Mechanism of the Kulinkovich Cyclopropanol Synthesis: Transfer-Epititanation of the Alkene in Generating the Key Titanacyclopropane Intermediate[‡]

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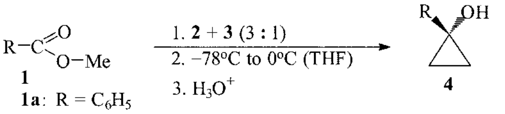
An investigation of the Kulinkovich cyclopropanol synthesis, the interaction of esters with 2:1 or 3:1 mixtures of alkyl Grignard reagents and $Ti(OiPr)_4$ at low temperatures, has been conducted, in order to ascertain which reactive intermediates are involved and how they are interconverted. Because of the nature of the ultimate product, one of the most obvious intermediates is the 1,1-diisopropoxy-1-titanacyclopropane stemming from the epititanation of the alkene set free from the alkyl Grignard reagent employed. A search for the formation of such a titanocycle by warming an ethereal solution of either $Et_2Ti(OiPr)_2$ or $iPr_2Ti(OiPr)_2$ between −78 °C and +25 °C was attempted by chemical trapping with either an ester or nitrile. In this manner it was shown that such a titanocycle was formed in the case of $Et_2Ti(OiPr)_2$ but not with $iPr_2Ti(OiPr)_2$. As to the role of two other potential intermediates, $Ti(OiPr)_2$ and $R_2Ti(OiPr)_2$, it was demonstrated that preformed $Ti(OiPr)_2$ in the presence of ethylene and an ester does not form the corresponding cyclopropanol. Thus, under the reaction conditions $Ti(OiPr)_2$ cannot perform the direct epimetallation necessary to produce the requisite titanacyclopropane. On the other hand, either $iPr_2Ti(OiPr)_2$ or $Et_2Ti(OiPr)_2$ can achieve the transfer-epititanation of ethylene at low temperatures and hence with methyl benzoate yield 1-phenyl-1-cyclopropanol. In contrast, neither $iPr_2Ti(OiPr)_2$ nor $Et_2Ti(OiPr)_2$ can at low temperatures transfer-epititanate propylene. This difference in alkene reactivity can be ascribed to steric factors operating in the proposed octahedral transition state for transfer-epimetallation. Finally, by introducing free ethylene into such Kulinkovich reaction mixtures, either by ethylene gas itself or a third equivalent of EtMgX, the isolated yields of cyclopropanols were more than doubled over those obtained with a 1:2 ratio of $Ti(OiPr)_4$/EtMgX. From this observation one can conclude that free ethylene catalytically initiates the Kulinkovich reaction by coordinating with $Et_2Ti(OiPr)_2$ and undergoes transfer-epititanation to produce the requisite titanacyclopropane and thereby liberates ethylene, which perpetuates the reaction.

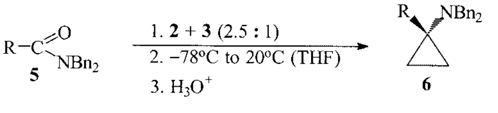
Introduction

One of the most remarkable transition-metal mediated reactions of recent origin has been the titanium-catalyzed Kulinkovich cyclopropanol synthesis.[2,3] In its prototypical form, reported by Kulinkovich and co-workers in 1989, the addition of various methyl esters **1** to an ethereal mixture of ethylmagnesium bromide (**2**) and titanium(IV) isopropoxide (**3**) in a 3:1 molar ratio, starting at −78 °C with hydrolysis at 0 °C, led to excellent yields of 1-substituted cyclopropanols **4** [Equation (1)].[4]



(1)

Soon thereafter, a cyclopropanol synthesis catalyzed by 5−10 mol % of **3** focused attention on this process[5] for the elaboration of natural products containing either 1-substituted- or stereoselective 1,2-disubstituted cyclopropanols.[6−8] The use of *N*,*N*-dialkylcarboxamides **5** in place of esters, using the original Kulinkovich procedure, allowed de Meijere and co-workers to obtain *N*,*N*-dibenzylcyclopropylamines **6** in moderate to good yields [Equation (2)].[9,10]



(2)

The course of the Kulinkovich reaction, when an ethyl Grignard reagent is employed, has been depicted as proceeding via diethyltitanium(IV) diisopropoxide (**7**) to give the titanacyclopropane **9**, without specifying whether titanium(II) diisopropoxide (**8**) is ever set free before it recombines to form **9** (path b), or whether **9** forms directly from

