

## Unprecedented Barbier-type reactions catalysed by titanocene(III)†

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Selective Barbier-type allylations, benzylations and propargylations of aldehydes and ketones can be carried out under extremely mild conditions employing titanocene(III) complexes as catalysts. In this way, chiral titanocene catalysts provided yields ranging from 50–80% of optically active products.

Allylation, benzylation and propargylation of carbonyl compounds are useful C–C bond forming reactions in organic synthesis. These reactions can be carried out under Barbier-type conditions employing magnesium, chromium, samarium and other metals,<sup>1</sup> among which titanium complexes<sup>2</sup> showed an outstanding capacity of promoting enantioselective processes.<sup>3</sup> Nevertheless, the requirement for stoichiometric proportions (often interpreted as considerable excesses) of chiral titanium complexes is a serious drawback in the methods described to date.<sup>4</sup> Therefore, we decided to develop a convenient procedure catalysed by titanocene complexes.

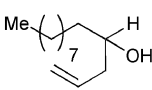
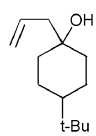
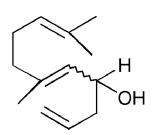
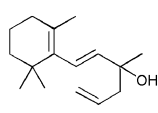
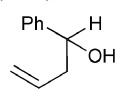
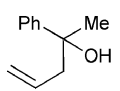
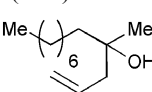
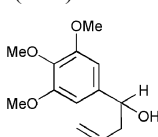
We have recently found that the combination Mn/Me<sub>3</sub>SiCl/collidine can effectively regenerate Cp<sub>2</sub>Ti<sup>III</sup>Cl *in situ*.<sup>5</sup> This observation prompted us to attempt Barbier-type reactions of allyl bromide (**1**) catalysed by titanocene(III). To this end we treated different aldehydes and ketones with **1**, a substoichiometric quantity of the commercial pre-catalyst Cp<sub>2</sub>TiCl<sub>2</sub> (0.2 equiv.), Mn dust, Me<sub>3</sub>SiCl and 2,4,6-collidine.<sup>6</sup> The results are summarised in Table 1.

The reaction worked well with aliphatic, unsaturated and aromatic aldehydes and ketones but after treatment under our conditions ethyl benzoate and ethyl cinnamate were recovered unchanged. This chemoselectivity profile is considerably better than that shown by allyl–samarium complexes, which do not discriminate between esters and carbonyl compounds.<sup>7</sup> It should be noted that despite the fact that acetophenone and benzaldehyde are prone to undergo pinacol coupling reactions in the presence of single-electron-transfer reagents, both substrates gave satisfactory yields of the corresponding allylated products.<sup>8</sup> Moreover, when cyclopropyl phenyl ketone was used as a radical clock,<sup>9</sup> no rearranged products were obtained, indicating that ketyl radicals were not involved in the process. Therefore, we propose the mechanism depicted in Scheme 1 to rationalise the catalytic cycle.<sup>10</sup>

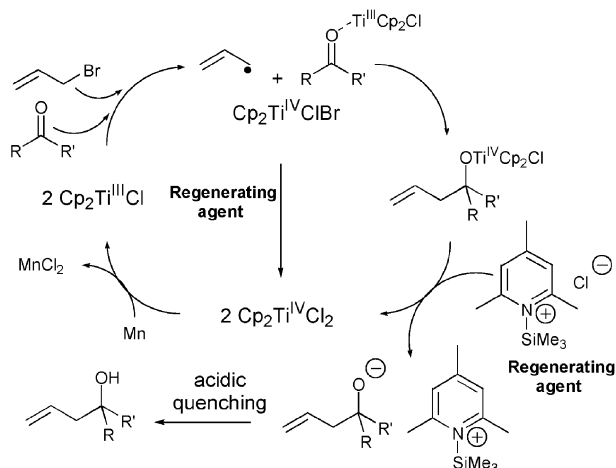
If our mechanistic proposal is correct, our catalytic procedure should also work well with other activated alkyl halides. As we expected, the reaction of decanal with allyl chloride, and benzyl and propargyl bromides catalysed by Cp<sub>2</sub>TiCl gave the corresponding condensation products at yields ranging from 70 to 90% (Table 2). Under similar conditions, the propargylation of 2-decanone provided a 60% yield of the expected acetylenic alcohol (Table 2). It should be noted that, in contrast to what occurs in the chromium-promoted Nozaki–Hiyama–Kishi propargylations,<sup>11</sup> allenic by-products were not detected.

