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Mini-Account

Addition–β-elimination: a new method for the preparation of organometallic compounds

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Dedicated fondly to Professor J.F. Normant on the occasion of his 65th birthday

Abstract

The addition–β-elimination mechanism is a powerful method for the production of organometallic derivatives. Using this new method, we report the first transformation of enol ethers into the corresponding vinyl zirconium derivatives. Moreover, the in situ formation of Ti(II) and subsequent reaction with halogeno alkynes offers a new route for the preparation of functionalized alkynyl titanium and trismetalated olefin derivatives. © 2001 Elsevier Science B.V. All rights reserved.

Numerous methods for the preparation of organometallic compounds are known in the literature and can be mainly divided into four categories [1]. The first, and probably the most important one, is the reaction between an organic halide or pseudo halide and a metal such as the classical oxidative metalation or the halogen–metal exchange [2]. The second category, also very popular and recently reviewed [3], concerns the exchange reactions between acidic hydrogens and basic organometallic derivatives, namely the metalation reactions. The third category concerns all the transmetalation reactions [1] whereas the fourth is related to the hydro- and carbometalation reactions across unsaturated systems [4]. This category is synthetically very powerful since we have to control, in many cases, the stereo-, diastero- and even enantioselectivity of the reaction. All these methods were abundantly used in organic synthesis and have played a major role both in academic laboratories and industries. However, despite these widespread methods of preparation, there are still some impossible synthetic transformations as for example the direct transformation of methoxy enol ethers into vinylic organometallic derivatives. So, in order to solve these challenging questions, new methods have still to be found.

Over the past two or three decades, organozirconium and organotitanium have emerged as synthetically useful reagents or intermediates in organic synthesis and their incredible efficiency, coupled to their unique ability to promote unusual transformations have aroused the imagination of chemists.

In this account, we would like to describe a new concept for the preparation of organometallic derivatives via a totally different mechanism than those previously cited above. This new formation of organometallic derivatives is based on the complexation (or oxidative coupling) of unsaturated compounds with low-valent transition metals (zirconocene and titanocene type) followed by a β-elimination reaction to give a σ-carbon metal bond. Indeed, early transition metal complexes show both types of reactivity, and thus, in addition to their utility either as a carbanion source or as a synthetic reagent based on transition metal behavior, it is possible to utilize them for synthetic transformations based on the characteristic fea-

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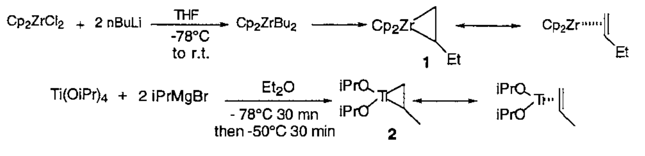
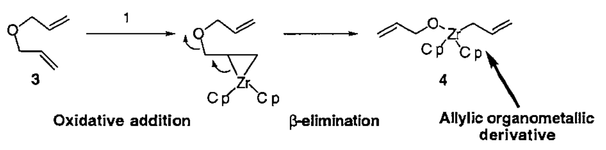
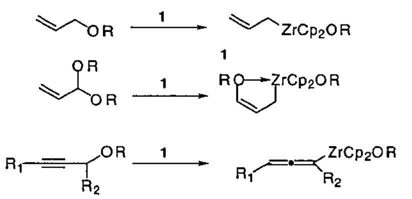


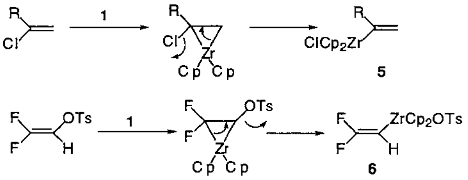
Scheme 1.