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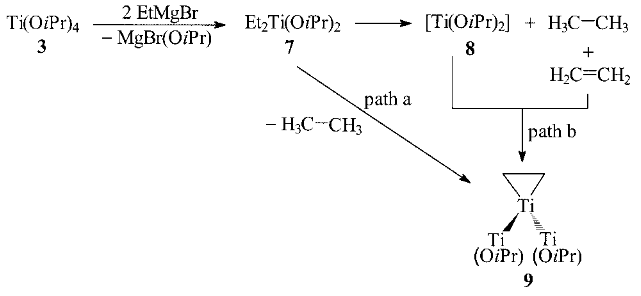
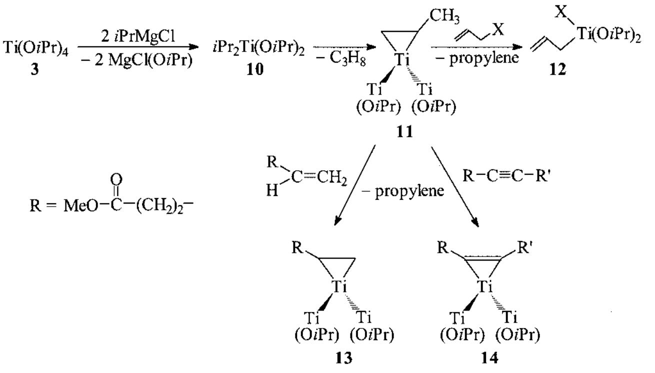
7 with the elimination of ethane (path a) (Scheme 1). The interaction of **9** with an ester to form the cyclopropanolate salt precursor to **4**, is viewed as occurring by the generally accepted reaction pathway for vicinal dimetalloethane reagents.[2,3,4,5]



Scheme 1

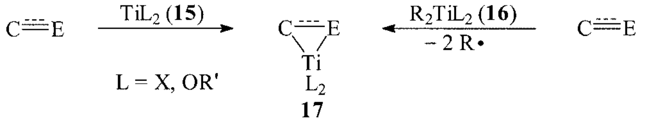
In modifications of the Kulinkovich procedure, where the Grignard reagent[7] (or an analogous organolithium reagent[11]) does not serve as the source of the olefin or acetylene but only as a reductant for the Ti(O*i*Pr)$_4$, it has been assumed without proof that the dialkyltitanium(IV) dialkoxide formed decomposes analogously to that mentioned above, namely **10** to **11** as does **7** to **9**, but then the added allylic halide, olefin or acetylene undergoes ligand exchange with the intermediate titanacyclopropane **11** to form the derived titanium reagents **12**, **13** or **14** (Scheme 2).



Scheme 2

This viewpoint is exemplified by the work of both the Sato group[7] and the Cha group.[8,12] Sato's approach uses mainly the isopropyl Grignard reagent to generate the putative Kulinkovich intermediate **11**, via **10**, with subsequent transfer of Ti(O*i*Pr)$_2$ (**8**) presumably by ligand transfer to an allylic halide,[7] olefin[13] or to acetylene,[14] to form the titanometallics **12**, **13** or **14**, respectively (Scheme 2). Although the final titanium-free products formed by the hydrolysis or oxidation of, or the insertion of unsaturated substrates into, the σ(C−Ti) bonds are consistent with the presence of **12**, **13** or **14** as precursors, the pathway of their formation via intermediates **10** and **11,** and subsequent ligand transfer between **11** and the unsaturated organic substrate has remained unproved and hence uncertain.

Our recent studies on the epititanation of unsaturated organic linkages, C=E or C≡E (E = C, O, N), either directly with TiL$_2$ (**15**)[11,15,16] or indirectly by transfer-epititanation with R$_2$TiL$_2$ (**16**)[17] to form three-membered titanocycles **17** have increased our understanding of the formation and reactivity of such metallocyclic intermediates (Scheme 3). Accordingly, in the present work we sought to employ such insights for determining the nature of the reactive intermediates in the Kulinkovich reaction and their possible pathways of generation.



Scheme 3

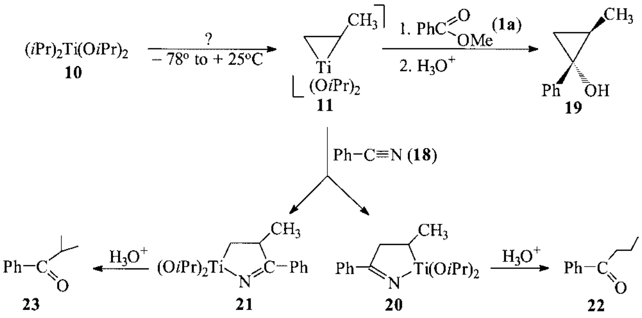
Results and Discussion

Reactive Intermediates in the Kulinkovich Reaction and Its Modifications

In the prototypical Kulinkovich reaction the thermal decomposition of diethyltitanium(IV) diisopropoxide (**7**) is thought to generate the titanacyclopropane **9** intermediate, since capture with the ester reactant provides a fitting rationale for the observed cyclopropanol ring formation [Scheme 1 and Equation (1)].

