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Reduction of titanocene dichloride with dysprosium: access to a stable titanocene(II) equivalent for phosphite-free Takeda carbonyl olefination[†]

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The reduction of titanocene dichloride with dysprosium yields a new titanocene(II) equivalent without the need for further stabilising ligands. This reagent can be employed in combination with dithioacetals for the olefination of different carbonyl groups and allows for a simplified all-in-one procedure.

Despite numerous synthetic attempts over the last 50 years, the genuine titanocene(II) complex [Cp2Ti] has not yet been isolated and crystallographically characterised.¹ The simple Cp ligand does not provide enough steric bulk to protect the highly reactive carbene-like metal center. In contrast, bulky t-butyl or tris(alkyl)silyl substituted cyclopentadienyl ligands have allowed the stabilisation and isolation of its heavier analogues.² Alternatively, stabilising organic ligands have given rise to titanocene(π) equivalents $[Cp_2Ti(L)_n]$ (L = CO, TMS-CC-TMS, PR₃) with widespread use in organic synthesis and organometallic chemistry.3 Among them, the triethylphosphite stabilised complex $[Cp_2Ti(P(OEt)_3)_2]$ (1) has shown good applicability in carbonyl olefination, cyclopropanation, allylation and olefin metathesis reactions.⁴ As the phosphite can be the source of unwanted side-reactions or purification issues,⁵ we now report on the preparation of a new titanocene(II) equivalent 2, which is only stabilised by dysprosium chloride, generated in situ during the reduction of titanocene dichloride with elemental dysprosium (Scheme 1). This new complex has been successfully employed in carbonyl olefination reactions using dithioacetals. Moreover, this efficient Ti(II) vector gives access to a simplified reaction protocol.

The closest attempt towards a stable ligand-free $[Cp_2Ti(n)]$ complex was reported recently by Eisch *et al.* using a salt metathesis reaction between a THF-soluble form of titanium dichloride and sodium cyclopentadienide.¹ The formed titanocene(n) complex was supposedly stabilised by sodium chloride

Takeda: $Cp_{2}TiCl_{2} \xrightarrow{Mg} [Cp_{2}Ti(P(OEt)_{3})_{2}] \xrightarrow{R^{1} \xrightarrow{SR}} R^{1} \xrightarrow{SR} R^{1} \xrightarrow{SR} R^{1} \xrightarrow{SR} R^{1} \xrightarrow{SR} R^{1} \xrightarrow{R^{2} \xrightarrow{R^{3}}} R^{2} \xrightarrow{R^{3}} R^{2} \xrightarrow{R^$





Scheme 2 A titanocene(II) equivalent by salt metathesis reaction.

and could be further reacted with internal alkynes to the corresponding titanacyclopentadiene (Scheme 2).

In recent years, we have investigated the reduction of Cp_2ZrCl_2 with lanthanides, leading to a number of new transformations in organic chemistry.⁶ This has driven our interest towards the reduction of Cp_2TiCl_2 by lanthanides. We presumed that the resulting titanocene(π) complexes might be stabilised by the *in situ* formed LnCl₃, without the further need for stabilising organic ligands. In contrast to the salt metathesis approach developed by Eisch, this strategy does not require the preparation of any air-sensitive starting compounds.

In order to verify our hypothesis, we replaced the $Mg/P(OEt)_3$ couple of a standard Takeda olefination reaction by various elemental lanthanides or yttrium (Table 1). After stirring Cp_2TiCl_2 and the metal in THF for 3 hours at room temperature, benzaldehyde derived dithioacetal **3a** was added, followed by methylbenzoate **4a** and the reaction was heated at 50 °C for 1.5 hours. Workup and purification by chromatography on silica gel afforded the alkene **5a** in varying yields,

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Cp₂TiCl₂/I n system

Table 2Scope of carbonyl olefination with the Cp_2TiCl_2/Dy system

3 Cp ₂ TiCl ₂ +	n M THF 3h, r.t.	Ph 3a SPh (1.2 eq.) 20min, r.t. Cp ₂ Ti(SPh) ₂	Ph $4a$ OMe (1.0 eq.) 90min, 50°C - Cp ₂ Ti=O	Ph Ph 5a
Entry	М	n	(eq.)	5a ^{<i>a</i>} (% yield)
1	La	2.4		24
2	Ce	2.4		20
3	Nd	2.4		38
4	Sm	2.4		0
5	Dy	2.	4	50
6	Yb		2.4	
7	Y	2.	4	36
8	Mg	3.6		33
Э	Dy	3.0		65
^z The selectivi	ty (Z/E) in all ca	ises was >95/	5.	
Cp ₂	TiCl + Ph—	< ^{SPh} ── SPh ──	F Ph	SPh
	3:	a	6	

Table 1 Preliminary results on the carbonyl olefination using the

Scheme 3 Formation of thioether from dithioacetal.

depending on the metal. As can be seen from Table 1, dysprosium furnished the best result,⁷ whereas lanthanum, cerium, neodymium and yttrium gave significantly lower yields. No alkene product was observed in the case of samarium and ytterbium.⁸ It should be noted that magnesium in the absence of triethylphosphite gave a low 33% yield (Table 1, entry 8), whereas in its presence 70% yield has been reported.^{4f}

