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Efficient Propargylation of Aldehydes and Ketones Catalyzed by Titanocene(III)

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Abstract: We describe a novel method for the propargylation of a wide range of aldehydes and ketones catalyzed by titanocene(III) complexes under mild reaction conditions and compatible with many functional groups. Homopropargylic alcohols are obtained as the sole products even when ketones are used as starting materials, which is unusual in Barbier-type propargylations.

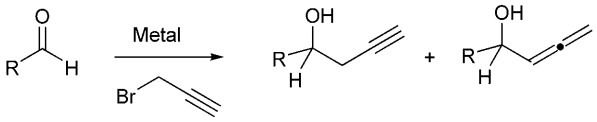
Keywords: homogeneous catalysis; propargylation; synthetic methods; titanium

In recent years many remarkable transition metal-based transformations using alkynes as substrates have been described.[1] Reactions allowing the efficient introduction of this functional group from suitable starting materials are extremely valuable.[2] Within this context, the synthesis of homopropargylic alcohols derived from the addition of organometallic reagents to carbonyl compounds is a very straightforward procedure. These unsaturated compounds are important intermediates in organic synthesis[3a–e] and are also present as structural motifs in many natural products.[3e] Nevertheless, propargylic organometallic reagents are difficult to prepare and manipulate.[4] To circumvent this problem Barbier-type protocols have been developed, using mainly propargylic halides as pronucleophiles.[5] Although many metals, some of them both expensive and toxic, may promote this transformation under heterogeneous conditions, mixtures of propargylic and allenic regioisomers are generally obtained.[6] This lack of regioselectivity constitutes the main drawback of this method. Heterogeneous reactions also present problems concerning the activation of the metal surface, problems which are undesirable from a practical point of view. Furthermore, mechanistic studies of these systems are complex and the development of enantioselective processes is difficult.

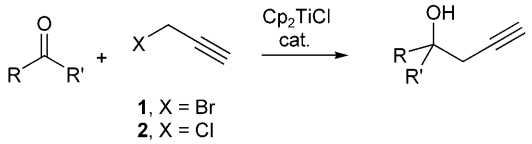
On the other hand, homogeneous reactions have many advantages, particularly with regard to the relative simplicity of controlling the reaction conditions. An excellent example of a Barbier-type reaction using homogeneus conditions is the Cr(II)-mediated propargylation reaction (Scheme 1).[7a] Nevertheless, this reaction usually produces mixtures of homopropargylic and allenic alcohols.[7,8] Moreover, because only a few examples of the propargylation of ketones with Cr(II)-reagents have been described[6f,9] it would seem to be limited to aldehydes as starting materials.

Bearing all this in mind it occurred to us that titanocene(III) (Cp_2TiCl), a mild single-electron transfer reagent extensively studied by RajanBabu and Nugent,[10] Gansäuer[11] and our group,[12] might achieve this interesting propargylation reaction with a better chemical profile. This working hypothesis was supported by our previous work on a general and efficient Barbier-type allylation and prenylation reaction of carbonyl compounds mediated/catalyzed by titanocene(III) complexes.[13] This reaction proceeds under mild conditions with high stereo- and regioselectivity, and has been used in the straightforward synthesis of some natural products.

As a result, we report here a new, efficient and completely regioselective addition of propargylic hal-



Scheme 1. General propargylation reaction under Barbier conditions.



Scheme 2. Barbier-type propargylation of aldehydes and ketones catalyzed by Ti(III).

ides to aldehydes and also to ketones catalyzed by titanocene(III) (Scheme 2). The reaction takes place under mild reaction conditions, compatible with many functional groups, and produces only the homopropargylic regioisomer. We also provide some insights into the mechanism of the reaction.

We began our study of this new propargylation reaction using various aldehydes **3**–**9**. In this case, propargyl bromide (**1**) gave the best results with these substrates.[14] All reactions were carried out using the starting aldehyde (1 mmol), propargyl bromide (2 mmol), a substochiometric amount of Cp_2TiCl (0.2 mmol) and a titanocene(III) regenerating agent developed by our group.[15] The regenerating mixture contained 2,4,6-collidine (7 mmol),[16] TMSCl (4 mmol) and Mn dust (8 mmol).[16] The results are summarized in Table 1.