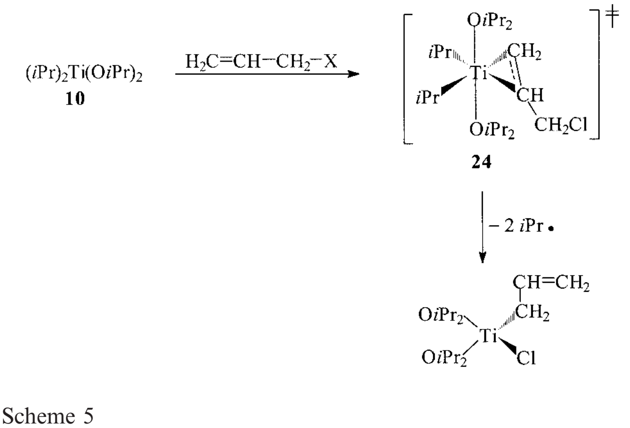
If, however, an ethereal solution of the titanium(IV) intermediate **7** is generated at −78 °C, in the absence of an ester, and then brought to 25 °C, the solution turns black, signaling the formation of **8**.[18] Introduction of the ester **1** to the foregoing reaction solution and further stirring for 7 h leads, upon the hydrolysis step, to no detectable amounts of cyclopropanol **4**. These results show that **9** is only stable, and hence available for cyclopropanol synthesis, at low temperatures (Scheme 1).

Similarly, decomposition of diisopropyltitanium(IV) diisopropoxide (**10**) at low temperatures has been proposed to occur via the titanacyclopropane **11**, the presumed source of Ti(O*i*Pr)$_2$ (**8**) for various organic synthetic procedures used by Sato's group involving allylic halides,[7] olefins[13] or alkynes[14] (Scheme 2). In order to determine whether alkyltitanium **10** does decompose at −78 °C or at higher temperatures to give the 2-methyltitanacyclopropane **11** [termed (η^2-propene)Ti(O*i*Pr)$_2$ by Sato, Scheme 4] two reactions were designed and carried out to chemically trap any of the intermediate **11** formed. In the first reaction, a mixture of presumed **11** and benzonitrile **18** was allowed to react in the temperature range of −78 °C to +25 °C; in the second reaction, a mixture of presumed **11** and methyl benzoate (**1a**) was subjected to the same reaction conditions. If any of intermediate **11** were generated in this temperature range, it would have undergone the Kulinkovich reaction with **1a** to produce cyclopropanol **19** and similarly would have inserted benzonitrile into the C−Ti bonds to form the titanocycles **20** and **21** and, upon hydrolysis, the ketones **22** and **23**.[19]



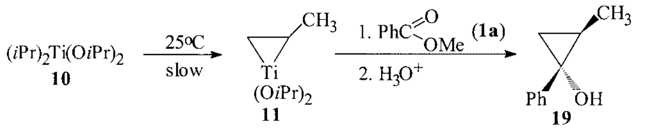
Scheme 4

However, from the ester experiment, no cyclopropanol **19** was formed and from the benzonitrile experiment, the nitrile was recovered unchanged. Therefore, the unavoidable conclusion is that **10** does not decompose to generate intermediate **11** under these experimental conditions. As a corollary it then follows that the reagent responsible for the transfer of the Ti(O*i*Pr)$_2$ unit to allylic halides, olefins or acetylenes in Sato's experiments (Scheme 2) is the diisopropyltitanium(IV) diisopropoxide (**10**) itself. With all these unsaturated substrates, the reaction pathway may rather be the well-documented transfer-epimetallation,[1,17] in which π-coordination of the ligand (in Scheme 5, the π-bond of the allylic halide) to titanium forms an octahedral transition state **24**.



