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$TiCl_4$-mediated olefination of aldehydes with acetic acid and alkyl acetates: a stereoselective approach to (*E*)-α,β-unsaturated carboxylic acids and esters

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ABSTRACT

A new method has been developed for the preparation of α,β-unsaturated carboxylic acids and corresponding esters with (*E*)-stereoselectivity via the $TiCl_4$-mediated olefination of aldehydes. The method, which uses readily available acetic acid or its alkyl esters as active methylene partners, is more flexible and complementary to conventional routes in the preparation of (*E*)-cinnamic acid derivatives.

α,β-Unsaturated carboxylic acids and esters are important substructures widely existing in biologically active natural products and medicines (Fig. 1) and can serve as useful building blocks in organic synthesis.[1] For their application in the food industry, polymer industry, perfume industry, medicine, and technical applications, they are synthesized on a commercial scale. Consequently, a number of powerful methods for their preparation have been developed and most of these methods are (*E*)-stereoselective.[2] However, they often suffer from unsatisfactory yields, use of expensive reagents, harsh reaction conditions, and/or lengthy protocols.[3–6] In the Wittig reaction, triphenylphosphine oxide is a stoichiometric byproduct and it has to be removed chromatographically and disposed of thus limiting the synthetic utility especially in large-scale preparations.[7]

The titanium-enolate based stereoselective aldol condensations are powerful carbon—carbon bond forming reactions in organic synthesis.[8] Recently we have reported an exceptionally stereoselective synthesis of (*Z*)-α-haloacrylates via olefination of aldehydes with α-haloacetates mediated by $TiCl_4$.[9] As part of our continuing investigations, we report herein an expedient and general synthesis of (*E*)-α,β-unsaturated carboxylic acids **1** and their esters **2** with high stereocontrol (>95%) via the reaction between an aldehyde and acetic acid or its alkyl esters.

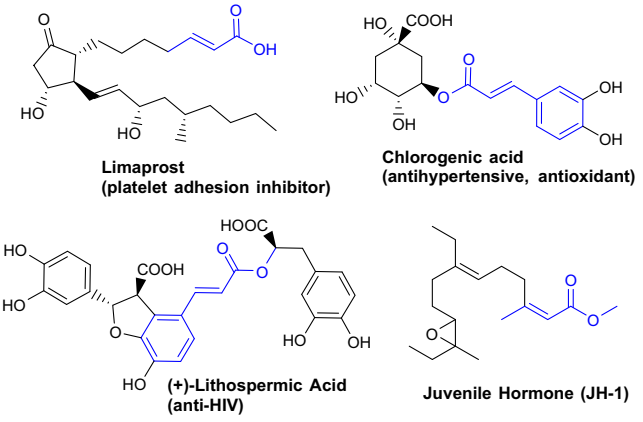
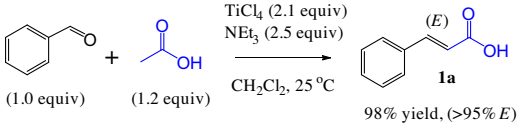


Figure 1. Some examples of biologically active compounds bearing an α,β-unsaturated carboxyl unit.



Scheme 1. $TiCl_4$-mediated synthesis of (*E*)-cinnamic acid.

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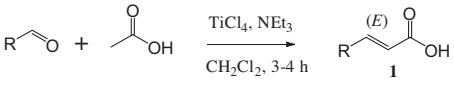
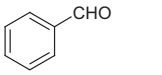
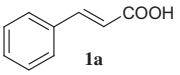
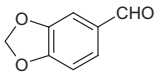
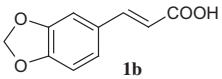
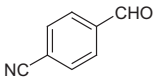
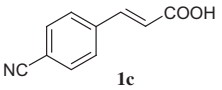
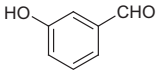
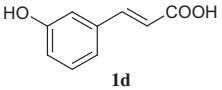
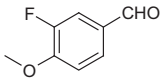
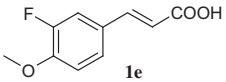
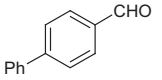
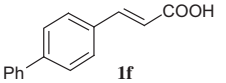
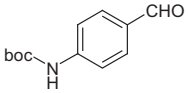
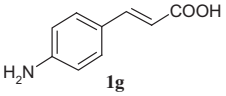
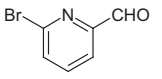
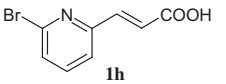
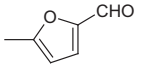
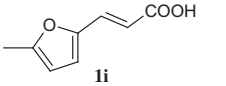
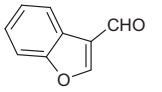
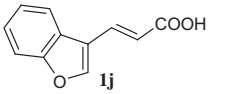
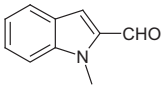
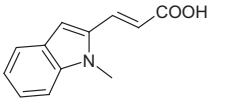
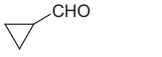
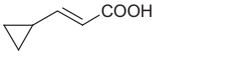
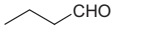
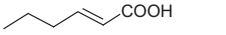
0040-4039/