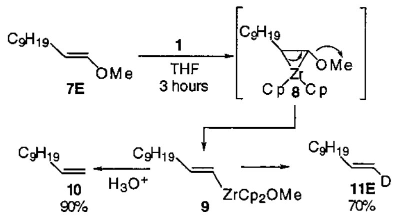
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

tures of both types of reactivity. These dialkylzirconocenes or dialkyltitanocenes can be easily prepared by treatment of Cp_2ZrCl_2 or Ti(O*i*-Pr)$_4$ with respectively *n*-BuLi [5] or RMgX [6] as described in Scheme 1.

The initial discovery of this mechanism occurred in Negishi's laboratory when he tried to promote the intramolecular carbocyclization of diallyl ether **3** with **1** [7]. Instead of producing the desired zirconabicycle, the reaction gave the allyl(allyloxy)zirconocene **4** via an η-complexation followed by a β-elimination as described in Scheme 2.

This originally unwanted side reaction has proved to be a synthetically useful route to allylzirconocene derivatives as nicely demonstrated by Hanzawa and Taguchi. According to this, several allylic [8], allenic [9], γ- [10] and γ-γ-alkoxy allylic [11] zirconium species were prepared (Scheme 3) [12].

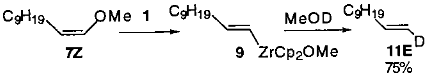
This strategy was also developed for the selective cleavage of allylic ether derivatives [13]. The same chemistry was described simultaneously between the titanocene **2** [14] (Scheme 1) and allylic [15] or propargylic derivatives [16]. More recently, an elegant synthesis of allylic titanium derivatives from vinyl halides, vinyl ethers and carboxylic ester derivatives was also reported [17].

However, this concept of addition–β-elimination was only used sporadically for the preparation of vinyl zirconium derivatives. The initial report, published by Takahashi et al., was the preparation of **5** by reaction of 2-chloroalkene derivatives [18] with **1** and more recently this strategy was applied successfully by Ichikawa and Minami [19] for the synthesis of fluorinated vinyl zirconium moieties **6** (Scheme 4).

In both cases, a good leaving group was used (halide or tosyloxy groups) for the β-elimination reaction and no information on the stereochemical outcome of this reaction was disclosed [20]. On the other hand, when the difluoroolefin bears a substituent with a lower leaving-group propensity than that of fluorine (i.e. OPh or OMEM), the preferential elimination of fluoride occurs in low yield (respectively 17 and 32% yield) [19].

So, we reasoned that the combined addition–β-elimination mechanism could be an interesting way to prepare specific organometallic derivatives such as unactivated enol ether [21], which had no precedent at the date of our study [22]. We indeed found that this reaction occurs smoothly at room temperature in THF by the addition of the *E* methoxy enol ether **7** [23] to 1.5 equivalents of zirconocene complex **1**. The vinyl zirconium derivative **9** is obtained quantitatively, as determined by gas chromatography analysis with internal standard. Hydrolysis of the reaction mixture gives undec-1-ene (**10**) in 90% yield after purification as described in Scheme 5.

The formation of a discrete organometallic species was checked by deuterolysis of the reaction mixture and only the *E* isomer of **11** was obtained. The postulated mechanism for this reaction is that the in situ formed zirconocene derivative **1** reacts with the methoxy enol ether **7***E*, via a ligand exchange, to give an unstable intermediate methoxy-zirconacyclopropane derivative **8**. Then, **8** undergoes a very fast β-elimination at room temperature to give the vinyl zirconium derivative **9**. An alternative mechanistic pathway could also be the oxidative addition of **1** into the vinylic carbon–methoxy bond. However, this can be ruled out since we do not observe any aromatic organometallic derivatives on treatment of anisole with **1**. Interestingly, when the same reaction is performed on the *Z* enol ether (**7***Z* instead of **7***E*), the same *E* isomer **11** is obtained after



Scheme 6.

treatment of the reaction mixture with MeOD (Scheme 6) [24].

So, whatever the stereochemistry of the initial methoxy-enol ether, the reaction is $>99\%$ stereoselective but non-stereospecific, producing the *E* vinyl zirconium in good overall yields.