Scheme 5

Confirmation of the stability of **10**, in the absence of any π-bonded substrate, in the temperature range of −78 °C to +25 °C comes from the persistence of the pale yellow to light brown color of the solution of **10** in this temperature range. If such an ethereal solution were to have turned black, this would indicate the decomposition of **10** to Ti(O*i*Pr)$_2$ (**8**) at room temperature (ca. 25 °C).[18] Furthermore, when an ethereal solution of **10** at 25 °C was treated with methyl benzoate (**1a**) and the resulting mixture was allowed to react for 7 h at this temperature, hydrolytic workup gave a 48 % yield of *cis*-2-methyl-1-phenylcyclopropanol (**19**) [Equation (3)].



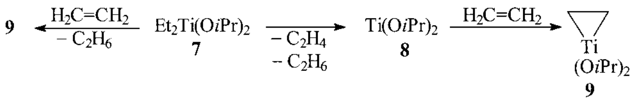
(3)

This result has led us to conclude that at 25 °C **10** does slowly form **11** by transfer-epititanation of free propylene and thus undergoes the Kulinkovich reaction.

A further pertinent observation made with respect to this reaction at 25 °C is that approximately half (52 %) of the ester **1a** was recovered as isopropyl benzoate (**25**). A possible route to this unexpected product will be given below.

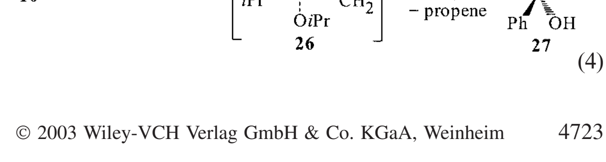
Modes of Forming Titanacyclopropane Intermediates

Although the foregoing studies offer an experimental, chemical-trapping approach for detecting any titanacyclopropane or related three-membered titanocyclic intermediates in the Kulinkovich reaction or its modifications, the question of the mode of formation of such titanocycles from R$_2$Ti(OR′)$_2$ remains to be addressed. With reference to the Kulinkovich alkyl-alkoxide intermediate **7**, one could inquire whether **7** spontaneously decomposes into **8**, which then epimetallates ethylene to yield **9** or whether ethylene coordinates with **7** and thereby induces transfer-epimetallation by elimination of ethyl groups from **7** as suggested in Scheme 6.



Scheme 6

In order to examine the mode of ring formation, (*i*Pr)$_2$Ti(O*i*Pr)$_2$ (**10**) was treated with ethylene gas at −78 °C for 30 min (as shown above, at −78 °C **10** is stable to decomposition). Subsequent workup gave 1-phenylcyclopropanol (**27**) in a 70 % yield without any evidence for the formation of 2-methyl-1-phenylcyclopropanol (**19**). In a parallel experiment, Et$_2$Ti(O*i*Pr)$_2$ was treated with propylene gas at −78 °C for the same amount of time but subsequent hydrolytic workup, as before, gave **27** in only a 55 % yield. This outcome shows that ethylene is able to undergo transfer-epimetallation with **10** via the transition state **26** [Equation (4)]. On the other hand, apparently for steric reasons operative in an octahedral transition state like **26**, propylene is unable to undergo a similar transfer-epimetallation by **7** at such low temperatures (cf. infra).

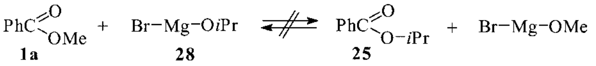


(4)

This finding supports the proposal that the Kulinkovich reaction is initiated by the presence of free ethylene necessary for the initial transfer epimetallation. Thereafter, the ethylene by-product formed in Equation (1) perpetuates the reaction. Several experimental observations support the importance of ethylene for initiation: 1) higher yields of cyclopropanols are obtained (> 80 %) when the ethyl Grignard reagent and $Ti(OiPr)_4$ are used in a 3:1 ratio. The extra equivalence of Grignard reagent with a Ti^{IV} catalyst can readily generate ethylene;[20] 2) when a 2**:**1 ratio of ethyl Grignard reagent to $Ti(OiPr)_4$ is employed, yields of the cyclopropanol are lower (30−35 %). However, yields in such experiments can be enhanced (to 60 % and higher) if ethylene gas is introduced both at −78 °C and during warming. In contrast, propylene is incapable of initiating the Kulinkovich reaction of $(iPr)_2Ti(OiPr)_2$, which as noted above occurs slowly at 25 °C or at higher temperatures [Equation (3)]. The yield obtained if propylene gas is introduced at 25 °C, 45 %, is not higher than that obtained without addition (48 %). Steric hindrance may be the cause of propylene's lower reactivity in such transfer epimetallation (cf. supra).

