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Mild and efficient allylation of aldehydes mediated by titanium(III) chloride

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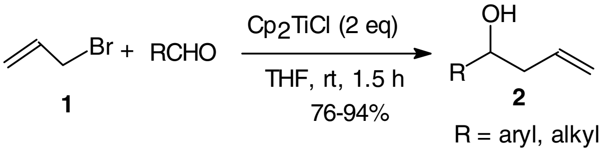
Abstract—A mild, chemoselective and efficient method for the allylation of aldehydes is described. Ketones remained unreacted under the reaction conditions.

The allylation of carbonyl compounds is a well-established procedure for the preparation of homoallyl alcohols. Homoallyl alcohols have attracted significant attention due to their versatile uses as important building blocks for natural product synthesis.[1] Various types of procedures have been reported[1c] for the allylation of carbonyl compounds using metals such as magnesium,[2a] zinc,[2b] tin,[2c] indium,[2d] aluminium,[2e] manganese,[2f] and cadmium.[2g] Lewis acid catalyzed and environmentally friendly green methodologies have also been reported.[3] However, many of these methods suffer from limitations such as lack of selectivity, extended reaction times, poor yields, harsh reaction conditions and the use of costly or toxic reagents. Therefore, a mild and efficient method is still desirable. In this report, we wish to disclose a mild and efficient methodology for chemoselective allylation of aldehydes mediated by titanium(III) chloride that overcomes many of the aforementioned complications.

Titanium(III) chloride has been extensively used as a mild and useful reagent for various chemical transformations such as reduction of aromatic aldehydes,[5] glycosyl halides,[6] vicinal dihalides,[7] sulfoxides,[8] etc. In particular, titanium(III)-promoted homolytic cleavage of epoxides[4] forming a carbon-centred radical opened a new era in synthetic organic chemistry. Radical cyclization reaction of epoxides using titanium(III) species has attracted much attention in recent years leading to the synthesis of a number of naturally occurring compounds and related products.[9,10] In continuation of our efforts towards the synthesis of natural products[10] by radical cyclization of epoxides, we have developed a mild and efficient method for allylation of aldehydes using 2 equiv of Cp_2TiCl as the radical initiator in excellent yields (Scheme 1). Cp_2TiCl was prepared[4] in situ from commercially available titanocene dichloride and zinc dust in THF under argon. In the optimized procedure,[11] a green solution of the reagent in THF was added slowly to the mixture of the aldehyde and allyl bromide at room temperature under argon. After completion of the reaction (monitored by TLC) an aqueous solution of sodium dihydrogen phosphate was added followed by usual work-up and purification.

Thus, a series of aldehydes were subjected to the allylation reaction[10] and the results are summarized in Table 1.

While aliphatic and aromatic aldehydes reacted smoothly, ketones for example, acetophenone, benzophenone and cyclopentanone remained unreacted under the reaction conditions. In a separate experiment, a 1:1 mixture of benzaldehyde and acetophenone was treated with allyl bromide in the presence of excess Cp_2TiCl in THF under the same reaction conditions. Benzaldehyde reacted completely to afford the desired allylated product (94%) but



Scheme 1.

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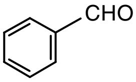
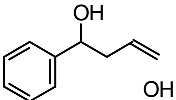
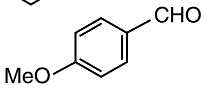
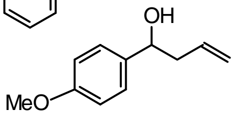
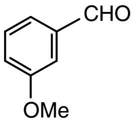
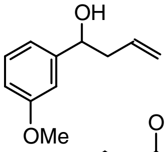
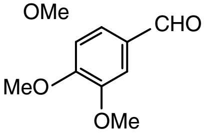
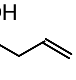
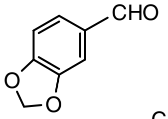
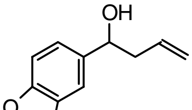
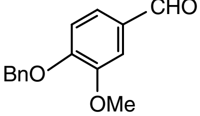
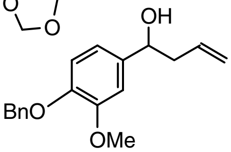
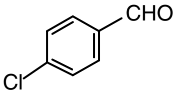
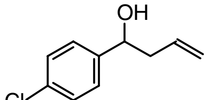
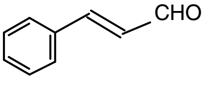
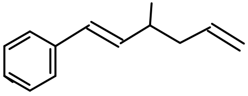
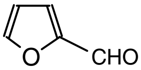
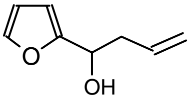
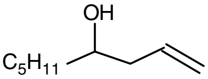
Table 1. Allylation of aldehydes using allyl bromide and Cp_2TiCl