The scope of this reaction is relatively broad since methoxy enol ethers **7** and **14** derived respectively from aliphatic (entries 1–4, Table 1) [23] and aromatic aldehydes (entries 7–10, Table 1) [25] as well as methoxy enol ether **15** derived from ketone (entry 11, Table 1) undergo this formal 'methoxy–zirconium exchange'. In all cases, only the *E* isomer was detected by crude NMR. In order to check whether the steric hindrance of the leaving group has an effect on the stereochemical outcome of this process, the reaction was also performed on the *ter*butoxy enol ether **12** (entry 5, Table 1) [26]. Here again, only the *E* isomer was obtained after deuterolysis albeit in lower yield [only 40% of **11** was obtained after 4 h at room temperature, the balance being the starting material (with the same *E*/*Z* ratio of 80/20)]. However, when the silyl enol ether **13** (entry 6, Table 1) was treated with **1**, the reaction occurred smoothly to give the corresponding vinyl zirconium derivative, which was trapped by iodine into **16** in 75% yield. Moreover, alkenyl zirconocenes participate in a wide range of ligand transfer reactions after transmetalation [27]. These can be transmetalated into palladium species [28] and coupled with aromatic iodide (entry 4, Table 1) [29] or transmetalated into vinyl copper by addition of a catalytic amount of copper salt and reacted with classical electrophiles of copper chemistry as with allyl chloride (entry 10, Table 1) [30].

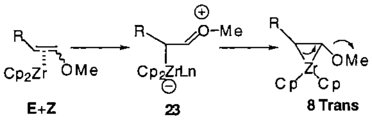


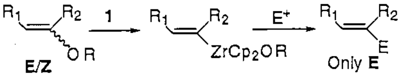
Fig. 1. Mechanistic hypothesis.

These transmetalation reactions increase the scope of this reaction since several electrophiles, classically of palladium or copper chemistry, can be introduced for the alkylation step. However, when tri- and tetrasubstituted enol ethers were treated with **1**, no reaction was observed.

Although the 'addition–β-elimination' sequence described in Scheme 5 seems to be reasonable, more complicated intermediates are probably involved during the complexation between the methoxy enol ether and the zirconocene **1**. Our hypothesis is that the initial step proceeds most likely via a dipolar zirconate species represented by **23** (Fig. 1) [31], and then isomerization should occur to give the *trans* methoxy zirconacyclopropane **8** before β-elimination. These types of non-concerted paths for reactions of alkene with zirconocene complexes were already discussed in the literature by Negishi and Takahashi [32]. Moreover, no stereoisomerization of 7*Z* was observed by using 10 mol% of *n*Bu_2ZrCp_2, which indicates that zirconocene **1** is not a catalyst for the isomerization of methoxy enol ether 7*Z* into 7*E* (and no other products were detected).

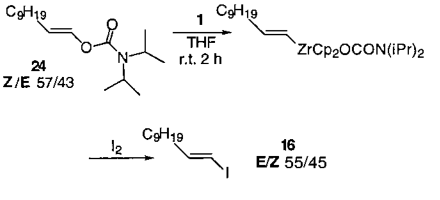
To probe further the interaction between the enol ethers and **1** via **23**, we thought that reducing the potentiality to form the oxonium of the vinylic oxygen would decrease the percentage of isomerization. For this purpose, we prepared the vinylic carbamate **24**. We

