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Diisopropyloxy(η^2-cyclopentene)titanium for the diastereoselective synthesis of various 1,2-disubstituted cyclopentanes

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Abstract—The reaction of 3 equiv of cyclopentylmagnesium chloride with 2 equiv of titanium(IV) isopropoxide at low temperature (−70 to −50 °C) leads to the formation of 1 equiv of diisopropyloxy(η^2-cyclopentene)titanium containing low amounts of the starting Grignard reagent. The sequential addition of two electrophiles onto this titanium complex involved as an intermediate in Kulinkovich-type reactions delivers various 1,2-disubstituted cyclopentane rings with generally high diastereoselectivity. Mechanistic considerations and possible extensions of this method are discussed.

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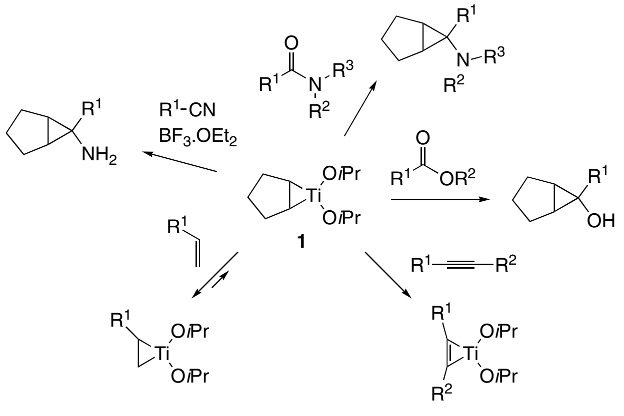
1. Introduction

Diisopropyloxy(η^2-cyclopentene)titanium **1** is a putative intermediate in Kulinkovich-type reactions,[1–12] and is believed to be a product of the reaction of titanium tetraisopropoxide or chlorotitanium triisopropoxide with 2 equiv of cyclopentylmagnesium chloride. It has been generated in the presence of carboxylic esters, amides or nitriles, leading to the corresponding cyclopropanols (Kulinkovich reaction)[13] or aminocyclopropanes (Kulinkovich–de Meijere and Kulinkovich–Szymoniak reactions).[14–16] When a functionalised alkene is also present, efficient ligand exchange usually takes place prior to cyclopropanation.[17,18] Ligand exchange reactions are also feasible with alkynes, leading to diisopropyloxy(η^2-alkyne)titanium complexes (Scheme 1).[19–21]



Scheme 1.

As we demonstrated a few years ago, it is possible to prepare complex **1** in the absence of any electrophilic trapping reagent, in spite of its instability. The addition of 2.4 equiv of cyclopentylmagnesium chloride to a diethyl ether solution of titanium(IV) isopropoxide at −78 °C followed by warming up to −30 °C in 5 min leads reproducibly to a 50% yield of **1**, as shown by the formation of β-deuteriated cyclopentanecarboxylic acid **4** upon reaction with carbon dioxide and deuterium oxide.[19,20] However, the solutions of complex **1** thus prepared always contain significant amounts of cyclopentylmagnesium chloride that may cause unwanted side reactions.[22,23] In the present letter, we would like to report a solution to this problem, as well as report the results of a fresh study of the reactivity of complex **1** illustrating the potential of this method.

2. Results

In the former procedure, an excess of Grignard reagent was needed to ensure a sufficiently fast formation of **1**

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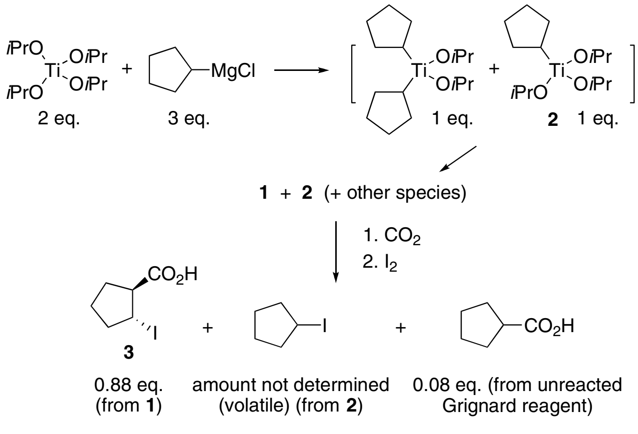
and win over its decomposition. We reasoned that another way of achieving this would be to use 2 equiv of titanium(IV) isopropoxide and 3 equiv of cyclopentylmagnesium chloride. As required, the reaction would be expected to be fast and if only minimal decomposition would occur, 1 equiv of **1** would be obtained, along with 1 equiv of **2**, whose presence would normally not be a problem because of its lower reactivity (Scheme 2).