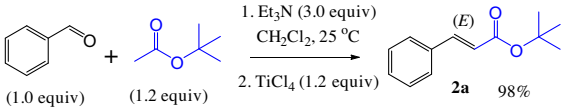
Table 1
$TiCl_4$-mediated synthesis of (*E*)-α,β-unsaturated carboxylic acids



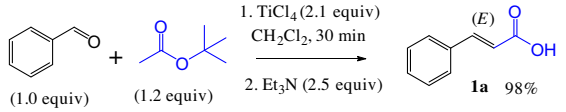
Entry	Aldehyde	Product	Yield[a] (%)
1		 **1a**	98
2		 **1b**	98
3		 **1c**	99
4		 **1d**	97
5		 **1e**	98
6		 **1f**	99
7		 **1g**	95[b]
8		 **1h**	98
9		 **1i**	99
10		 **1j**	97
11		 **1k**	97
12		 **1l**	94
13		 **1m**	0

[a] Isolated yields.
[b] *N*-Boc protection was lost during the reaction.

By careful investigation we established that acetic acid (1.2 equiv) could easily be transformed into cinnamic acid **1a** in 98% yield with high (*E*)-stereoselectivity (>95%) by treatment with benzaldehyde (1.0 equiv) in dichloromethane (DCM) in the presence of $TiCl_4$ (2.1 equiv) and Et_3N (2.5 equiv) at room temperature (Scheme 1). The product **1a** was isolated as white solid following an aqueous work up. No trace of the (*Z*)-isomer could be detected by NMR analysis of the crude reaction mixture, signifying >95% stereochemical purity. The above conditions were most suitable for the transformation. For instance, when the amount of Et_3N was decreased from 2.5 equiv to 2.0 equiv or decreasing the amount of $TiCl_4$ from 2.1 equiv to 1.8 equiv led to an incomplete reaction



Scheme 2. Synthesis of *tert*-butyl cinnamate from *tert*-butyl acetate.



Scheme 3. Synthesis of (*E*)-cinnamic acid from *tert*-butyl acetate.

even after prolonged stirring, while the same reaction took just 3 h for complete conversion under the optimized conditions. Similarly, $TiCl_4$ or Et_3N failed to promote the reaction when used separately.

The optimized reaction conditions for Ti(IV)-mediated (*E*)-olefination were then generalized by reacting acetic acid with a group of representative aldehydes and the results are summarized in Table 1. Diverse aromatic aldehydes (Table 1, entries 1–7) and heterocyclic aldehydes (Table 1, entries 8–11) reacted smoothly with acetic acid in the presence of $TiCl_4$, and gave the respective α,β-unsaturated carboxylic acids with high stereoselectivities (>95% *E*) and excellent yields. While cyclopropane carboxaldehyde, a branched aliphatic aldehyde, gave **1l** in 94% yield (Table 1, entry 12), the method did not prove beneficial for straight chain aliphatic aldehydes as represented by *n*-butanal (Table 1, entry 13). As observed by us, *n*-butanal polymerized under the optimized reaction conditions yielding no trace of product **1m**.

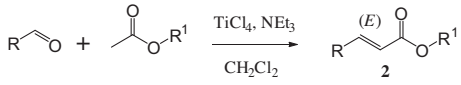
Compounds possessing *tert*-butyl carboxylate functionality are practical building blocks in organic synthesis, due to their ease of deprotection to the subsequent carboxylic acid in acidic medium. It was of interest to explore if we could extend the methodology involving Ti(IV)-mediated (*E*)-olefination for the synthesis of *tert*-butyl α,β-unsaturated carboxylates. Accordingly, $TiCl_4$ (1.2 equiv) was added dropwise to a mixture of benzaldehyde (1.0 equiv), Et_3N (3.0 equiv), and *tert*-butyl acetate (1.2 equiv) in DCM. The mixture was then stirred for 3 h at room temperature to afford *tert*-butyl cinnamate **2a** in 98% yield with excellent (*E*)-stereoselectivity (Scheme 2). In contrast to the optimized conditions for **1a** (Scheme 1) wherein 2.1 equiv of $TiCl_4$ was employed, the synthesis of *tert*-butyl cinnamate **2a** required only 1.2 equiv of $TiCl_4$ for complete conversion (Scheme 2).