Table 1
Reaction of **1** with enol ethers and trapping with electrophiles

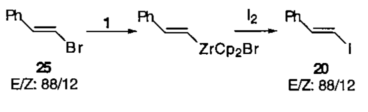


Entry	R_1	R_2	OR	Starting materials	*E*/*Z* ratio	Electrophile	Product	Yield (%) [a]
1	C_9H_{19}	H	OMe	**7**	75/25	H_3O^+	**10**	90
2	C_9H_{19}	H	OMe	**7**	75/25	MeOD	**11**	70
3	C_9H_{19}	H	OMe	**7**	75/25	I_2	**16**	89
4	C_9H_{19}	H	OMe	**7**	75/25	PhI, CuCl 5% $Pd(PPh_3)_4$	**17**	75
5	C_9H_{19}	H	O*t*-Bu	**12**	80/20	MeOD	**11**	40
6	C_9H_{19}	H	OSi*t*-$BuMe_2$	**13**	65/35	I_2	**16**	75
7	Ph	H	OMe	**14**	70/30	H_3O^+	**18**	70
8	Ph	H	OMe	**14**	70/30	MeOD	**19**	75
9	Ph	H	OMe	**14**	70/30	I_2	**20**	70
10	Ph	H	OMe	**14**	70/30	AllylCl 10% CuCl/2LiCl	**21**	60
11	H	Ph	OMe	**15**		MeOD	**22**	70

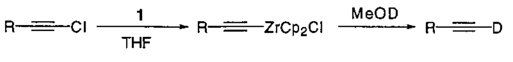
[a] Yield of isolated products after purification by column chromatography.



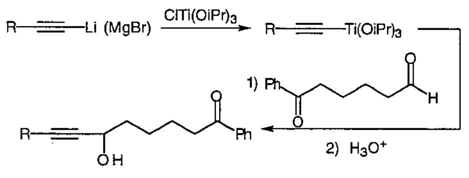
Scheme 7.



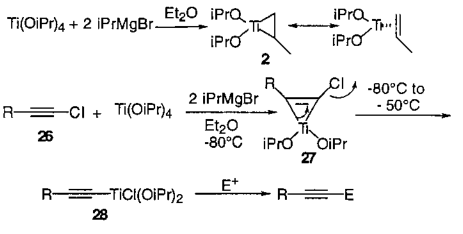
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

were pleased to find that treatment of the geometrical mixture of the vinylic carbamate **24** (*Z*/*E*: 57/43) with zirconocene **1** gives, after iodinolysis, the corresponding vinyl iodide **16** in a 55/45 *E*/*Z* ratio (Scheme 7). So, indeed only a slight isomerization was observed [33].

Moreover, in order to confirm that the isomerization occurs effectively via a dipolar zirconate **23**, we repeated the same experiment on the commercially available β-bromo styrene **25** with an *E*/*Z* ratio of 88/12. When the latter is treated first with the zirconocene equivalent **1** at room temperature for 3 h, and then with iodine, the expected β-iodo styrene **20** is obtained in 77% yield, as a mixture of two isomers in the same ratio as the starting material (*E*/*Z*: 88/12) (Scheme 8). Clearly, when no oxonium is formed, we do not observe any isomerization.

This new formation of organometallic derivatives via a mechanism of addition–β-elimination can also be applied to heterosubstituted alkynes. In this case, metallo alkynes are obtained in good to excellent yields (Scheme 9).

However, most organic molecules are polyfunctional compounds requiring in the retrosynthetic analysis the reaction between a functionalized carbon electrophile and a functionalized carbon nucleophile. Although a large part of the carbon nucleophiles are organometallic derivatives, the highly reactive nature of the carbon–metal bond precludes the presence of functional groups in the carbon skeleton of these reagents. Indeed, as these transition-metal organometallics were usually prepared from lithium or magnesium reagents, functionalized titanium or organozirconium organometallics are still in their infancy [34]. Moreover, organotitanium reagents undergo chemo- and stereoselective carbon–carbon bond forming reactions [35] with *bifunctional electrophiles* as described in Scheme 10 (> 99% reaction on the aldehyde) [36].