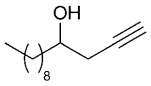
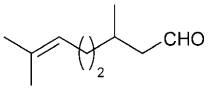
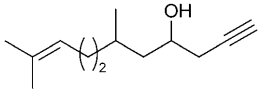
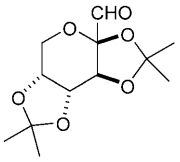
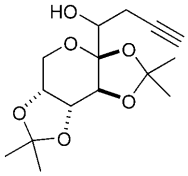
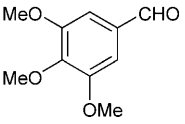
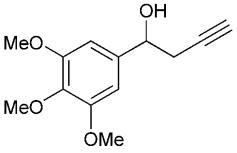
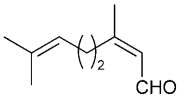
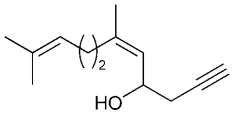
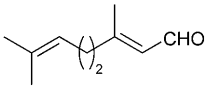
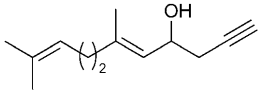
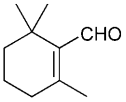
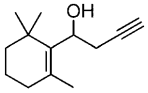
In all the experiments we detected only the homopropargylic regioisomer, underlining the remarkable regioselectivity of this titanium-catalyzed process. As mentioned above, chromium(II)-promoted Nozaki–Hiyama–Kishi propargylations of aldehydes yield high proportions of allenic derivatives.[17] The same tendency has been observed in closely related SmI_2-mediated propargylation reactions.[18]

The titanocene(III)-catalyzed propargylation reaction gave good to excellent yields with aldehydes of different natures: aliphatic (entries 1, 2 and 3), aromatic (entry 4) and α,β-unsaturated (entries 5, 6 and 7). It is worth noting that aromatic and α,β-unsaturated aldehydes are substrates prone to pinacolize under reductive conditions. It is also interesting from a synthetic point of view that the configuration of the Δ^2-double bond in substrates **7** and **8** was retained after the coupling process.

It is noteworthy that complete regioselectivity was also observed when different kinds of ketone were used as substrates (Table 2). In fact, the present method is one of the few examples of homogeneous Barbier-type propargylation[19] procedures using ketones as starting materials. We obtained the best results using less reactive propargyl chloride (**2**) as pronucleophile.[14]

We obtained good to excellent yields (63–100%) of the propargylation products. The reaction took place with simple substrates (entries 1–5) and also with functionalized ones (entries 7–10), including alkyl halides, esters, and phenols. The lactonization occurring

Table 1. Titanocene(III)-catalyzed Barbier-type propargylation of aldehydes **3–9** using propargyl bromide **1**.

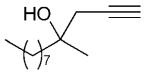
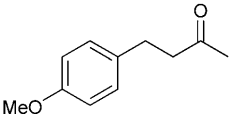
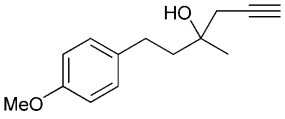
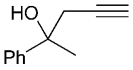
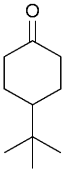
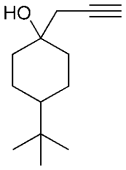
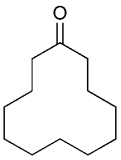
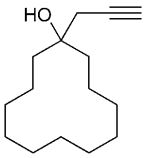
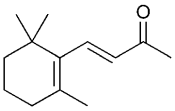
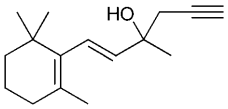
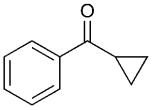
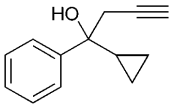
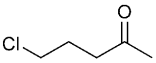
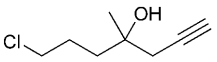
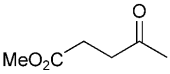
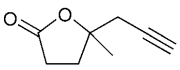
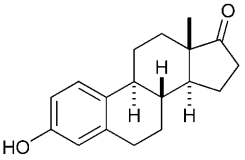
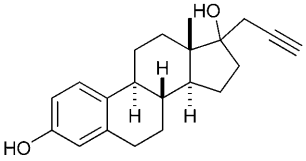
Entry	Carbonyl compound	Product	Yield [%]
1	**3** 	**10** 	96
2	**4** 	**11** 	97[a]
3	**5** 	**12** 	64[b]
4	**6** 	**13** 	90
5	**7** 	**14** 	83
6	**8** 	**15** 	57
7	**9** 	**16** 	65