Ester Interchange as Side Reaction in Kulinkovich Processes

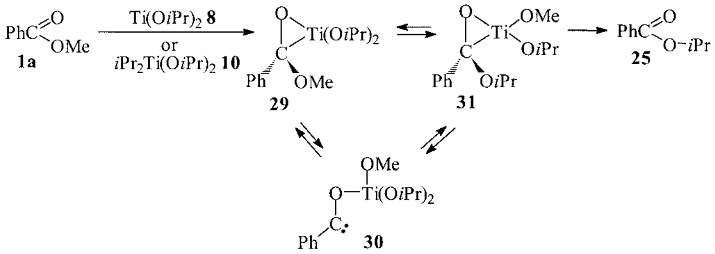
Under experimental conditions where certain dialkyltitanium(IV) dialkoxides do not or cannot undergo a rapid Kulinkovich reaction, it has been found that the starting methyl benzoate (**1a**) was converted into about a 1**:**1 mixture of **1a** and isopropyl benzoate (**25**) (cf. supra). Since $MgBr(OiPr)$ (**28**) is the by-product formed in producing $Et_2Ti(OiPr)_2$ according to Scheme 1, we first examined the action of **28** on **1a** as the possible path of ester interchange [Equation (5)].


1a **28** **25**

$$PhC(=O)OMe + Br{-}Mg{-}OiPr \rightleftharpoons PhC(=O)O{-}iPr + Br{-}Mg{-}OMe \quad (5)$$

However, no ester exchange was found to occur between **1a** and **28** in an ethereal solution at room temperature. But when **1a** was treated with $Ti(OiPr)_2$ (**8**) in diethyl ether at ambient temperatures (ca. 25 °C), ester interchange took place readily.

Accordingly, as an attractive alternative, we propose a reversible epimetallation of **1a** either directly with $Ti(OiPr)_2$ (**8**) or by transfer with $iPr_2Ti(OiPr)_2$ (**10**) to form **29**, which by a reversible redox process could lead to **31**, via **30** and thus to ester interchange (Scheme 7). The importance and utility of intermediates like **29** and **30** will become evident in our future report on reductive dimerizations of esters by transition metal reagents.[21]



Scheme 7

Conclusions

When a 3:1 mixture of ethylmagnesium chloride and titanium(IV) isopropoxide was warmed from −78 °C to +25 °C, it turned black, signaling the formation of $Ti(OiPr)_2$ (**8**) and the usual by-products, ethylene and ethane (the typical Kulinkovich procedure, part e; cf. Scheme 1). Since subsequent addition of methyl benzoate (**1a**) did not lead to the formation of the cyclopropanol **27**, we can conclude that **8** is unable to epititanate directly the ethylene present (formed either from **7** or from the excess EtMgCl present[20]) to form the titanacyclopropane **9**.

Since either a third equivalent of EtMgX (the typical Kulinkovich procedure, part a) or addition of ethylene gas (part c) at −78 °C enhanced the yield of the cyclopropanol obtained, in comparison with that produced using a 2:1 mixture of titanium(IV) isopropoxide and EtMgCl (part b), we conclude that the free ethylene (as such or via EtMgX[20]) fosters the formation of the essential titanacyclopropane **9** by the transfer-epititanation specifically depicted for the conversion of **7** to **9** in Scheme 6 and occurring via a transition state like **26**. The ethylene set free by such epititanation of **7** perpetuates the reaction.

Diisopropyltitanium(IV) diisopropoxide (**10**) has been shown to be kinetically stable in the temperature range of −78 °C to +25 °C and hence we conclude that **10** does not decompose within this temperature range into the titanacyclopropane **11**, as assumed in the work reported by the Sato group.[7,13,14] Reliable chemical trapping agents for titanacyclopropanes, such as esters and nitriles, failed to detect the presence of **11** when **10** was warmed from −78 °C to +25 °C.

Although **10** does not undergo the Kulinkovich cyclopropanol reaction with methyl benzoate (**1a**) below 25 °C, it does form the cyclopropanol **19** slowly at room temperature (ca. 25°C) and at a rate which remains unchanged on addition of propylene. We conclude that the rate limiting step is the transfer-epititanation of propylene by **10**. Steric hindrance in a transition state similar to **26** (involving propylene instead of ethylene) is the likely barrier retarding the reaction.

A further indication of this crucial steric factor emerges from the comparative transfer-epitatanations of ethylene with **10** and of propylene with **7**. The former reaction occurs smoothly to produce **9** and subsequently **27** (69 %) upon workup , without any indication of the formation of **19** (the corresponding epititanated product from the reaction with propylene). In the latter reaction, propylene with **7**, none of cyclopropanol **19** was detected but only the autotitanated product of ethylene from **7**, namely **9**, was produced and transformed into **27** (55 %). We conclude that the transfer-epititanation transition state **26** is at a much lower level in energy than the similar, sterically hindered transition state involving propylene coordination.