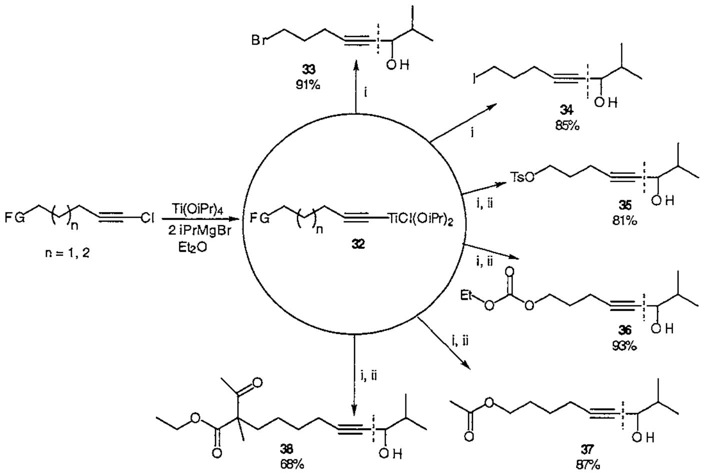
So, the addition–β-elimination mechanism should be a very interesting source for the preparation of functionalized alkynyl titanium derivatives (by reaction of **2** with halogeno alkyne, see Scheme 11) since Grignard reagents are relatively unreactive towards many functional groups at low temperature in Et_2O [37]. Indeed in order to succeed, the transmetalation reaction between titanium tetra*iso*propoxide and *i*-PrMgBr to give **2** should be faster than the reaction of *i*-PrMgBr with functional groups in R as described in Scheme 11.

We checked first the reactivity of **28** with aldehydes on model compounds (**26** R = alkyl or *p*-tolyl) as described in Scheme 11 and Table 2. Quenching the reaction with MeOD at −78°C (Table 2, entry 1) proved the presence of the metalated alkyne **28** since the deuterioalkyne **29** (R = Oct, %D > 95, 93%) was obtained quantitatively. Addition of aldehydes to **28**

Table 2
Reactivity of the alkynyl titanium **28**

Entry	R	E	Product	Lewis acid	Yield (%) [a]
1	Oct	MeOD	**29**	None	93
2	*p*-Tolyl	*i*-PrCHO	**30**	None	70
3	*p*-Tolyl	*i*-PrCHO	**30**	$ClTi(Oi\text{-}Pr)_3$	84
4	*p*-Tolyl	PhCHO	**31**	None	70

[a] Isolated yields after hydrolysis.



i) iPrCHO, 1 equiv. –50°C to –30°C. ii) ClTi(OiPr)$_3$, 1 equiv. –50°C.

Scheme 12.

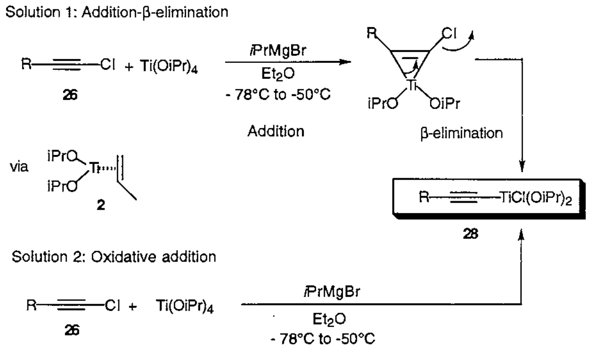
leads to the corresponding propargylic alcohols in good overall yields (entries 2, 3, 4). However, the co-addition of a mild Lewis acid such as ClTi(O*i*-Pr)$_3$ is beneficial for the reaction with an aldehyde (Table 2, compare entries 2 and 3).

Once the experimental conditions were set up on the model substrates (as described in Scheme 11 and Table 2), we focussed our attention on the preparation of functionalized alkynes, readily prepared from ω-alkyn-1-ol, and their transformations into functionalized alkynyl titanium derivatives as described in Scheme 12. Thus, treatment of an ethereal solution of functionalized chloroalkynes and Ti(O*i*-Pr)$_4$ (1.2 equivalents) with *i*-PrMgBr (2.4 equivalents) at − 78°C leads, by warming the reaction mixture up to − 50°C, to the desired functionalized alkynyl titanium derivatives **32** in excellent yield [38].

