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Diastereoselectivity in the synthesis of bicyclic titanacyclopentenes from chiral 6-hepten-1-ynes

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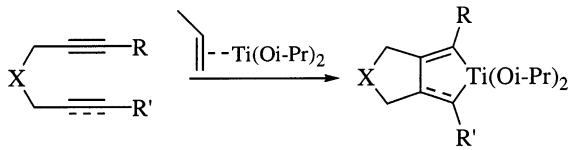
Abstract

A variety of chiral 6-hepten-1-ynes have been found to undergo cyclization to titanabicyclopentenes by (η^2-propene)Ti(O*i*-Pr)$_2$ with excellent yields and degrees of *exo*-stereoselectivity depending on the substrate steric requirements. In the framework of a plausible cyclization mechanism several conformational features which can regulate the stereoinduction have been suggested. © 2000 Published by Elsevier Science Ltd.

Keywords: cyclisation; titanium; titanium compounds; enynes; diastereoselection.

Titana and zircona metallacyclic complexes are versatile organic intermediates which can be directed towards the synthesis of cyclic or acyclic compounds by reaction with various electrophiles, notably carbon monoxide or unsaturated substrates.[1] The Sato titanium promoted intramolecular cyclization of α,ω-enynes and α,ω-diynes, which selectively affords metallabicyclic complexes (Scheme 1),[2] has attracted much interest and a variety of synthetic methodologies based on these reagents have been developed.[3] Despite the activity in the area, relatively little is known regarding the influence of peripheral stereocontrol on titanium based cyclization of simple enynes. Only few data have been reported on the 'Cp_2Ti' stereoselective annulation of oxygen-substituted substrates.[4]



Scheme 1.

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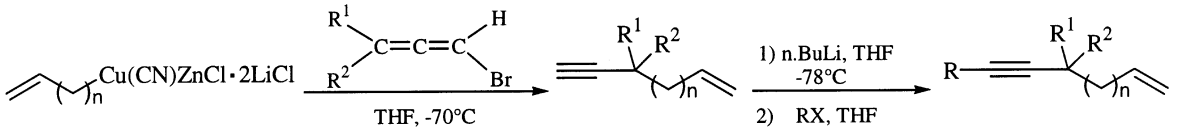
We recently reported[5] a general strategy for the synthesis of chiral α,ω-enynes, with side chains in the α position next to the triple bond, via a cross-coupling process between 3- or a 3,3-substituted 1-bromo-1,2-dienes and unsaturated zinc-cyanocuprates (Scheme 2). This reaction is very clean and chiral products can be obtained with good yields and almost complete chemo-, regio- and 1,3-*anti* stereoselectivity.



Scheme 2.

Herein we report that the so obtained 6-hepten-1-ynes, **1**, eventually modified by subsequent acetylenic alkylation[6] (Scheme 2), can be converted into chiral bicyclic titanacyclopentenes **3** characterized by tertiary or quaternary stereogenic centres (Scheme 3); in this ring closure reaction a new stereocentre is formed and we found that the diastereoselection depends on the steric requirements of the starting substrate (Table 1).

Table 1
Reaction of chiral 6-hepten-1-ynes, **1**, with (η^2-propene)Ti(O*i*-Pr)$_2$[a]

Entry	**1**	R^1	R^2	R	Yield (%)[b]		**4**, DS[c]
					4	**5**	
1	a	H	*t*-Bu	H	100(53)	–	69:31
2	b	H	*t*-Bu	Me	100(92)	–	100:–
3	c	H	*t*-Bu	$SiMe_3$	–	100(76)	–
4	d	Me	Et	H	100(74)	–	57:43
5	e	Me	*t*-Bu	H	100(67)	–	55:45
6	f	Me	*t*-Bu	$SiMe_3$	–	100	–
7	g[d]	H	*i*-Pr	*i*-Pr	100(86)	–	100:–
8	h	H	Ph	H	100(80)	–	70:30
9	i	H	Ph	Me	100(90)	–	85:15
10	l	H	Ph	Et	100(88)	–	86:14
11	m	H	Ph	$SiMe_3$	36	64	86:14
12[e]	m	H	Ph	$SiMe_3$	49	51	86:14