Experimental Section

Instrumentation, Analysis and Starting Reagents: All reactions were carried out under a positive pressure of anhydrous, oxygen-free argon. All solvents employed with organometallic compounds were dried and distilled from a sodium metal-benzophenone ketyl mixture prior to use.[22] The IR spectra were recorded with a Perkin−Elmer instrument (model 457) and samples were measured either as mineral oil mulls or as KBr films. The NMR spectra (^{1}H and ^{13}C) were recorded with a Bruker spectrometer (model EM-360) and tetramethylsilane (Me_4Si) was used as the internal standard. The chemical shifts reported are expressed on the δ scale in parts per million (ppm) from the Me_4Si reference signal. The GC/MS measurements and analyses were performed with a Hewlett−Packard GC 5890/Hewlett−Packard 5970 mass-selective-detector instrument. The gas chromatographic analyses were performed with a Hewlett−Packard instrument (model 5880) provided with a 2-m OV-101 packed column or with a Hewlett−Packard instrument (model 4890) having a 30 m SE-30 capillary column. Melting points were determined with a Thomas−Hoover Unimelt capillary melting point apparatus and are uncorrected.

The Typical Kulinkovich Procedure. a) Three Equivalents of EtMgCl (usual modus operandi): To a stirred solution of titanium(IV) isopropoxide (2.84 g, 10 mmol) in diethyl ether (80 mL) at −78 °C was added 15 mL of a 2.0 M solution of ethylmagnesium chloride (2.67 g, 30 mmol) in diethyl ether. The red-brown mixture was stirred at −78 °C for 90 min, before addition of methyl benzoate (1.36 g, 10 mmol). The reaction mixture was warmed to room temperature (ca. 25°C) and was stirred for a further 10 h. Hydrolytic workup with 1 N aqueous HCl, extraction of the organic products using diethyl ether, drying of extracts over Na_2SO_4 and evaporation of volatiles gave an organic residue, which by ^{1}H NMR spectral analysis showed signals for 1-phenyl-1-cyclopropanol (**27**) (90−95 %). The only other significant product, present in the crude reaction mixture with this Kulinkovich procedure and all other modifications leading to **27** was 1-phenyl-1-propanol to the extent of 5−10 %.[23] A pure sample of **27** could be obtained by distillation under reduced pressure: b.p. 93−95 °C (30 Torr).

b) Two Equivalents of EtMgCl (stoichiometric mode): A trial reaction carried out in an identical manner to that described in part a, except that two equivalents of EtMgCl (20 mmol) were employed. ^{1}H NMR spectral analysis of the organic liquid recovered showed the presence of 1-phenyl-1-cyclopropanol (**27**) (34 %) and methyl benzoate (**1a**) (66 %).

c) Two Equivalents of EtMgCl and Added Ethylene: Ethylmagnesium chloride (20 mmol) and titanium(IV) isopropoxide (10 mmol) in a ratio of 2**:**1 were mixed in diethyl ether (60 mL) at −78 °C. After 90 min methyl benzoate (10 mmol, 1 equiv.) was added, as in part b. Thereafter, ethylene gas at 40 psi was bubbled through the cold solution for a period between 30 min and 2 h, before the reaction mixture was warmed to room temperature (ca. 25°C) and subjected to ^{1}H NMR spectral analysis. The yield of 1-phenyl-1-cyclopropanol (**27**) now ranged from 60 % (30 min ethylene treatment) to over 75 % (2 h).

d) 2.5 Equivalents of EtMgCl and Added Propylene (attempted transfer-epimetallation): To a stirred solution of titanium(IV) isopropoxide (10 mmol) and methyl benzoate (10 mmol) in diethyl ether (60 mL) at −78 °C was added a solution of ethylmagnesium chloride (25 mmol) in diethyl ether (15 mL). After 10 min at −78 °C the red-brown mixture was treated with a current of propylene gas at 40 psi for 30 min. The resulting reaction mixture was warmed to room temperature over 3 h and then subjected to the usual hydrolytic workup and NMR spectral analysis. 1-Phenyl-1-cyclopropanol (**27**) was obtained in a 55 % yield, with the remainder being recovered ester.

