41% ^{b,d}
4. $n\text{-C}_3\text{H}_7\text{-C}\equiv\text{C}-\text{OBn}$	$n\text{-C}_3\text{H}_7\text{-CH=CH-CO}_2\text{H}$	87%
5. $n\text{-C}_3\text{H}_7\text{-C}\equiv\text{C}-\text{OTBS}$	$n\text{-C}_3\text{H}_7\text{-CH=CH-CO}_2\text{H}$ $n\text{-C}_3\text{H}_7\text{-CH=CH-CO}_2\text{H}$ (isomer)	19% ^{a,e} 29% ^a
6. $\text{Ph-C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{OTBS}$	$\text{Ph-CH=CH-CO}_2\text{H}$ $\text{Ph-CH=CH-CO}_2\text{H}$ (isomer)	38% ^a 29% ^a
7. $\text{Ph-C}\equiv\text{C}-\text{CH}_2\text{CH}_2\text{OBn}$	$\text{Ph-CH=CH-CO}_2\text{H}$ $\text{Ph-CH=CH-CO}_2\text{H}$ (isomer)	41% ^a (2:1)
8. $\text{Ph-C}\equiv\text{C}-\text{TMS}$	$\text{Ph-CH=CH-CO}_2\text{H}$	19% ^a
9. $\text{Ph-C}\equiv\text{C}-\text{Ph}$	$\text{Ph-CH=CH-CO}_2\text{H}$ $\text{Ph-CH=CH-CO}_2\text{H}$ (isomer)	30% ^a 5% ^a

^a Isolated yield after flash column chromatography. ^b Isolated by crystallisation as a single isomer. ^c The other regioisomer was also detected in the crude (selectivity $\approx 86 : 14$). ^d The reaction was quenched with D_2O (deuterium incorporation $\approx 86\%$). ^e Two minor isomers were also detected by ^1H NMR of the crude (Ratio $\approx 3 : 1 : 1$).

results were obtained when a deficiency of alkyne was used (Table 1).

The method appears to be quite general, highly stereoselective, and moderately (entry 7) to highly (entries 2 and 8) regioselective. However, it is poorly efficient in several cases (entries 4, 5, 8 and 9). The variable amounts of triple-bond reduction products isolated indicate that the intermediate titanacyclopropenes are formed but react incompletely with carbon dioxide or do not react at all. To explain this fact, steric hindrance may be invoked for the examples shown in entries 5 and 8. In the case of 1-benzyloxyhex-2-yne (entry 4), we believe the titanacyclopropene is stabilised by coordination with the oxygen atom. When the benzyl group is replaced with a bulky TBS group (entry 5), the oxygen loses its coordination ability

and the reaction with CO_2 is observed again. Improvement of the efficacy of the carbon dioxide addition step is currently being studied.

The extension of the process to the hydrocarboxylation of terminal alkenes *via* ligand exchange from **3** was also investigated. Preliminary results show that the reaction is feasible, but further work is needed to obtain useful yields of alkylcarboxylic acids. ‡

In conclusion, dialkoxytitanacyclopropanes and dialkoxytitanacyclopropenes react with one molecule of carbon dioxide, leading to carboxylic acids after hydrolysis. We hope the present method will complement the existing procedures for the hydrocarboxylation of alkynes,¹¹ only a few of which use carbon dioxide under standard pressure as the carbonyl source.¹² The possibility of extending this result to the use of carbon disulfide, as well as trapping the intermediate five-membered cyclic titanium complexes with other electrophiles is currently under study in our laboratory and will be reported in due course.

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Notes and references

† **3** appears to be reasonably stable at -70°C : when the solution was stirred for one hour at that temperature before the CO_2 addition, the yield in deuterated **2** was 43%.

‡ For instance, 5-benzyloxy-pentanoic acid was obtained from 4-benzyloxybut-1-ene as a single isomer, but in 8% yield only.

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