Indeed, these expectations were fulfilled, provided the reaction was performed under relatively high concentration conditions with a careful control of the time and temperature parameters. This is shown by the reaction with carbon dioxide and iodine,[24] according to the following representative procedure: to a solution of titanium(IV) isopropoxide (2.0 equiv, 2.0 mmol) in diethyl ether (5.0 mL) was added cyclopentylmagnesium chloride (2.0 M in Et_2O, 3.0 equiv, 3.0 mmol) at −78 °C. The yellow mixture was warmed to −50 °C in 5 min, then maintained at that temperature for 8 min and became dark-brown to black. After cooling back to −78 °C, carbon dioxide was bubbled through the solution, which at the same time was allowed to warm to −30 °C in 30 min and became orange. Iodine (2.0 equiv, 2.0 mmol) was then introduced into the flask and the cold bath was removed. After 2 h of stirring at 20 °C, 1 N HCl aqueous solution and $Na_2S_2O_5$ crystals were added. The mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica-gel flash chromatography and crystallisation led to the isolation of 0.88 mmol of **3** (88% yield based on the expected 1 equiv of intermediate complex **1** formed). Retrospective analysis of the ^1H NMR spectrum of the crude product showed that cyclopentanecarboxylic acid had only been produced in a small amount: 80 μmol (Scheme 2).

Other results obtained using various electrophiles are presented in Table 1. Using carbon dioxide and deuterium oxide (entry 2), cyclopentanecarboxylic acid was obtained with 86% of deuterium incorporation at the β-position, which is a significant improvement over our previous method. *N*-Bromosuccinimide could also be used as the subsequent electrophile, delivering the corresponding β-bromocarboxylic acid **5**. Our attempts to make a second carbon–carbon bond by adding allyl bromide in the presence of copper(I) cyanide and lithium chloride met with very limited success, the expected product **6** being isolated in 13% yield only.



Scheme 2.

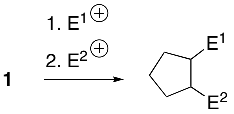
As expected from the known reactivity of titanacyclopropanes with nitriles,[15,16,25–29] the reaction of **1** with benzyl cyanide and benzonitrile leads to the formation of ketones (entries 5–7), with the former giving better results. Complex **1** also reacts with imides (entries 8 and 9), in agreement with a previously published study featuring similar compounds, which were then isolated as unwanted by-products.[30] Using diethyl carbonate and ethyl 2-methoxyacetate as the first electrophiles, iodinolysis at low temperature gave the corresponding ester **12** and ketone **13**, albeit in a rather low yield.[31] To the best of our knowledge, these are the first examples where intermediates of intermolecular Kulinkovich reactions are being trapped (Scheme 3).[32]

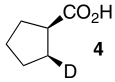
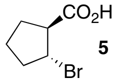
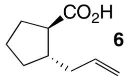
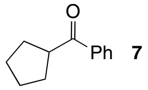
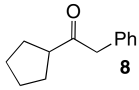
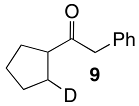
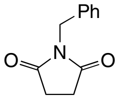
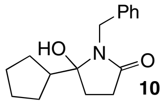
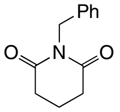
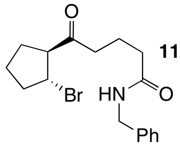
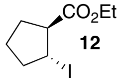
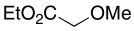
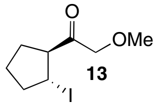
To finish with, we carried out a couple of experiments to examine a possible extension to six-membered rings (Table 2). The results reveal a dramatic difference when switching from cyclopentylmagnesium chloride to cyclohexylmagnesium chloride. The only products observed using carbon dioxide and iodine as electrophiles were cyclohexyl alcohol and iodocyclohexane (Table 2, entry 1). Even when the reaction mixture had been allowed to warm to 0 °C before the addition of carbon dioxide from −78 to −30 °C, no carboxylic acid was formed (entry 2). In contrast, when the mixture of titanium(IV) isopropoxide and cyclohexylmagnesium chloride in Et_2O was warmed from −30 to 0 °C, *while bubbling carbon dioxide* with the ultimate addition of iodine, the expected iodoacid **14** was isolated, albeit in a low yield (entry 3). Deuteriated cyclohexylcarboxylic acid **15** was prepared similarly (entry 4). Interestingly, dicyclohexylketone was isolated as a by-product in both cases.