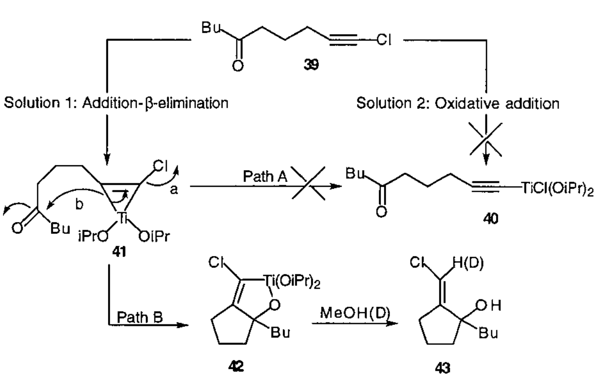
These derivatives tolerate a large variety of functional groups on the carbon skeleton. Halides like bromide or iodide (**33** and **34** in respectively 91% and 85% yield), tosylate **35** (81%), carbonate **36** (93%), ester **37** (87%) and β-keto ester **38** (68%) are compatible with the formation of the organometallic derivatives. They present a good reactivity with standard aldehyde even if, in some cases, the addition of Lewis acid is necessary in order to reach a good chemical yield. For example, **36** was obtained only in 50% yield without the addition of ClTi(O*i*-Pr)$_3$, whereas it was formed in 70% yield in the presence of a catalytic amount of ClTi(O*i*-Pr)$_3$ (10%) and in 93% when an equimolar amount of Lewis acid was added.

Although the formation of **28** from **26** is synthetically useful, we still have to prove that the reaction occurs as described, namely via an addition followed by a β-elimination and not by the classical oxidative addition of a low-valent transition metal such as **2** into the carbon chlorine bond of **26** as described in Scheme 13.

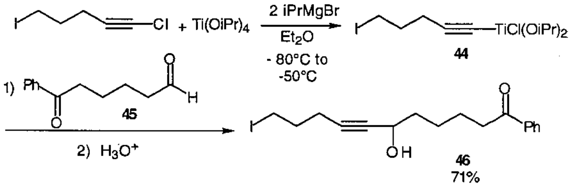
Thus, in order to have a clear answer to this question, we have designed the following experiment. From the functionalized ketone **39**, if the reaction occurs via an oxidative addition, the only possible product from this mechanism is the titano alkyne **40**. However, if the reaction occurs from the addition–β-elimination mechanism, the intermediate **41** is first formed. It can β-eliminate according to the pathway A to give also the titano alkyne **40**, but can also undergo an intramolecular nucleophilic acyl substitution reaction [39] with the ketone moiety to lead to the vinylic carbenoid **42**. Then, when we treated the functionalized ketone **39** with Ti(II) (**2**), the only product formed was the synthetically interesting vinylic carbenoid **41** [40] (path B) which gives **43** after hydrolysis (or deuterolysis) [41]. This result indicates clearly that the reaction occurs through an oxidative addition followed by a β-elimination. Then, when no intramolecular nucleophilic substitution is possible (no formation of the favorable five-membered ring), **41** follows the pathway A and the β-elimination occurs to give the metalated alkyne as described originally in Scheme 11. Thiophenyl alkyne as well as several heterosubstituted alkynes react under this condition to give the corresponding titano alkyne (Scheme 14) [42].



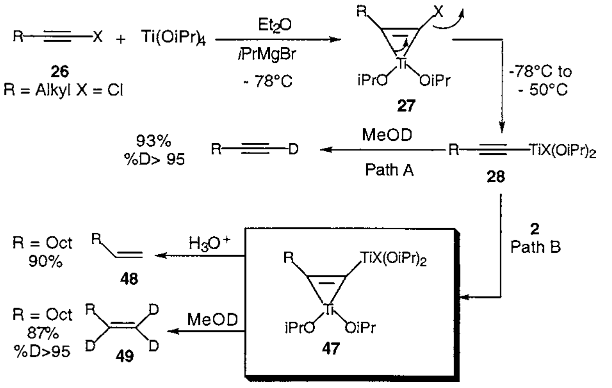
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

Table 3
Generalization for the synthesis of metalated titanacyclopropenes

Entry	R	X	Compound	Yield (%) [a]
1	Oct	Cl	**48**	90
2	Hex	Br	**50**	75
3	Hex	I	**50**	65
4	Hex	SPh	**50**	70
5	*p*-Tolyl	Cl	**51**	95
6	*tert*-AmylO(CH)$_2$	Cl	**52**	93

[a] Isolated yields after hydrolysis.