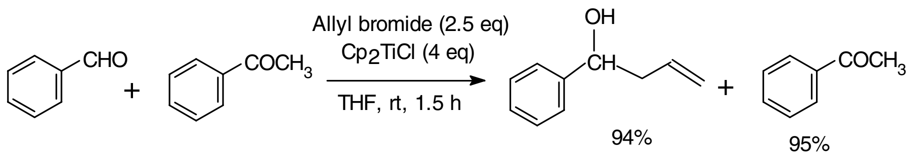
Entry	Substrate	Product	Yield (%)[a]
1			94
2			92
3			94
4			94
5			93
6			93
7			80
8			94
9			76
10	$C_5H_{11}CHO$		88

[a] Yield refers to pure isolated product.

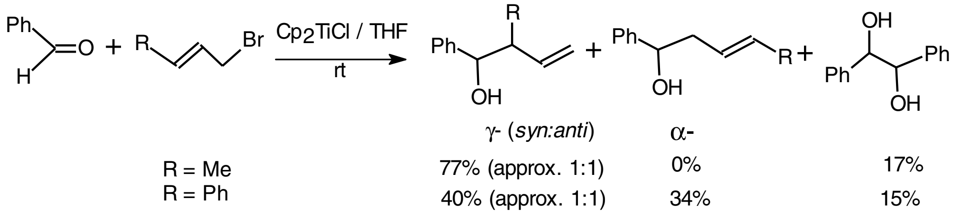
acetophenone did not undergo allylation at all and was recovered unchanged (95%) (Scheme 2). It is noteworthy that *p*-nitrobenzaldehyde did not react at all.

Substituted allyl bromide namely, crotyl or cinnamyl bromide was also used as allylating agent. In both cases, the reaction was found to be regioselective, giving mainly the γ-regioisomer (Scheme 3). The reaction was, however, less diastereoselective, giving an inseparable 1:1 mixture of *syn*- and *anti*-diastereomers. In all the cases, about 15–17% of the pinacol product was isolated.

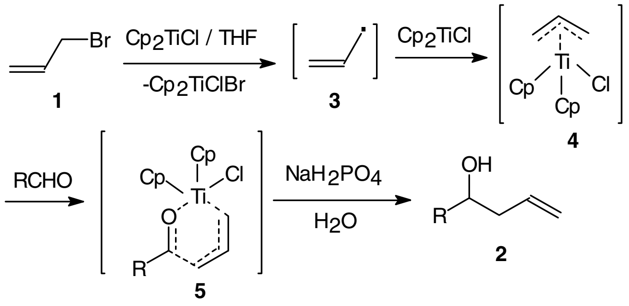
It is noteworthy that 2equiv of Cp_2TiCl with respect to the aldehyde are essential for complete conversion. We presume that the bromine from allyl bromide **1** is abstracted via a single electron transfer by 1equiv of Cp_2TiCl to produce the allylic radical **3**, which is stabilized by another equivalent of Cp_2TiCl through the complex **4**. Trapping of this radical complex with an aldehyde



Scheme 2.



Scheme 3.



Scheme 4.

leads to the observed product **2** via the six-membered transition complex **5** (Scheme 4).

In conclusion, we have developed a mild, chemoselective and efficient methodology for allylation of aldehydes using titanium(III) chloride and allyl bromide in THF.

Acknowledgements

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11. *General procedure*: A solution of titanocene dichloride (2mmol) in dry THF (15mL) was stirred with activated zinc dust[10a] (7mmol) for 1h under argon. The resulting green solution was then added dropwise to a stirred solution of the aldehyde (1mmol) and allyl bromide (1.1mmol) in dry THF (5mL) at room temperature under argon over 30min. The reaction mixture was then stirred for an additional 1.5h and finally decomposed with saturated aqueous sodium dihydrogen phosphate solution (5mL). Most of the volatiles were removed under reduced pressure and the residue obtained was extracted with diethyl ether (4 × 25mL). The ether layer was washed with brine (2 × 10mL) and dried (Na_2SO_4). After removal of solvent the crude residue obtained was purified by column chromatography over silica gel eluting with ethyl acetate and light petroleum to afford the desired product.