The reaction conditions were then further optimized using dysprosium as the reducing agent. The major by-product in the above reactions was thioether **6**, probably resulting from a Ti(m)-mediated reduction of dithioacetal **3a** (Scheme 3).^{8,9}

Indeed, EPR studies on the reduction of Cp_2TiCl_2 with dysprosium (0.8 equiv.) in THF confirmed the presence of Cp_2TiCl after 3 hours. An increase of dysprosium metal (1.0 equiv.) led to the quasi complete disappearance of Ti(m) (see the ESI†). When the olefination of **4a** was carried out with Cp_2TiCl_2/Dy in 1:1 ratio, a better yield was obtained than with the initial 1:0.8 ratio (Table 1, entry 9). The formation of thioether **6** was not observed under these conditions.

We next studied the olefination of a range of carbonyl groups under the optimised conditions (Table 2). Ketones, esters and lactones gave good to moderate yields with different dithioacetals (entries 1–8). In the case of the aldehyde **4f** the amount of the dysprosium metal needed to be decreased in order to obtain acceptable results (entry 9). This is probably due to the higher reactivity of the aldehyde function towards the metal. In the case of two different carbonyl groups present



^a 2.4 equivalents of dysprosium were employed.

in the same molecule (entry 10), the ketone was transformed preferentially over the ester group. It should be revealed that in this reaction the ester group does not react with the excess of the dysprosium metal, even on heating at 50 °C for 90 min.

The major advantage of the Takeda olefination procedure over other titanocene-based systems is the large variety of alkyl, alkenyl or aryl groups that can be incorporated into the final alkene.^{4b} Although aryldithioacetals provided satisfying results with the new titanocene 2, a screening with α , β -unsaturated dithiane or alkyldithioacetal showed major differences with phosphite-stablised 1 (Scheme 4). In the case of dithiane **3d**, the reaction took place with 2, however under harsher reaction conditions (50 °C, 90 minutes) compared to the mild conditions (room temperature, 25 minutes) reported with 1.^{4f} In the case of decanal derived dithioacetal **3e**, the difference was



Scheme 4 Reactivity differences between 1 and 2.

even more striking. Though with 1 the olefination of ester 4a at room temperature gave a 57% yield of alkene 5i, the reaction with 2 did not yield any 5i, even after heating at reflux for 1 hour. To solve this problem, dithioacetal 3f derived from pfluorothiophenol was prepared. This clearly led to an improved reactivity towards 2 as the alkene 5i could now be obtained in 31% yield (Scheme 4). The reason for this difference in reactivity between 1 and 2 may be found in the coordination of the stabilising ligands. For 1, it can be assumed that the second triethylphosphite molecule is rather labile,^{3d} hence readily providing a coordination site on titanium. In contrast, for 2, the Lewis basic chloride anions of DyCl₃ should bind strongly to the Lewis acidic titanium centre. This may possibly lead to the formation of more complex structures involving several titanocene and DyCl₃ moieties, hence more reactive dithioacetals are necessary in this case. To date no crystals of 2 suitable for X-ray diffraction analysis could be obtained and further studies to elucidate the nature of 2 are in progress.

Lanthanides are known to have a relatively good functional group tolerance, as confirmed by the above competition experiment (Table 2, entry 10). It was therefore investigated whether a simplified "all-in-one" procedure could be realized with 2 and 3a.

Indeed, promising results were obtained with several carbonyl compounds when all the starting materials were present at

3 Cp ₂ ⊺	FiCl ₂ + 3 Dy + Ph	$SR^{1} + SR^{2} + R^{2}$ a,3g R^{2} (1.0) (3a) (3a) (5-C ₆ H ₄ (3g))	$ \begin{array}{c} O \\ 4 \\ 0 \text{ eq.} \end{array} $ $ \begin{array}{c} THF \\ 4h, r.t. \\ 0 \text{ eq.} \end{array} $	R ² R ³ 5
Entry	Carbonyl compound	Alkene	Yield (%) with 3a	Yield (%) with 3g
1	4a	5a	33	65
2	4b	5ba	12	35
3	4 c	5ca	35	45
4	4e	5e	32	57

the beginning and the reaction was carried out at room temperature for 4 hours (Table 3, entries 1–4, column 4). In order to increase the yield, the supposedly more reactive *p*-fluoro-substituted dithioacetal **3g** was employed. An important improvement in the yields was observed in all cases (entries 1–4, column 5). The formation of pinacol coupling products under these conditions was not detected. Most intriguingly, these "all-in-one" reactions work at room temperature, whereas in the sequential procedure, heating for 90 min at 50 °C was required to obtain good yields with **3a**. In contrast, the use of dithioacetals **3d** or **3f** was not successful under these "allin-one" conditions. Further studies on the understanding of this promising process are underway.

In conclusion, a new titanocene(π) equivalent without additional organic ligands has been obtained from the reduction of Cp₂TiCl₂ with dysprosium. This system has been successfully employed in a phosphite-free Takeda carbonyl ole-fination procedure and has shown good potential in an unprecedented "all-in-one" procedure. The structural elucidation of the new bimetallic titanocene(π) and its further applications are currently under investigation.

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Table 3 A simplified "all-in-one" procedure

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