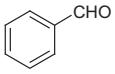
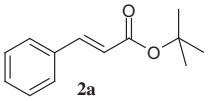
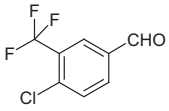
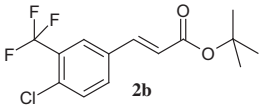
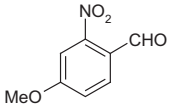
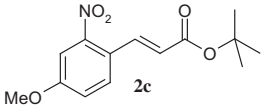
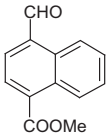
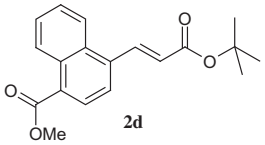
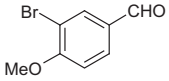
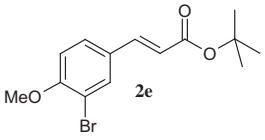
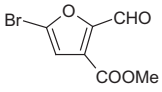
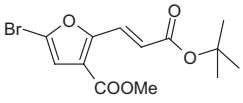
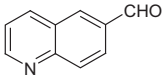
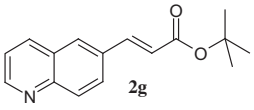
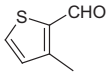
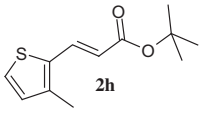
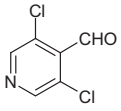
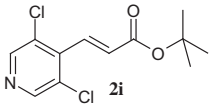
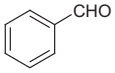
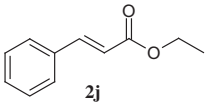
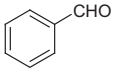
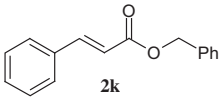
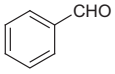
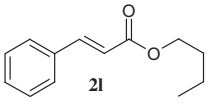
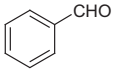
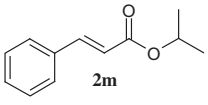
As opposed to the observations in Scheme 2, cinnamic acid **1a** was obtained in 98% yield when Et_3N was added dropwise to a pre-complexed mixture of benzaldehyde, *tert*-butyl acetate, and $TiCl_4$ in DCM (Scheme 3). It is likely that the *tert*-butyl acetate underwent hydrolysis prior to the addition of Et_3N owing to the acidic nature of $TiCl_4$. However, 2.1 equiv of $TiCl_4$ was essential for optimal conversion.

Diverse aromatic and heterocyclic aldehydes were then reacted with *tert*-butyl acetate under the standard conditions (Scheme 2) to afford *tert*-butyl α,β-unsaturated carboxylates in excellent yields (Table 2, entries 1–9). The reaction was complete within 2–3 h for all the substrates tested. The scope of the reaction was then generalized by treating benzaldehyde with various alkyl acetates in the presence of $TiCl_4$ and Et_3N to afford the respective cinnamates in excellent yields, and the high stereoselectivity (>95% *E*) still remained.

In conclusion, a new method has been developed for the preparation of α,β-unsaturated carboxylic acids[10] and corresponding esters[11] with (*E*)-stereoselectivity via the $TiCl_4$-mediated olefination of aldehydes. The method, which uses readily available acetic

Table 2
$TiCl_4$-mediated synthesis of (*E*)-α,β-unsaturated carboxylates



Entry	Aldehyde	R^1	Product	Yield[a] (%)
1		*t*-Butyl	 **2a**	98
2		*t*-Butyl	 **2b**	98
3		*t*-Butyl	 **2c**	97
4		*t*-Butyl	 **2d**	98
5		*t*-Butyl	 **2e**	98
6		*t*-Butyl	 **2f**	95
7		*t*-Butyl	 **2g**	96
8		*t*-Butyl	 **2h**	95
9		*t*-Butyl	 **2i**	96
10		Ethyl	 **2j**	99
11		Benzyl	 **2k**	99
12		*n*-Butyl	 **2l**	98
13		Isopropyl	 **2m**	98

[a] Isolated yields.

acid or its alkyl esters as active methylene partners, is more flexible and complementary to conventional routes in the preparation of (*E*)-cinnamic acid derivatives.

Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR for all the products listed in Tables 1 and 2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.098.

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10. *General procedure for the $TiCl_4$-mediated synthesis of (E)-α,β-unsaturated carboxylic acids (**1a**–**l**):* To a mixture of an aldehyde (0.1 mol) and acetic acid (0.1 mol) in dichloromethane (15 mL) was added $TiCl_4$ (0.21 mol). The resulting reaction mixture was stirred at room temperature for 20 min under nitrogen atmosphere. To this was added Et_3N (0.25 mol) dropwise over a period of 10 min and the mixture was stirred for further 3–4 h at room temperature. When the reaction was complete as confirmed by TLC, the mixture was diluted with water (25 mL) and the organic layer was separated. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the corresponding (*E*)-α,β-unsaturated carboxylic acid (**1**) in excellent yield and purity.
11. *General procedure for the $TiCl_4$-mediated synthesis of alkyl (E)-α,β-unsaturated carboxylates (**2a**–**m**):* To a mixture of an aldehyde (0.1 mol) and alkyl acetate (0.1 mol) in dichloromethane (15 mL) was added Et_3N (0.3 mol). The resulting reaction mixture was cooled to 0 °C under nitrogen atmosphere. To this was added $TiCl_4$ (0.12 mol) dropwise over a period of 15 min and the mixture was stirred for further 2–4 h at room temperature. When the reaction was complete as confirmed by TLC, the mixture was diluted with water (25 mL) and the dichloromethane layer was separated. The organic phase was washed with 0.5 M aqueous HCl, water and brine. It was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the corresponding alkyl (*E*)-α,β-unsaturated carboxylate (**2**) in excellent yield and purity.