Finally, we decided to use our method for asymmetric catalysis, one of the most powerful tools in organic synthesis.<sup>12</sup> For this purpose we selected the commercial Brintzinger complex **2** and the

**Table 1** Titanocene(III)-catalysed addition of allyl bromide to carbonyl compounds

Carbonyl compound	Product (yield)	Carbonyl compound	Product (yield)
Decanal	 (90%)	4- <i>tert</i> -Butylcyclohexanone	 (52%, <sup>a</sup> 81% <sup>b</sup> )
Citral	 (75%)	β-Ionone	 (50%, 67% <sup>b</sup> )
Benzaldehyde	 (80%)	Acetophenone	 (86%)
2-Decanone	 (100%)	3,4,5-Trimethoxybenzaldehyde	 (70%)

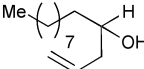
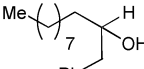

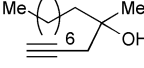
<sup>a</sup> 2:1 Mixture of stereoisomers. <sup>b</sup> Based on recovered starting material.

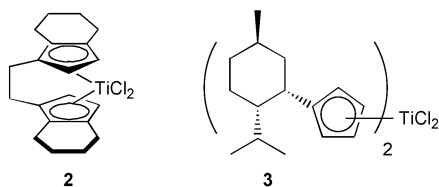


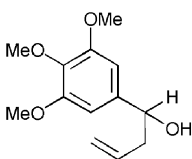
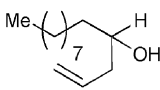
**Scheme 1** Catalytic cycle for Ti(III)-mediated addition of allyl bromide to carbonyl compounds.

† Electronic supplementary information (ESI) available: Alternative experimental protocol for reactions with unsaturated carbonyl compounds. See <http://www.rsc.org/suppdata/cc/b4/b411173g/>

**Table 2** Titanocene(III)-catalysed addition of activated alkyl halides to decanal and 2-decanone

Halide	Carbonyl compound	Product (yield)
Allyl chloride	Decanal	 (90%)
Benzyl bromide	Decanal	 (70%) <sup>a</sup>
Propargyl bromide	Decanal	 (80%)
Propargyl bromide	2-Decanone	 (60%)

<sup>a</sup> Using 2 equiv. of Cp<sub>2</sub>TiCl<sub>2</sub>.**Fig. 1** Titanium chiral catalysts **2** and **3**.**Table 3** Enantioselective reactions with chiral **2** and **3** using **1**

Chiral titanocene	Carbonyl compound	Product	Yield (ee)
<b>2</b>	3,4,5-Trimethoxybenzaldehyde		50% (33%)
<b>3</b>	Decanal		80% (20%)

chiral titanocene **3** prepared in our laboratory.<sup>13</sup> Treatment of allyl chloride with 3,4,5-trimethoxybenzaldehyde or decanal, in the presence of one of the chiral pre-catalysts (**2** or **3**) (0.2 equiv., Fig. 1) and the combination Mn/Me<sub>3</sub>SiCl/collidine gave optically active condensation products at acceptable yields (50 and 80%, respectively) (Table 3). Despite the moderate enantiomeric excesses (ee) obtained, these results demonstrate for the first time that

titanocene complexes are capable of catalysing enantioselective Barbier-type reactions. It is possible that with more effective chiral titanocene complexes, as those reported by Urabe *et al.* for example,<sup>14</sup> ee values might be increased.

In summary, here we demonstrate that the Barbier-type reaction between carbonyl compounds and activated alkyl halides can be carried out at room temperature, under really mild conditions using titanocene(III) complexes as catalysts. When chiral titanocene catalysts were employed, we obtained acceptable yields of optically active products. We are engaged in further studies into these reactions, including assays to try to increase the ee values.

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