3. Stereochemistry

Iodoacid **3**, formed as a single diastereoisomer, possesses the trans relative configuration at the carbons bearing the acid group and the iodine atom as shown by X-ray crystallography of a single crystal (Scheme 4).[33] The six-membered ring analogue **14** is also the trans single diastereoisomer as revealed by the $^3J_{H-H}$ coupling constants of the hydrogen α to the acid group, in agreement with equatorial conformations of this group and the iodine atom. Bromoacid **5**, bromoketone **11**, iodoester **12** and iodoketone **13** were obtained as trans single diastereoisomers as well as shown by the ^1H and ^{13}C NMR spectra of the crude and isolated products. For these compounds, the ^1H NMR signal of the cyclopentyl CH group displays a similar pattern to that of **3**, with comparable $^3J_{H-H}$ coupling constants. The allyl derivative **6** is tentatively assigned the trans relative configuration as well. In contrast, deuteriated cyclohexylcarboxylic acid **15** appears to possess the cis relative configuration. The ^1H NMR signal of the hydrogen α to the acid group is an enlarged doublet with

Table 1. Sequential addition of complex **1** prepared from 2 equiv of Ti(O*i*-Pr)$_4$ and 3 equiv of *c*C$_5$H$_9$MgCl at low temperature in Et$_2$O onto two electrophiles



Entry	$E^{1\oplus}$	$E^{2\oplus}$	Product	Yield (%)[a]
1	CO_2	I_2	**3**	88[b]
2	CO_2	D_2O	 **4**	90[b,c]
3	CO_2	NBS	 **5**	77[b]
4	CO_2	CuCN, 2LiCl, allyl bromide	 **6**	13[b,d]
5	PhCN	H_3O^+	 **7**	10[d]
6	BnCN	H_3O^+	 **8**	52
7	BnCN	D_2O	 **9**	52[e] (≥92%-*d*)[f]
8		H_3O^+	 **10**	84
9		NBS	 **11**	16[b]
10	$EtOCO_2Et$	I_2	 **12**	35[b]
11		I_2	 **13**	16[b,e]

Except in the cases of CO$_2$ gas, H$_3$O$^+$ and D$_2$O, which were added in excess amounts, 2 equiv of the electrophiles were used. Yields are not optimised.

[a] Based on the expected 1 equiv of complex **1** formed. Unless otherwise stated, isolated yield.

[b] Single diastereoisomer.

[c] 1.05 equiv of cyclopentanecarboxylic acid were obtained with 86% of deuterium incorporation as measured by ESI$^-$ mass spectroscopy.

[d] The yield was estimated by ^{1}H NMR spectroscopy of the crude product using an internal standard.

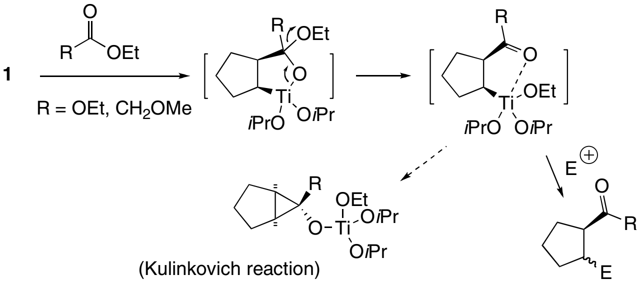
[e] Isolated yield of the corresponding hydrazone prepared by reaction with 2,4-dinitrophenylhydrazine.

[f] Measured by ESI$^-$ and EI mass spectroscopy.

$^3J_{H–H}$ coupling constants of 11 Hz, in agreement with an equatorial conformation of the carboxylic acid group and an axial conformation of the deuterium atom. Besides, the ^{1}H NMR signal of the axial hydrogen atoms β to the acid, at 1.46 ppm, integrate for one proton only. The relative configuration of the cyclopentyl analogue **4** is tentatively assigned as cis by analogy with **15**.

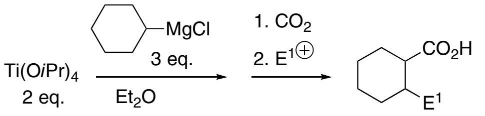
4. Discussion

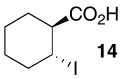
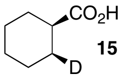
Our results are in agreement with the hypothesis that titanacyclopropane **1** is formed at low temperature as shown in Scheme 2, and then trapped with the various electrophiles used. In the cases of carbon dioxide addition, we believe titanalactone **16** is formed (Scheme 1). Deuteriolysis of this complex is expected to deliver the corresponding deuteriated acid with retention of configuration, which is consistent with our observations. On the contrary, the observed stereochemistry of compound **3** suggests that iodinolysis proceeds with inversion of configuration. This could be rationalised by invoking a S$_E$2 (back) mechanism, with an attack of iodine from the least hindered *exo*-face of the titanalactone, possibly activated as an *ate* complex. To our



Scheme 3.

