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Cp_2TiCl-mediated selective reduction of α,β-unsaturated ketones

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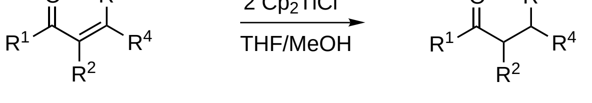
Abstract—A mild method for the selective reduction of α,β-unsaturated ketones is reported. The process described herein involves, as the active species, the low-valent titanium complex Cp_2TiCl. © 2002 Elsevier Science Ltd. All rights reserved.

The chemoselective reduction of α,β-unsaturated ketones has been extensively studied.[1] However, while the reduction of the carbonyl group is often achieved with relative ease,[2] the selective transformation of the adjacent double bond remains limited. Numerous methodologies have been developed to perform this conversion and include H_2/cat.-,[3] hydride-,[4] SmI_2-,[5] Sn-[6] and chalcogenide-based[7] reductions. In this paper we disclose a novel reaction for the selective reduction of α,β-unsaturated ketones to the corresponding saturated ketones. Our approach is based on the utilization of Cp_2TiCl as the active species[8] where the low-valent titanocene reagent operates via a single electron transfer (SET) process similar to the pinacol coupling of aldehydes and ketones.[9] In addition, Cp_2TiCl promotes the selective reduction of α,β-epoxy ketones to aldols.[10] With these results in mind, we examined the reactivity of α,β-unsaturated ketones towards Cp_2TiCl, and found that, upon treatment with 2 equiv. of Cp_2TiCl in THF/MeOH, conjugated enones could be selectively reduced to saturated ketones (Scheme 1).

To gauge the scope and limitations of this methodology, various 1,2-enones were reacted with Cp_2TiCl at −25°C (see experimental procedure). The low-valent titanium(III) complex was readily prepared by the in situ reduction of 2.5 equiv. of Cp_2TiCl_2 with 5 equiv. of powdered zinc for 45 min at room temperature. Results are summarized in Table 1.



Scheme 1.

In most cases, the overall yields were satisfactory. The selective reduction of 1-phenylprop-2-en-1-one (entry 1) afforded the expected 1-phenylpropan-1-one in 89% yield. The reaction was successfully extended to di- (entry 2) and trisubstituted (entry 3) olefinic systems. Treatment of chalcone (entry 4) under the above-mentioned conditions led not only to reduced 1,3-diphenylpropan-1-one, but also to the *cyclo*-dimerized product in a stereoselective fashion. This dimerization has previously been observed by others when SmI_2 is used as the reducing agent.[11] The procedure worked equally well on aliphatic ketones (entry 5), as well as in the case of a 1,2-ynone system (entry 6). However, in addition to the saturated ketone, the pinacol coupling product was obtained in a 65/35 ratio. Our attempts to selectively reduce an α,β-unsaturated ester (e.g. ethyl β-methylcinnamate) were unsuccessful as the starting ester remained unaffected by Cp_2TiCl.

A postulated reaction mechanism is illustrated in Scheme 2 for the selective reduction of 3-methyl-1-phenylbut-2-en-1-one **1**. In the first step, the single electron transfer from Cp_2TiCl to the carbonyl generates a radical intermediate **2** which, upon reaction with a second equivalent of Cp_2TiCl, produces enolate **3**. Subsequent protonation of **3** by methanol then affords 3-methyl-1-phenylpropan-1-one **4**.

The emergence of **3** as an intermediate during this transformation was upheld by the observation that when methanol-*d* was used as co-solvent instead of methanol, the reduced product **5** (analogous to **4**) was labeled both α and β to the carbonyl (>90% isotopic enrichment) (Scheme 3).

Keywords: enone; reduction; titanium.

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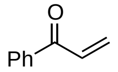
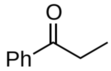
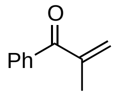
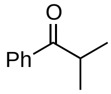
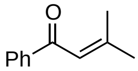
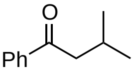
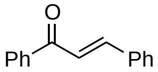
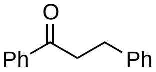
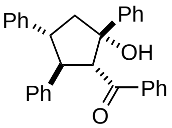
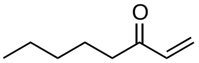
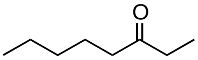
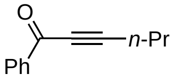
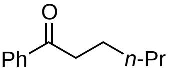
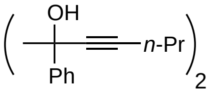
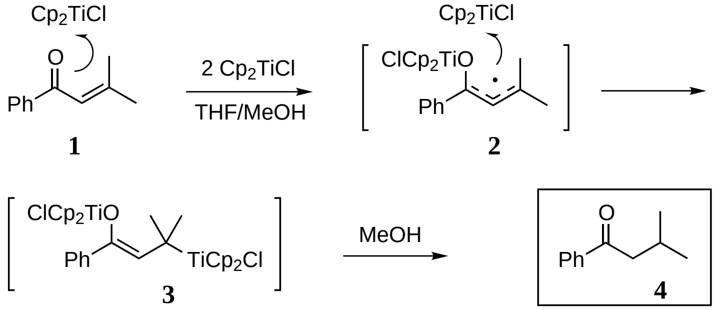
Table 1. Example of selective reduction of α,β-unsaturated ketones

entry	substrate	products	ratio[a]	yield (%)[b]
1				89
2				70
3				56
4		 	55/45	68
5				77
6		 	65/35	71[c]

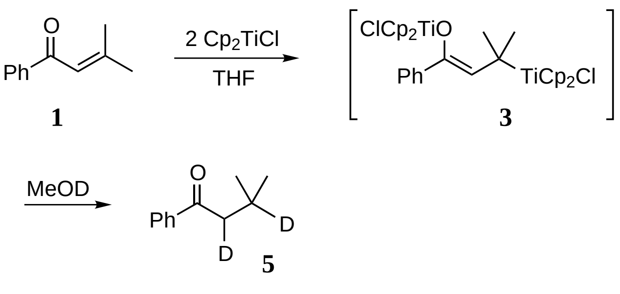
[a] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Combined isolated yields. [c] The reaction was run with 4.5 equiv. of Cp_2TiCl.



Scheme 2.

In conclusion, we have shown that the low-valent Cp_2TiCl selectively reduces selected α,β-unsaturated ketones to the corresponding saturated ketones under mild conditions.

Typical experimental procedure: THF (5 mL) was added to a mixture of Cp_2TiCl_2 (0.47 g, 2.5 equiv.) and powdered Zn (0.25 g, 5 equiv.) in an oven-dried flask purged with N_2. The heterogeneous solution was degassed under vacuum, purged with N_2 (this operation was repeated three times) and stirred vigorously for 45 min at room temperature. The green slurry of Cp_2TiCl was cooled to −25°C. Anhydrous MeOH (1 mL) was added. A solution of 1-phenylprop-2-en-1-one (0.1 g, 0.76 mmol, 1 equiv.) in 5 mL of THF was then added dropwise over a period of 1 h. The reaction was warmed to room temperature and the stirring was continued until completion of the reaction (1 h as



Scheme 3.

monitored by TLC). The excess of zinc was decanted. The organic phase was transferred to a flask and quenched with 10 mL of saturated K_2CO_3. The aqueous layer was extracted three times with Et_2O. The combined organic layers was filtered through a fritted glass funnel, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to column chromatography over silica (hexane:EtOAc, 9:1).

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