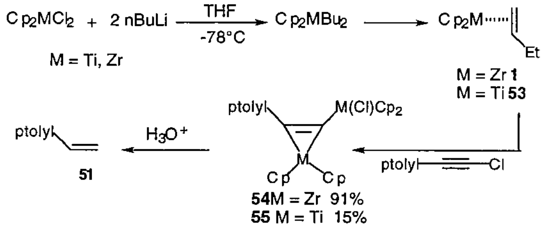
Finally, the chemoselective reaction between a functionalized alkynyl titanium derivative **44** and a functionalized electrophile **45** was performed in order to prepare, in a one-pot procedure, the polyfunctional compound **46** (Scheme 15).

When the Ti(II)/halogeno alkyne is used in a 2 to 1 ratio, the reaction can develop further. Indeed, the in situ formed di*iso*propyloxy(η^2-propene) titanium **2** (generated as described in Scheme 1) reacts first at −60°C with chloroalkyne **26** to give **28** (Schemes 11 and 16, path A) and then, the second equivalent of **2** reacts with **28** to give quantitatively the titano-titanacyclopropene **47** (Scheme 16, path B). After hydrolysis, **48** is isolated in high yield. The presence of three carbon–metal bonds was proven by reaction with MeOD to give **49** (> 95% D in 87% yield). Results for a variety of alkynes are shown in Table 3 after hydrolysis. In all cases, only the polymetalated species were obtained whatever the nature of the R group [43].

Indeed, several chloroalkynes with an alkyl, phenyl or homopropargylic ether group led to the products in good to high yields (entries 1, 5 and 6). Interestingly, according to the nature of the leaving group, minor variations in the chemical yields are observed (compare entries 1, 2 and 3). Whereas the first step is still quantitative (formation of the metalated alkyne **28**), the second is dependent on the nature of the halogen X on alkynyltitanium **28**. Even in the case of the alkynyl thiophenyl ether (entry 4), a good chemical yield was obtained.

On the other hand, further investigations revealed interesting reactivities of zirconocene-(1-butene) **1** and titanocene-(1-butene) **53** derivatives with a chloroalkyne. Indeed, whereas the reaction of **1** with *p*-tolylchloroacetylene (see Scheme 17) afforded the corresponding trismetalated olefin **54** in high yield (91% of **51** after hydrolysis), the same reaction with Cp$_2$Ti-(1-butene) **53** [44] led only to 15% of **51**. When the same strategy is applied to **26** (R = alkyl) either with **1** or **53** only low conversions to trimetallated olefins are obtained.

In summary, we have been able to demonstrate that the oxidative addition–β-elimination mechanism is a powerful method for the production of organometallic derivatives. Indeed, using this new concept we have reported the first transformation of methoxy enol ethers and silyl enol ethers into the corresponding vinyl zirconium derivatives. This reaction occurs stereoselectively, irrespective of the stereochemistry of the starting material. Moreover, due to the potential transmetalation step, a large variety of electrophiles can be added. Moreover, the in situ formation of Ti(II) (**2**) and subse-



Scheme 17.

quent reaction with halogeno alkynes offer a new route for the preparation of functionalized alkynyl titanium derivatives. These can further react chemoselectively with functionalized electrophiles. This strategy can be easily generalized to a large variety of alkynes since several mild methods are known for the transformation of alkynes into halogeno alkynes [45]. Finally, the use of di*iso*propyloxy(η^2-propene)titanium (**2**) provides an efficient one-pot method for synthesizing trimetalated olefins from common starting materials.

We strongly believe that this new approach for the synthesis of organometallic derivatives will be very useful since it allows new transformations in organic synthesis.

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