Table 2. Sequential addition of a complex prepared from 2 equiv of $Ti(Oi\text{-}Pr)_4$ and 3 equiv of $cC_6H_{11}MgCl$ in Et_2O onto carbon dioxide and an electrophile, either H_2O or D_2O. Yields are not optimised



Entry	$E^{1\oplus}$	Product	Yield (%)[a]
1	I_2	—	0[b,c]
2	I_2	—	0[b,d]
3	I_2	 **14**	14[e]
4	D_2O	 **15**	18[e] (93%-*d*)[f]

[a] Isolated yield based on the expected 1 equiv of titanacyclopropane formed.

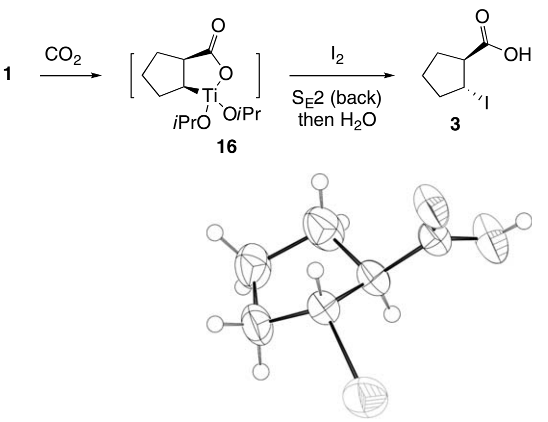
[b] The crude product contained essentially iodocyclohexane and cyclohexanol (in lesser amount).

[c] The same conditions were used as for the synthesis of **3**.

[d] The same conditions were used as for the synthesis of **3**, except the mixture was allowed to warm to 0 °C and stirred at that temperature for 30 min prior to CO_2 addition from −78 to −30 °C.

[e] CO_2 was added in 15 min from −30 to 0 °C. The acid is formed as a single diastereoisomer.

[f] Measured by ESI^- mass spectroscopy.



Scheme 4.

knowledge, there are no previous reports regarding the stereochemistry of halogenolysis reactions of organotitanium compounds at sp^3 chiral carbon centres. Although reactions of this type have been shown to proceed with retention in the case of zirconium derivatives,[34,35] we, as well as others, were recently led to propose a S_E2 (back) mechanism for the cyclopropane ring closures of some organotitanium intermediates.[36,37] In contrast, it cannot be excluded that the trans stereochemistry of **11**, **12** and **13** may result from an epimerisation of the initial reaction products, and no definite conclusion can be drawn in these cases.[38]

In the case of the cyclohexane derivatives **14** and **15**, the results are consistent with a titanalactone intermediate as well. Nonetheless, the difference with the five-membered ring system is striking. The results seem to rule out the hypothesis of the formation of a titanacyclopropane species homologous to **1** under the conditions we used. We tentatively propose that the dicyclohexyltitanium(IV) isopropoxide intermediate is stable in Et_2O at least up to 0 °C and is the species that reacts with carbon dioxide. Indeed, it has been advocated recently that transfer-epimetalation may take place from dialkyltitanium(IV) derivatives with unsaturated organic compounds, rather than titanacyclopropane formation followed by ligand exchange.[39,40] The outcome of such a reaction could be the eventual formation of the titanalactone or, following a different mechanistic pathway, the dicyclohexyl ketone by-product. Further studies will be carried out to get a better insight into the mechanism and improve the yields.

5. Conclusion

The present work shows that diisopropyloxy(η^2-cyclopentene)titanium **1** can be generated quickly at low temperature following a simple experimental procedure, the main by-product being the lowly reactive cyclopentyltitanium(IV) triisopropoxide **2**. The reaction of complex **1** with various electrophiles has an interesting potential since it can provide an access to a variety of 1,2-disubstituted cyclopentane derivatives in one-step and in a highly diastereoselective fashion. It may in principle be extended to the preparation of homologous six-membered ring systems. We will devote our forthcoming work to the improvement of the generality and the development of an asymmetric version of this method.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.117.

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31. From ethyl 2-methoxyacetate, quenching the reaction with saturated ammonium chloride solution delivered the corresponding cyclopentylketone in 21% yield. From the same substrate, bubbling oxygen gas through the reaction mixture prior to the aqueous work-up led to the formation of the *cis* and *trans* β-hydroxyketones, that were isolated in 6% and 3% yield only, respectively. The low diastereoselectivity can be imputed to a radical mechanism in this case, as already evocated by us to explain a related result.[19,20]
32. The corresponding Kulinkovich reactions were performed at room temperature under standard conditions from diethyl carbonate and ethyl 2-methoxyacetate, and delivered the expected bicyclic cyclopropanols in 31% and 22% yield, respectively.
33. Crystallographic data (excluding structure factors) for the structure of **3** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 608937. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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