[a] 1:1 mixture of isomers.
[b] 3:2 mixture of *R* and *S* epimers at C-1′.

after the propargylation of keto ester **25** suggests that this procedure might become a useful tool for the synthesis of propargylated γ-lactones. Interestingly, the absence of cyclopropane-opening compounds in the propargylation reaction of cyclopropylacetophenone (**23**) suggests that ketyl radical intermediates are not involved in this reaction. In entry 4, a 2:1 mixture of equatorial/axial alcohols was obtained. The predominance of an equatorial isomer can be put down to the formation of a bulky titanocene(IV) alkoxide in equatorial position, leading the propargyl group to adopt an axial disposition.

From this experimental evidence we feel able to propose the following mechanism for the transformation (Scheme 3).[20] The process begins with a reaction between Ti(III) and the corresponding propargyl halide, yielding an allenyl titanocene(IV) intermediate (**I**),[21] the presence of which is hypothesized to explain the complete regiochemistry of the addition reaction. In fact, it is well-known that these allenyltitanocene(IV) species add to carbonyl compounds, yield-

Table 2. Titanocene(III)-catalyzed Barbier-type propargylation of ketones **17**-**26** using propargyl chloride **2**.

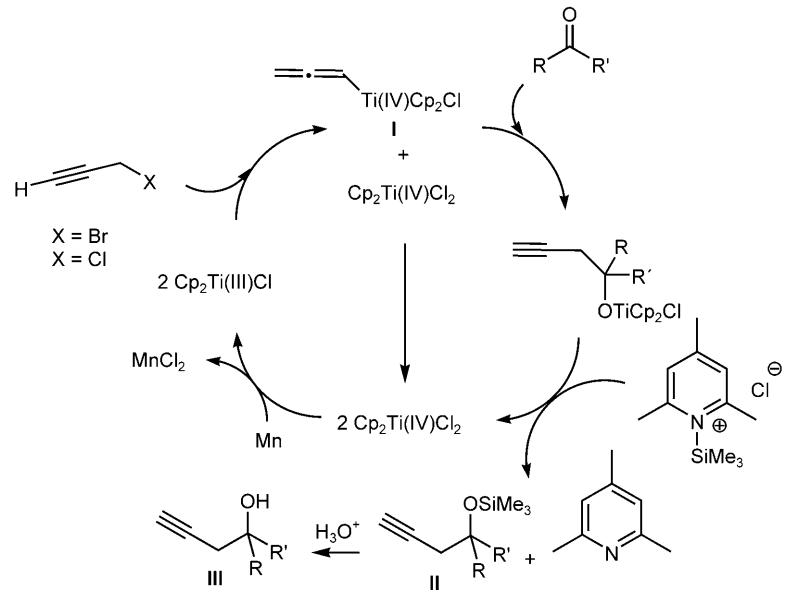
Entry	Carbonyl compound		Product		Yield [%]
1	**17**		**27**		91
2	**18**		**28**		70
3	**19**		**29**		80
4	**20**		**30**		83[a]
5	**21**		**31**		70
6	**22**		**32**		97
7	**23**		**33**		100
8	**24**		**34**		64
9	**25**		**35**		63
10	**26**		**36**		85

[a] 2:1 mixture of equatorial:axial alcohols.

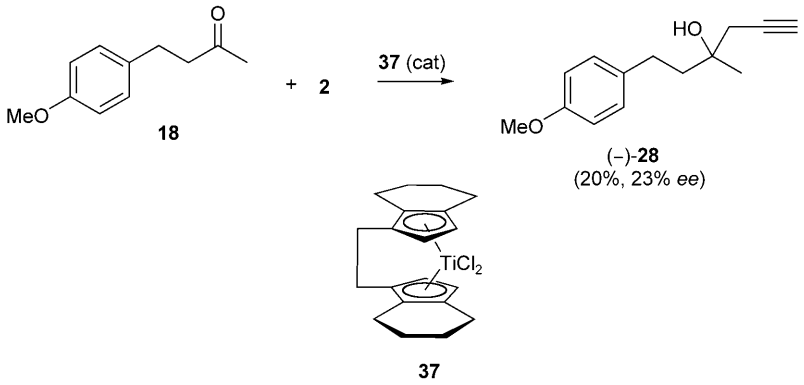
ing homopropargylic alcohols.[21] Subsequently, the resulting alkoxytitanocene is quenched with a 2,4,6-collidine/TMSCl mixture,[15] regenerating the Ti(IV) species and leading to intermediate **II**, which after acid treatment yields propargylic alcohol **III**. Finally, Mn dust reduces Cp_2TiCl_2 to the active species Cp_2TiCl, thus completing the catalytic cycle.

