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Titanacyclopentene complexes and their application as 1,4-dicarbanion equivalents†

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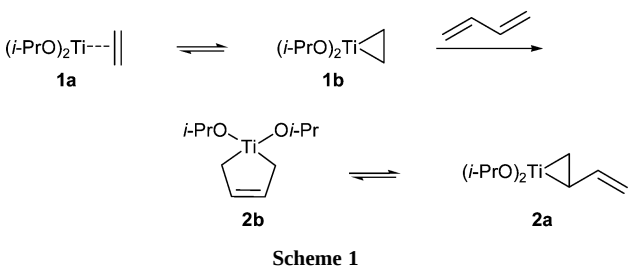
The treatment of Ti(O*i*Pr)$_4$ with 3-butenylmagnesium chloride generates titanacyclopentene complexes which effectively add to carbonyl compounds and nitriles to afford the 1,4-coupling products with high *Z:E* selectivities.

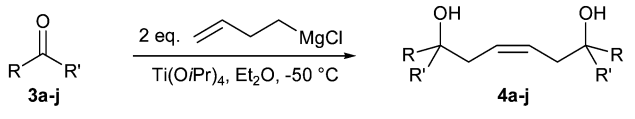
Since the discovery of the Ti(O*i*Pr)$_4$-catalysed conversion of esters with Grignard reagents to substituted cyclopropanols,[1] this practical method has turned out to be a powerful tool in synthetic organic chemistry. It has significantly encouraged further investigation of similar reactions.[2] An important feature of this methodology is the facile ligand exchange of the *in situ* generated (η^2-alkene)Ti(O*i*Pr)$_2$ **1a** with other alkenes and dialkenes to enable inter- and intramolecular reactions. Intermediate **1a** may also be interpreted as a titanacyclopropane **1b** (Scheme 1), having a 1,2-dicarbanionic reactivity pattern, as such species react with two equivalents of an electrophile.[3]

The ligand exchange of complex **1** with 1,3-dienes has been little investigated. Sato *et al.* reported the conversion of hexa-3,5-dienyl ethyl carbonate with complex **1** and proposed a 1,4-dicarbanionic titanacyclopentene intermediate similar to structure **2b**.[4] On the other hand, de Meijere *et al.* observed that conjugated dienes and trienes were accepted by **1** as particularly good ligands, but the resulting intermediate **2** behaved selectively as a 1,2-dicarbanionic vinyltitana-cyclopropane when trapped with dibenzylformamide.[5]

We now report an effective intermolecular coupling of but-3-enylmagnesium chloride with 2 equivalents of an electrophile in the presence of Ti(O*i*Pr)$_4$. This offers a new access to *cis*-configured hex-3-ene-1,6-diols, 6-hydroxy ketones and 1,6-diones.† This coupling worked most selectively with aldehydes and ketones of low steric demand (Scheme 2, Table 1). Not only was an exclusive 1,4-double addition of the carbonyl compound to complex **2** observed, but also high *Z:E* ratios of >95:5 were determined in products **4** (Entries 1–8). Increasing bulk of the substrates (Entries 9,10) led to lower yields and the *Z:E* ratio changed for the worse as well. In the case using methyl *tert*-butyl ketone as an electrophile, the *Z:E* selectivity was found to be reversed.



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b311572k/

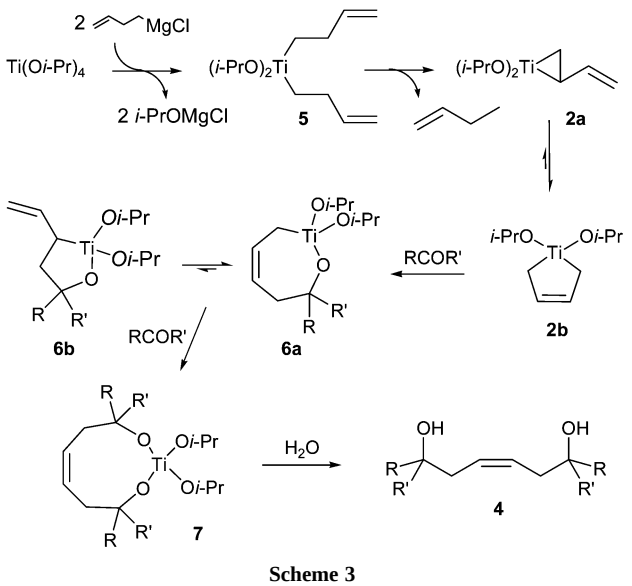
A rationale for these observations is depicted in Scheme 3. The addition of butenylmagnesium chloride to Ti(O*i*Pr)$_4$ gives dibutenyltitanium species **5** which undergoes a β-hydride elimination/reductive elimination sequence to the putative intermediate **2**. Since we did not observe any 1,2-dicarbanion reaction products, we assume titanacyclopentene **2b** to be the much favoured species in this equilibrium.[6,7] The carbonyl compound inserts now into the titanacyclopentene **2b** giving rise to complex **6**. The second equivalent presumably reacts with oxatitanacycloheptene **6a** to the 9-membered intermediate **7** in which the *cis*-geometry found in the coupling products **4** is still preserved. However, bulky electrophiles may preferentially add to the oxatitanacyclopentane **6b** which results in a higher portion of *E*-configured diol **4**.[9]

Higher substituted Grignard reagents generally resulted in lower yields. The sequential insertion of electrophiles may even be blocked completely. For instance, the reaction of 4-methylpent-3-enylmagnesium bromide with cyclopentanone afforded a mixture of the monoalkylation products **8** and **9** in 25% yield (Scheme 4), both isomers having *E*-configuration.

