Bis alkoxytitanacyclopropanes and -propenes (Kulinkovich reagents): Versatile reagents for carbon–carbon bond formation

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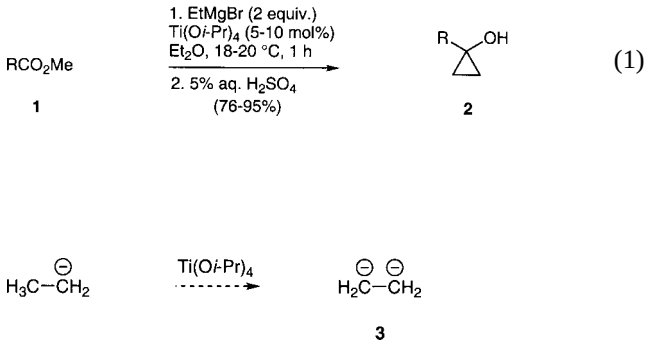
In 1989 Kulinkovich reported that ethylmagnesium bromide in the presence of catalytic amounts of titanium tetraisopropoxide, when added to simple carboxylic esters **1**, furnished cyclopropanols **2** in a one pot operation (equation 1) [1]. Hence, the ethyl group of the Grignard reagent has served as a synthetic equivalent of a two-carbon dianion synthon **3** – a quite unusual reactivity pattern (Scheme 1). Additionally, the reaction products – the cyclopropanols **2** – are of considerable interest since they are not only valuable synthetic intermediates which allow for facile, selective ring-opening reactions [2] but which may be used as building blocks for the construction of cyclopropane containing natural products [3].

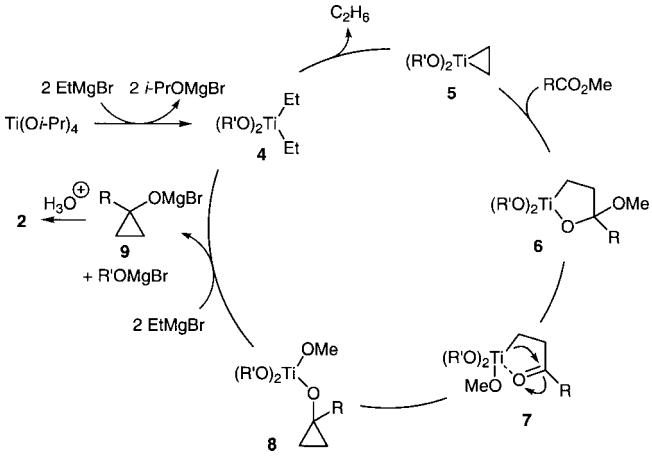


Scheme 1 EtMgBr/Ti(Oi–Pr)$_4$ – the Kulinkovich reagent: Synthetic equivalent of a two-carbon-1,2-dianion synthon

Not surprisingly, soon after Kulinkovich's discovery this reaction has attracted worldwide a number of research groups which has lead to the development of a variety of useful synthetic methods. The purpose of this article is to provide the reader with a brief overview of the current state of this rapidly developing area of synthetic organic chemistry based on the Kulinkovich reagent.

Mechanistic Proposal

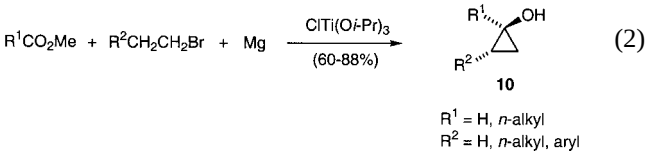
The catalytic cycle proposed [1] for the above transformation is depicted in scheme 2. Thus, in a first step ligand exchange reaction between titaniumtetraalkoxide and ethyl magnesium bromide provides the diethyl titanium intermediate **4** which immediately undergoes β-elimination with formation of the titanacyclopropane **5**. Next, a nucleophilic attack at the ester carbonyl furnishes the titanaoxacyclopentane **6**. Rearrangement to the homoenolate **7** with concomitant activation of the carbonyl group allows for an intramolecular attack of the titanium–carbon bond to the carbonyl function to give the titanium cyclopropane alkoxide **8**. Metal exchange reaction with excess of Grignard reagent liberates the product as the magnesium alkoxide **9** and regenerates the catalytically active species **4**.



Scheme 2 Mechanism of the Kulinkovich reaction with esters.

Reaction Scope and Limitation

One drawback of the original Kulinkovich procedure has been the limitation to use ethyl Grignard reagent. Thus, it seemed as if only an ethyl titanium species would undergo a rapid β-H elimination to give the titanacyclopropane **5** – the Kulinkovich reagent. However, with chloro titanium trisisopropoxide as the titanium(IV)source also higher substituted organomagnesium compounds (equation 2) could be applied to give substituted titanacyclopropane intermediates [4]. This finding largely extended the preparative value of this cyclopropanation reaction. In situ formation of the Grignard reagent is possible and simplifies the synthetic procedure even further.