For this hypothesis we assume that the titanium catalyst is involved in the C–C bond-forming step, which is essential for the future development of an enantioselective process. Thus we decided to assay an enantiomerically pure titanium catalyst to check our initial mechanistic assumption and the potential future of enantioselective propargylation processes using our Ti-catalyzed method. To this end we chose commercially available Brintzinger complex, dichloro(*R*,*R*)-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)titanium(IV) (**37**), which we had previously used in our studies on allylation and prenylation reactions.[13]

Propargylation of aliphatic ketone **18** catalyzed by **37** gave a 20% yield of (−)-**28**, with a 23% enantiomeric excess (*ee*) (Scheme 4).[22] Despite this low yield and *ee* value, the optical activity observed for product (−)-**28** demonstrated that Ti-catalyzed Barbier-type propargylations can be conducted enantioselectively by using chiral titanium catalysts. This result strongly



Scheme 3. Mechanistic proposal for Ti-catalyzed propargylation reactions.



Scheme 4. Asymmetric propargylation of **18** catalyzed by Brintzinger's complex (**37**).

supports the idea that the titanium catalyst is actually participating in the crucial C–C bond-forming step of the intermolecular coupling process (see Scheme 3). The low *ee* obtained is in agreement with the reported *ee* values (4–40%) in related allylation reactions of aldehydes using allyl-Brintzinger complexes.[23]

In conclusion, we have developed a novel method for the propargylation of a wide range of aldehydes and even ketones catalyzed by titanocene(III) complexes. Moreover, these reactions take place at room temperature under mild conditions, thus being compatible with many functional groups, and they provide good to excellent yields of homopropargylic alcohols. It should also be noted that the reaction can be conducted enantioselectively by using chiral titanium catalysts, although currently available titanium complexes have only afforded poor *ee* so far. At the moment we are engaged in the study of this reaction using substituted propargyl halides and in the rational design and synthesis of novel, more efficient chiral titanium catalysts.

Experimental Section

General Procedure for Ti(III)-Catalyzed Barbier-Type Propargylations of Non-Conjugated Aldehydes and Ketones (GP 1)

Completely deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.2 mmol) and Mn dust (8 mmol) under an argon atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of carbonyl compound (1 mmol) and 2,4,6-collidine (7 mmol) in THF (1 mL) and Me_3SiCl (4 mmol) were added. Allylic halide (2 mmol) in THF (1 mL) was then added slowly for 1 h and the mixture was stirred for a further 6 h. The reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc.

The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and the solvent removed. Products **10–12**, **27–28**, **30–31**, and **34–36** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. The yields are set out in Table 1 and Table 2. In some experiments trimethylsilyl derivatives were observed. Whenever this happened the residue was dissolved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine, dried (anhydrous Na_2SO_4) and the solvent removed.

General Procedure for Ti(III)-Catalyzed Barbier-Type Propargylations of Conjugated Aldehydes and Ketones (GP 2)

Completely deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.2 mmol) and Mn dust (8.0 mmol) under an argon atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of carbonyl compound (1 mmol), 2,4,6-collidine (7 mmol), and allylic halide (2 mmol) in THF (2 mL), and Me_3SiCl (4 mmol) were added slowly and the solution was stirred for a further 6 h. The reaction was then quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine, dried (anhydrous Na_2SO_4) and the solvent removed. Products **13–16**, **29** and **32–33** were purified by flash chromatography on silicagel (hexane/EtOAc) and characterized by spectroscopy. The yields are set out in Table 1 and Table 2. In some experiments, trimethylsilyl derivatives were observed. Whenever this happened the residue was dissolved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine, dried (anhydrous Na_2SO_4) and the solvent removed.

Supporting Information

Spectral data for non-described propargylation products are available as Supporting Information.

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