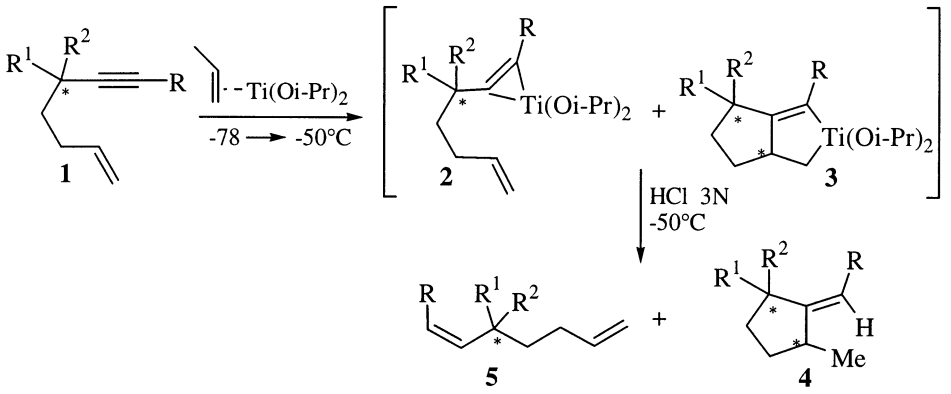
[a] Reactions were performed in ether, with a slight excess of the titanium reagent at $-78° > -50°C$ for 2.5 h.

[b] Determined by GLC of the reaction mixture after work-up. (Isolated yields are shown in parentheses.) All new compounds were identified and characterized by FTIR, NMR (^1H and ^{13}C) and elemental analysis. Configuration of the olefinic moiety in **4** was assigned by NOE experiments.

[c] Diastereoselectivity, evaluated by ^1H NMR analysis.

[d] The synthesis of **1g** was performed by a cross coupling reaction between 3-butenyl zinc-cyanocuprate and 3-bromo-2,6-dimethyl-3,4-heptadiene obtained according to the Corey method.[9]

[e] Reaction time = 4 h.



Scheme 3.

6-Hepten-1-ynes, **1**, were reacted with (η^2-propene)Ti(O*i*-Pr)$_2$, prepared in situ from Ti(O*i*-Pr)$_4$ and 2 equiv. of *i*-PrMgCl[2] in ether, first at −78°C and finally at −50°C to ensure the complete enyne transformation (2.5 h). After aqueous HCl work-up, in general, a sole product **4** was obtained in good yield[7] and the presence of the intermediate titanabicycle **3** was confirmed by subjecting the reaction mixture to deuterolysis. However, the cyclization process appears sensitive to steric interactions: with highly hindered substrates, such as those with a Me_3Si group at C1 of the acetylenic moiety, we isolated, after hydrolysis, substantial amounts of 1,6-heptadienes **5** from a selective *syn* reduction of the acetylenic function (entries 3 and 6). Deuterolytic work-up suggests for such reduction products a titanacyclopropene precursor **2** for which the subsequent intramolecular carbometallation to complex **3** is disfavoured even on increasing the reaction time (see entries 11 and 12). In these cases higher reaction temperatures and longer reaction times afford complicated mixtures of unidentified products.[8]

When cyclization is possible, the relative steric hindrance at C1 and C3 of the eneyne moiety exerts an influence on the configuration of the new stereocentre formed, and we found that it is possible to obtain just one of the two diastereomers (Table 1); in particular, the presence of an alkyl group at C1 strongly enhances the diastereoselectivity, which was evaluated by ^{1}H NMR analysis on isolated chemically pure alkylidenecyclopentanes, **4**. NOE ^{1}H NMR experiments performed on 1-[(*Z*)-ethylidene]-2-*tert*-butyl-5-methyl cyclopentane, **4b**, (Fig. 1) also demonstrate the predominant *exo*-stereochemistry of the annulation process.