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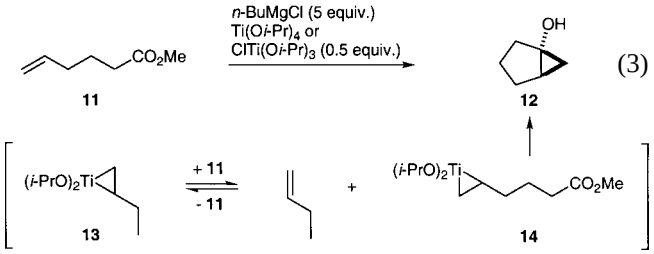
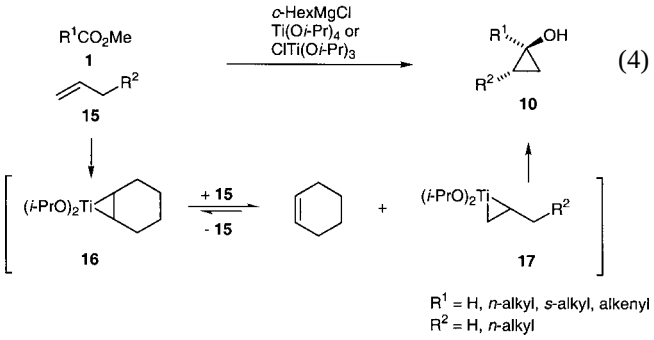
However, this protocol failed for α-branched and aromatic esters.

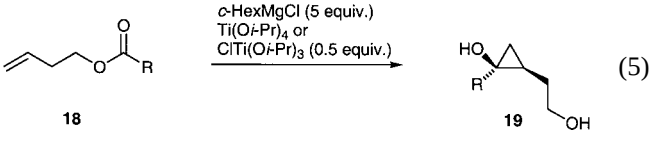
Substitution at the dianion synthon raises the question of diastereoselectivity. Interestingly, in all cases investigated the reaction was found to be completely diastereoselective yielding the *cis*-cyclopropane **10** only.

The major shortcoming of this and the original Kulinkovich procedure lies in the requirement of at least two equivalents of the Grignard reagent (one equivalent is lost as the corresponding hydrocarbon, see scheme 2). This problem was solved independently by Sato and Cha [5, 6]. Both found that the primarilly formed Kulinkovich reagent – the titanacylcopropane **13** – can undergo ligand exchange with other monosubstituted alkenes to give substituted titanacyclopropanes (*e.g.* **14**) which show similar reactivity (equations 3 and 4).





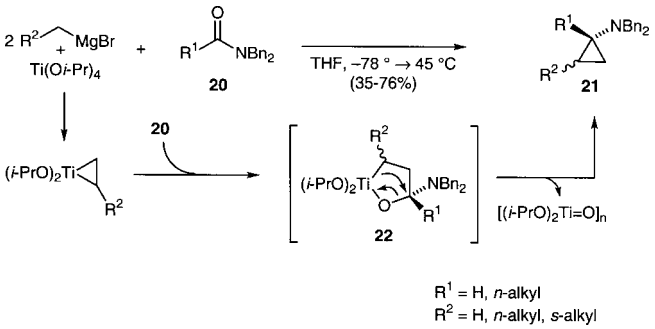
This improvement allows for both intra- and intermolecular cyclopropanation reactions (equation 3, **11** → **12**; equation 4, **15** → **10**). For intermolecular variants the use of *c*-hexyl- or *c*-pentyl-Grignard reagent is of benefit since it shifts the crucial olefin exchange reaction (**16** → **17**) to the desired monoalkene complex **17**. The reaction tolerates silylethers, di- and trisubstituted alkene moieties as well as primary bromide functions.



Interestingly, the intramolecular reaction of homoallylic ester **18** yielded the *trans*-cyclopropanol **19** (equation 5). This stereochemical result is of interest since it complements the *cis*-selectivity of the intermolecular Kulinkovich reaction (see equations 2 and 4).

Aminocyclopropanes

Whereas esters afford cyclopropanols the corresponding amides **20** gave access to the biologically interesting class of aminocyclopropanes **21** [7]. Here, the reaction mechanism must have followed a slightly different pathway (Scheme 3).