e) Three Equivalents of EtMgCl and One Equivalent of $Ti(OiPr)_4$ at 25 °C: Formation of Titanium(II) Isopropoxide: A red-brown mixture of ethylmagnesium chloride (30 mmol) and titanium(IV) isopropoxide (10 mmol) in diethyl ether (80 mL) was prepared at −78 °C. When the mixture was warmed to room temperature (3 h), it turned black, indicating the decomposition of $Et_2Ti(OiPr)_2$ (**7**) into $Ti(OiPr)_2$ (**8**). Methyl benzoate (10 mmol) was then added and the mixture was allowed to stirred for 7 h at ambient temperature (ca. 25°C). The usual workup gave only recovered methyl benzoate (no isopropyl benzoate **25**: cf. infra for a comparable reaction with EtMgBr, where **25** was found).

Modified Kulinkovich Procedure. Reactions with Diisopropyltitanium(IV) Diisopropoxide. a) Methyl Benzoate (stoichiometric mode): To a stirred solution of titanium(IV) isopropoxide (2.84 g, 10 mmol) and methyl benzoate (1.36 g, 10 mmol) in diethyl ether (80 mL) at −78 °C was added a solution of isopropylmagnesium chloride (20 mmol) in diethyl ether (30 mL). The brown mixture was stirred for 90 min before being quenched at −78 °C with methanol. Usual hydrolytic workup of the quenched mixture at 25 °C gave only recovered methyl benzoate. A similar reaction was conducted by slowly addiing a solution of isopropylmagnesium bromide (20 mmol) in diethyl ether (30 mL) to a solutionof titanium(IV) isopropoxide (6.25 mmol) and methyl benzoate (6.25 mmol) in diethyl ether (30 mL) at 25 °C. The red-brown reaction mixture formed was stirred for 7 h at 25 °C; hydrolytic workup and ^{1}H NMR spectral analysis revealed the formation of *cis*-2-methyl-1-phenyl-1-cyclopropanol (**19**) (48 %) and isopropyl benzoate (**25**) (25 %), together with recovered methyl benzoate (25 %).

b) Methyl Benzoate with Added Propylene: A similar reaction at 25 °C was conducted as in part a, except that propylene gas was slowly passed into the reaction mixture during the 7 h reaction period. Usual hydrolytic workup provided **19** in a 45 % yield, a yield essentially unchanged from that of **19** (48 %) obtained without addition of propylene. From these results it is clear that propylene does not promote the formation of the titanacyclopropane **11** by transfer epititanation.

c) Methyl Benzoate with Added Ethylene: To a stirred solution of titanium(IV) isopropoxide (10 mmol) and methyl benzoate (10 mmol) in diethyl ether (50 mL) at −78 °C was passed a current of dry ethylene gas at 40 psi for 30 min. A solution of isopropylmagnesium chloride (25 mmol) in diethyl ether (10 mL) was then added slowly by syringe to the reaction mixture maintained at −78°C for 30 min. The reaction mixture was warmed to room temperature (ca. 25 °C) over 1 h, followed by the usual hydrolytic workup and ^{1}H and ^{13}C NMR spectral analyses, which showed the formation of 1-phenyl-1-cyclopropanol (**27**) (43 %) and 1-phenyl-1-propanol (12 %), together with recovered methyl benzoate (45 %). No ^{1}H or ^{13}C NMR spectral signals characteristic of *cis*-2-methyl-1-phenyl-1-cyclopropanol (**19**) were present.

A reaction similar to that described above (the same scale) was conducted , except that 5 mmol of methyl benzoate was employed. The reaction gave an increased yield of 1-phenyl-1-cyclopropanol (**27**) (69 %) and of 1-phenyl-1-propanol (21 %), with a lower recovery of methyl benzoate (10 %).

Attempts to Detect the Presence of the (η^2-Propene)Titanium Diisopropoxide 11 in the Thermal Decomposition of Diisopropyltitanium(IV) Diisopropoxide (10): To a stirred solution of titanium(IV) isopropoxide (10 mmol) in diethyl ether (80 mL) at −78 °C was added a solution of isopropylmagnesium bromide (20 mmol) in diethyl ether (30 mL). After 90 min of stirring at −78 °C, benzonitrile (1.03 g, 10 mmol) was introduced. The reaction mixture was allowed to attain room temperature (ca. 25°C) before being heated at reflux for 5 h. The usual hydrolytic workup led only to the recovery of benzonitrile.

A similar reaction involving the admixture and reaction of isopropylmagnesium bromide (20 mmol) and titanium(IV) isopropoxide (10 mmol) in diethyl ether (80 mL) at 20 °C, followed by the addition of benzonitrile and heating at reflux for 3 h, likewise led to the complete recovery of benzonitrile, without trace of any carbonyl products.