Table 1 Symmetrical coupling of aldehydes and ketones

Entry	R, R′	Product (%)[a]	d.r.[b]	*Z:E*[b]
1	H, *i*-Pr	**4a** (85)	2.5:1	>95:5
2	H, n-Bu	**4b** (82)	1.3:1	>95:5
3	H, CH=C(CH$_3$)$_2$	**4c** (57)	1:1	>95:5
4	(CH$_2$)$_4$	**4d** (78)	—	>95:5
5	(CH$_2$)$_5$	**4e** (78)	—	>95:5
6	Me, Me	**4f** (63)[8]	—	>95:5
7	Me, CH=CH$_2$	**4g** (54)	1.4:1	>95:5
8	Me, CH$_2$CH$_2$CH=C(CH$_3$)$_2$	**4h** (67)	1.4:1	>95:5
9	Me, *t*-Bu	**4i** (42)	5:1	1:1.4
10	Me, Ph	**4j** (30)	1.8:1	9:1

[a] isolated by chromatography, [b] determined by NMR.



Scheme 3

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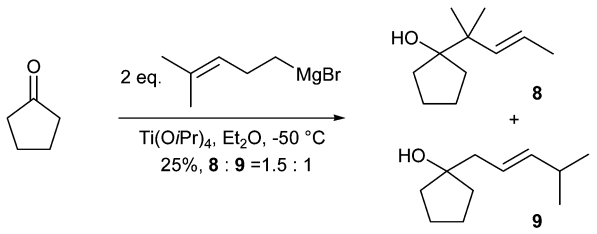
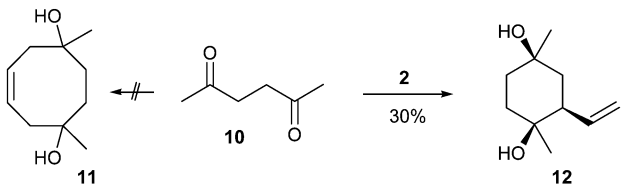


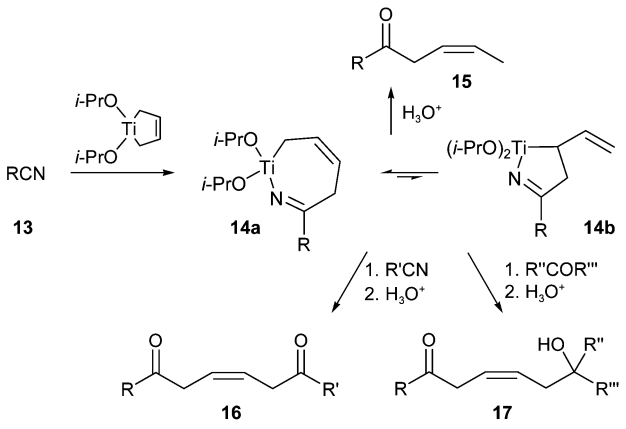
Scheme 4

The above results suggested utilising this methodology for a macrocyclisation with *e.g.* diketones (Scheme 5). However, an attempt to react acetonylacetone with complex **2** did not furnish the expected cyclooctendiol **11** but gave stereoselectively the vinyl cyclohexanediol **12**. This was the only example obtained, in which complex **2**, treated with a ketone, displayed its 1,2-dicarbanion properties. Reactions of species **2** with higher homologues of **10** led to non-uniform mixtures.

While the symmetrical coupling (2 equivalents of the same carbonyl compound) provided useful results, subsequent treatment of complex **2** with two different aldehydes or ketones led to statistical mixtures of symmetrical and unsymmetrical coupling products. Apparently, intermediate **6** possesses a reactivity not very different from that of **2**. In order to circumvent this problem, complex **2** was first reacted with a nitrile at −50 °C, resulting in the formation of iminotitanacycloheptene **14** (Scheme 6) which we assumed to be less reactive than the oxa-analogue **6**. Indeed, after hydrolysis of intermediate **14** at −30 °C with 2N HCl, ketone **15a** was obtained in 76% yield without any observable isomerisation of



Scheme 5



Scheme 6

Table 2 Unsymmetrical coupling products

Entry	R	R′	R″, R‴	Time/h	*T*/°C	Product (%)[a,b]
1	Et			1	−50→(−30)	**15a** (76)
2	*i*-Pr			1	−50→(−30)	**15b** (79)
3	Et	Et		4	−50→(+35)	**16** (33)
4	Et		$(CH_2)_4$	2	−50→(−10)	**17a** (76)
5	Et		Me, $CH{=}CH_2$	2	−50→(−10)	**17b** (53)
6	Et		H, Et	2	−50→(−10)	**17c** (60)

[a] isolated by chromatography, [b] *Z:E* ratio > 95:5.

the deconjugated *cis*-configured double bond (Scheme 6, Table 2, Entries 1 and 2). On the other hand, **14** was reactive enough to add an additional equivalent of a nitrile at elevated temperature (Entry 3) leading to a diketone **16**. Moreover, intermediate **14** also tolerated a subsequently added ketone or aldehyde (Entries 4–6) which produced the unsymmetrical coupling products **17a–c**, also having the *cis*-double bond preserved.

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Notes and references

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