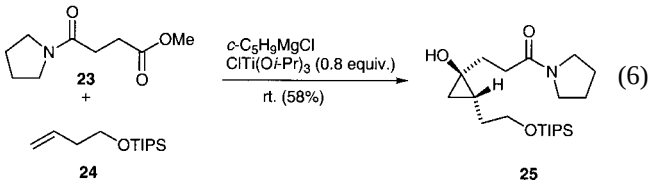


Scheme 3 Reaction of the Kulinkovich reagent with *tert*-carbonamides

Thus, leaving group propensity – a function of the pK_a of the corresponding acid – of the amide in **22** is smaller than that of the alkoxide in **6**. Hence, nature had to find an alternative reaction pathway which turned out to be the elimination of a titanium oxo-species. The fact that stoichiometric amounts of titanium tetraisopropoxide are required to drive the reaction to completion, supports the mechanistic proposal. The Cha/Sato modification of the Kulinkovich protocol is applicable to the synthesis of aminocyclopropane derivatives as well [8]. Inter- as well as intramolecular variants have been realized.

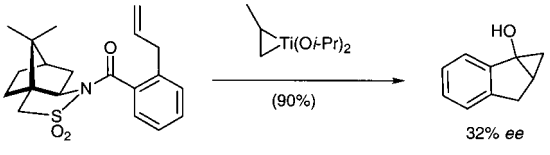
Chemoselectivity

With different types of carbonyl functions present in the same molecule, intramolecular competition experiments allowed to establish the following order of relative reactivity. Thus esters, acid chlorides and anhydrides are most reactive towards the Kulinkovich reagent. Less reactive are carbonates and thioesters. The least reactive carbonyl groups are carbonamides [8]. Equation 6 gives an instructive example for this chemoselectivity profile of the Kulinkovich reaction. Thus, intermolecular Kulinkovich reaction of the alkene **24** with the succinic-ester-amide derivative **23** resulted in chemoselective cyclopropanation of the ester carbonyl of **23** to give the cyclopropanol **25** [8].

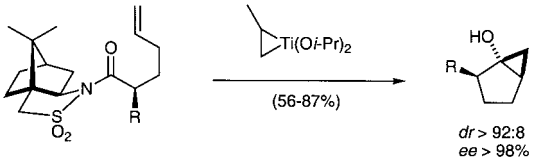


Control of Absolute Configuration

Control of the absolute configuration of the new stereocenters formed in the course of the Kulinkovich reaction has been achieved employing both an auxiliary strategy as well as asymmetric catalysis. As an efficient auxiliary Oppolzer's campher-based sultam was identified [9]. A particular advantage of the sultam auxiliary is its spontaneous elimination in the course of the cyclopropanation reaction providing an auxiliary free cyclopropanol product (equations 7 and 8).



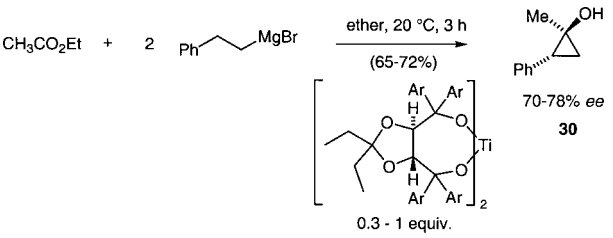
(7)



(8)

With derivative **26** only moderate facial selection was obtained (→ **27**). Interestingly, it was found that an additional stereocenter in α-position to the carbonyl (see **28**) enforces diastereofacial selection significantly. A cooperative effect between auxiliary and additional stereocenter is thought to be the decisive factor for efficient stereocontrol. Hence, compound **28** yielded the bicyclic cyclopropanol **29** with high levels of both diastereo- and enantioselectivity [9].

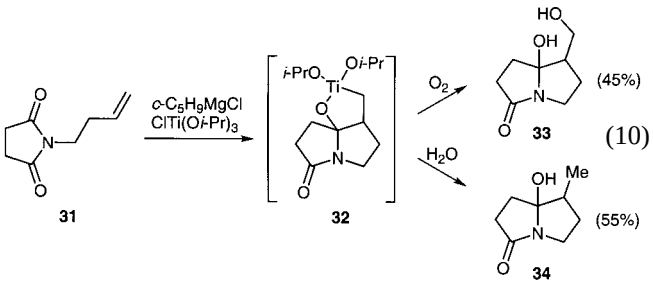
A first step towards an asymmetric catalysis of the Kulinkovich reaction has been undertaken by Corey [4]. Thus, reaction of ethylacetate with two equivalents of phenethyl magnesium bromide in the presence of 30 mol% of a TADDOL-based titanium reagent gave the cyclopropanol **30** in 70% *ee* (equation 9). Stoichiometric use of the chiral titanium bistaddolate improved the *ee* to 78%.