Ester Interchange. a) Attempted Ester Interchange with Magnesium Chloride Isopropoxide: A solution of magnesium chloride isopropoxide (20 mmol) in diethyl ether (50 mL) was generated by treating a solution of ethylmagnesium chloride (20 mmol) in diethyl ether (10 mL) with anhydrous isopropyl alcohol (1.20 g, 20 mmol) as a solution in diethyl ether (40 mL). To the resulting solution at 25 °C was then added methyl benzoate (10 mmol). The mixture was stirred for 10 h at ambient temperature (ca. 25°C) and then treated as described above. The NMR spectral analyses of the crude organic product showed only the presence of methyl benzoate without trace of isopropyl benzoate.

b) Ester Interchange with Titanium(II) Isopropoxide (8): To a stirred solution of titanium(IV) isopropoxide (12.5 mmol) in of diethyl ether (15 mL) at −78 °C was added a solution of ethylmagnesium bromide (40 mmol) in diethyl ether (40 mL). When the initial red-brown mixture had warmed to 25 °C over 10 h, it turned black. Methyl benzoate (12.5 mmol) was then injected into the black mixture and stirring at ambient temperature continued for 7 h. The usual workup and analyses showed that the crude material contained only methyl benzoate and isopropyl benzoate **25** as approximately a 50**:**50 (±5) mixture.

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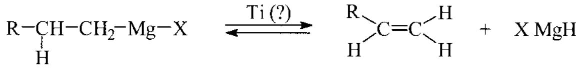
[18] The dialkyltitanium(IV) diisopropoxides, generated in alkanes or in ethers by the interaction of two equivalents of RLi with one equivalent of $\mathrm{Ti(O\mathit{i}Pr)_4}$, decompose above −78 °C into black $\mathrm{Ti(O\mathit{i}Pr)_2}$: Ref.[11]; cf. also procedures given in the Exp. Sect. for the $\mathrm{Ti(O\mathit{i}Pr)_2}$ formed from two equivalents of EtMgCl or EtMgBr and one equivalent of $\mathrm{Ti(O\mathit{i}Pr)_4}$, when such mixtures were then warmed to room temperature.

[19] The generation and chemical trapping of such titanacyclopropane intermediates have been achieved recently with two different olefins: a) The transfer-epimetallation of 1-butene by $\mathrm{Bu_2Ti(O\mathit{i}Pr)_2}$, trapping with benzonitrile and hydrolysis gave butyl phenyl ketone in a good yield (ref.[11]); and b) The transfer-epimetallation of propylene by $t\mathrm{Bu_2TiCl_2}$, followed by analogous treatment with benzonitrile, gave upon hydrolytic workup, a 4:1 ratio of ketones **22**:**23** (ref.[1]). These precedents verify that the present test for the possible formation of **11** is valid.

[20] Titanium-catalyzed magnesium hydride halide transfer from ethyl or isopropyl Grignard reagents to olefins or functionalized olefins leads to the liberation of ethylene or propylene, respectively. Apparently the titanium catalyst (of unknown oxidation state) promotes the following equilibrium:



$$\mathrm{R{-}\underset{\textstyle H}{\underset{|}{C}}H{-}CH_2{-}Mg{-}X} \xrightleftharpoons{\mathrm{Ti\,(?)}} \mathrm{R(H)C{=}CH_2} + \mathrm{X\,MgH}$$

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[21] J. J. Eisch, J. N. Gitua, A. A. Adeosun: in ongoing studies we have observed that 2:1 mixtures of RLi and $\mathrm{Ti(O\mathit{i}Pr)_4}$ convert methyl benzoate into products hydrolyzable into principally benzoin with minor amounts of benzil.

[22] A detailed description for conducting organometallic reactions in a safe and reproducible manner is given in: J. J. Eisch, *Or-*

ganometallic Syntheses, Vol. 2, Academic Press, New York, **1981**, pp. 1−84.

[23] The origin of the 1-phenyl-1-propanol side-product in this Kulinkovoich reaction is still under investigation. However, we can rule out the reductive scission of the cyclopropane ring in **1**. When a pure sample of **27**, free of any 1-phenyl-1-propanol, was treated with a mixture formed by reacting EtMgCl (3 equiv.) and $Ti(OiPr)_4$ (1 equiv.) at −78 °C in diethyl ether and then allowing the resulting system to warm to and react at 25 °C, no ring cleavage reduction was observed.

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