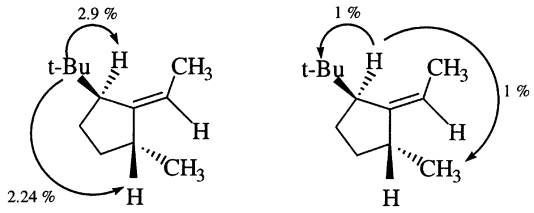
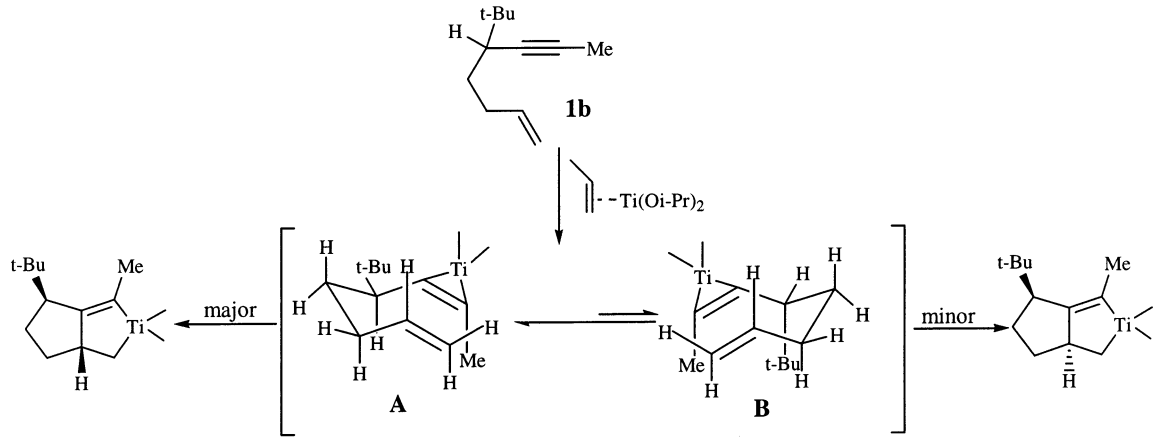


Figure 1.

These results support the mechanism already proposed for the cyclization process,[2,3] where an initial complexation of the acetylenic function to the metal is followed by a subsequent intramolecular carbometallation. The stereochemical outcome of the ring closure may be explained by the two likely models for the titanacyclopropene attack to the olefinic double bond to obtain the bicyclic derivative, as depicted in Scheme 4 for reaction with **1b** as substrate. In the

more favoured conformation **A**, leading to the major product, the sterically demanding *tert*-butyl group occupies an equatorial position opposite to the methyl group bonded to the cyclopropene moiety.



Scheme 4.

Apart from the mechanistic implications, our data indicate for the (η^2-propene)Ti(O*i*-Pr)$_2$ promoted cyclization of chiral enynes, a high potential for the building of chiral carbocycles.

Acknowledgements

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7. 1-[(*Z*)-Ethylidene]-2-*tert*-butyl-5-methylcyclopentane, **4b** (representative procedure): An ethereal solution of *i*-PrMgCl (9.6 mmol) was added, at −78°C, to a mixture of 4-*tert*-butyl-7-octen-2-yne, **1b** (0.51 g, 3.1 mmol) and Ti(O*i*-Pr)$_4$ (1.23 mL, 4.2 mmol) in Et$_2$O (30 mL). After stirring for 30 min, the mixture was warmed to −50°C over a period of 30 min and kept at this temperature for 1.5 h; the progress of the reaction was monitored by GLC analyses. The mixture was treated, at −50°C, with 25 mL of water and then, at room temperature, with 3N HCl.

The organic materials were extracted with ether, washed with aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated to an oil, which was chromatographed on silica gel (hexane–ether) to afford the title compound (0.47 g, 92%). ^{1}H NMR: δ 0.84 (9H, s); 0.97 (3H, d, $J=6.3$ Hz); 1.45–1.90 (4H, m); 1.62 (3H, dd, $J=2.2$ and 6.9 Hz); 2.23 (1H, m); 2.52 (1H, m); 5.21 (1H, tq, $J=1.9$ and 6.9 Hz); ^{13}C NMR: δ 16.2, 17.2, 25.1, 28.5, 34.0, 36.2, 39.0, 49.4, 115.0, 150.1; MS, m/z (rel. intensity): 166 (M^+, 0.5%), 165 (0.8), 110 (58), 109 (25), 108 (20), 95 (38), 81 (100), 79 (13), 67 (22), 57 (34); anal. calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.84; H, 13.15.

8. Chiral titanabicyclopentadienes are also obtained from 1,3-substituted 7-trimethylsilyl-1,6-heptadiynes (Scheme 1); an increase in the diyne steric requirements results once again in the *syn* reduction of a triple bond (the less hindered). So, reaction of 3-ethyl-3-methyl-1,7-bis(trimethylsilyl)-1,6-heptadiyne with (η^2-propene)Ti(O*i*-Pr)$_2$ selectively affords (*Z*)-3-ethyl-3-methyl-1,7-bis(trimethylsilyl)-6-hepten-1-yne.
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