(9)

Other than Cyclopropanol Formation

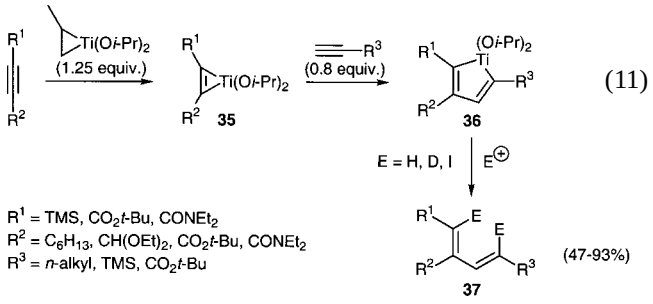
When cyclic imide **31** was reacted under the Cha conditions of the Kulinkovich reaction no cyclopropanol formation was observed (equation 10) [10]. Instead the titanaoxacyclopentane intermediates **32** could be trapped with either oxygen or water. Thus, oxidation with molecular oxygen gave the bicyclic pyrrolidine **33**. Hydrolysis of the titanium–carbon bond furnished the half-aminal **34**.



(10)

The above transformation should offer an interesting synthetic entry into the natural product class of izidine alkaloides [11]. Additionally, these bicyclic aminals can be functionalized further, since they serve as ideal precursors to entry immonium-type chemistry [12].

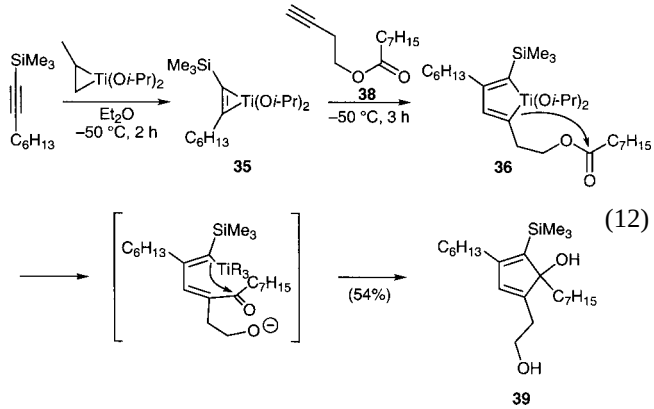
With internal alkynes ligand exchange reaction of the titanacyclopropane occurs to give the corresponding titanacyclopropenes **35** (equation 11). This fundamental reaction served as the starting point for the development of a stereoselective synthesis of functionalized 1,3-dienes [13].



(11)

Thus, insertion of a terminal alkyne into a titanium carbon bond of **35** occurs regioselectively to give the intermediate titanacyclopentadienes **36**. This insertion reaction is position-selective for silyl-substituted alkyne–titanium complexes **35** (R^1 = SiR_3). Thus, the silyl-substituent controls the subsequent alkyne insertion to occur exclusively at the carbon β relative to the silyl group. The titanacyclopentadienes **36** could be trapped with electrophiles (H, D, I) to give the corresponding 1,3-dienes **37** in moderate to good yield.

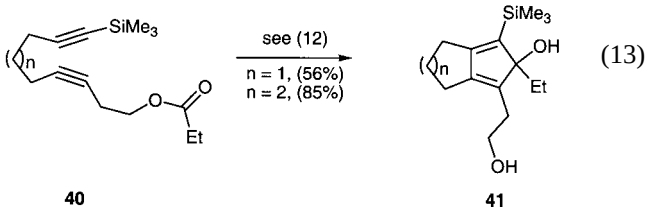
Alternatively, if homopropargylic esters **38** are employed as substrates, the ester carbonyl may serve as an internal electrophile (equation 12) [14]. Thus, both titanium–carbon bonds



(12)

add to the ester–carbonyl to give cyclopentadienols **39** which are of interest as synthetic intermediates since they allow further functionalization of up to five carbon atoms. Remarkably, primary iodides are tolerated under these reaction conditions.

Intramolecular coupling of diynes (**40**) is possible and provides [5,5]-, and [5,6]-bicyclic cyclopentadienols **41** (equation 13).



40 **41** (13)

Conclusion

Starting from Kulinkovich's discovery in 1989 a variety of titanacyclopropanes and -cyclopropenes can be entered today. These species have proven to be versatile synthetic intermediates which can serve as synthetic equivalents of 1,2-dianion synthons. This paves the way to a hitherto unknown chemistry leading to synthetically valuable products such as cyclopropanols, aminocyclopropanes, highly substituted 1,3-dienes as well as bicyclic functionalized cyclopentadienes. Further exciting discoveries in this rapidly developing area of organometallic chemistry should be expected soon.

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