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LETTERS

Synthesis of Sterically Hindered Esters via Titanium Catalyzed Transesterification

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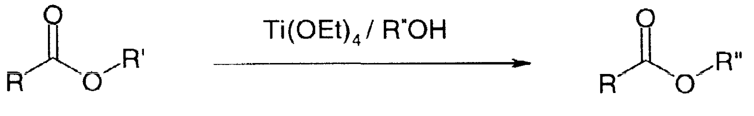
Abstract: Titanium (IV) ethoxide was used as a catalyst in transesterification reactions to synthesize esters of sterically hindered alcohols in good to high yields.

Transesterification reactions constitute a powerful method to synthesize a variety of organic esters.[1-3] Typically the reaction is catalyzed by strong acids and bases[1-4], enzymes.[5] There are reports on using titanium (IV) alkoxides[6-9], alkylsdistannoxanes[10] and alumuna oxide[11] as transesterification catalysts. Using titanium (IV) alkoxides as a catalyst allows transesterification to be carried out under neutral conditions compatible with a large variety of acid and base sensitive functional groups.[6] Titanium (IV) alkoxides were applied to prepare esters of primary,[6-9] and simple secondary[6,7] alcohols. To the best of our knowledge, synthesis of sterically hindered esters using titanium (IV) alkoxides catalyzed transesterification have not been reported. Moreover, we were able to find in the literature only one report describing synthesis of sterically hindered esters by transesterification using DMAP as a catalyst.[4]

We would like to report herein an application of titanium (IV) alkoxides to prepare esters of sterically hindered secondary alcohols.

As a part of a development program we tried to generate a number of esters bearing hindered chiral alcohols. The most appealing synthetic pathway was transesterification of easily available methyl and ethyl esters using titanium (IV) alkoxides as reagents of choice. (Scheme 1).



Scheme 1

As a model reaction transesterification of methyl phenylacetate with menthol was studied. In order to achieve a high conversion in the transesterification a large excess of the alcohol is often needed.[1,2] Since using a large excess of the expensive chiral alcohols is not desirable, attempts were made to remove the volatile methyl or ethyl alcohol formed during the reaction by co-distillation with a solvent (Table 1).

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Table 1. Titanium (IV) Ethoxide Catalyzed Transesterification of Methyl Phenylacetate with Menthol.

Entry No	Solvent / (temperature °C)	Reaction time (h)	Conversion (%)	Yield (%)
1	1,2-dichloroethane /83	5	20	N/D
2	toluene / 112	5	40	N/D
3	neat / 80	12	100	89

Using 1,2-dichloroethane or toluene resulted in relatively sluggish reaction. Constant addition of fresh solvent was required throughout the reaction resulting in large volume of distillate (5-6 times initial reaction volume). Alternatively running the reaction neat and removing the volatile alcohol under reduced pressure (140 mm Hg) resulted in a clean reaction that afforded the ester in high yield.

Similar conditions were applied then to different alcohols using the methyl phenylacetate as a case study[10] (Table 2). Esters of phenylacetic acid were synthesized high yields. In most of the cases the reaction was very clean, the only impurity being the excess alcohol.

Table 2. Titanium (IV) Ethoxide Catalyzed Transesterifications of Methyl Phenylacetate

Entry No	Alcohol	Yield[a] (%)
1	(1S,2R,5S) Menthol	89
2	(-)Isopinocampheol	94
3	(-)-Borneol	76
4	R-(-)-Indanol	98
5	2-Adamantane-methanol	93
6	9-Hydroxyfluorene	91[b]

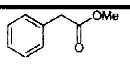
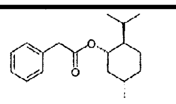
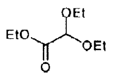
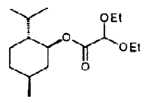
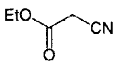
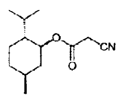
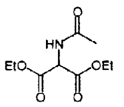
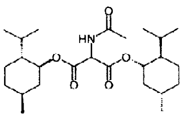
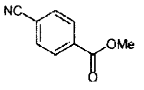
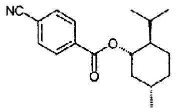
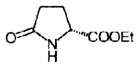
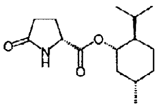
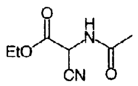
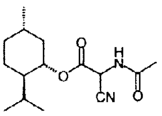
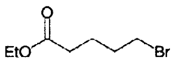
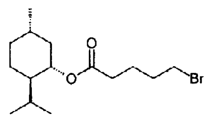
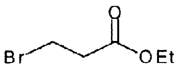
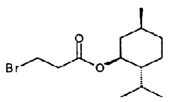
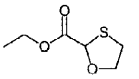
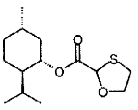
(a) Chiral integrity of alcohols 1-4 under the reaction conditions was checked by optical rotation values (chiral alcohols were recovered by base hydrolysis of the esters 1-4). (b) Toluene (2 mL) was used to homogenize the reaction mixture. Reaction time was 48h

Bulky tertiary alcohols such as triphenylmethanol fail to react under the same conditions presumably due to the difficulty of the titanium alcoxide species formation.

Our next goal was to demonstrate the generality of the reaction conditions[12] with various substrates and to investigate the utility of this reaction towards esters bearing acid or base sensitive functional groups (Table 3). Menthol was used as a case study.

Menthyl esters were generated in clean high yielding reactions with no significant by-products.

Table 3. Menthyl Esters via Titanium (IV) Ethoxide Catalyzed Transesterifications

Entry No	Substrate	Product	Yield (%)
1			89
2			86
3			72
4			58[a]
5			74
6			69
7			60
8			73
9			80
10			70[b]

(a) The yield refers to that of disubstituted derivative. Monosubstituted derivative (menthylethylacetamidomalonate) was isolated in 35% yield. (b) The reaction was carried out on 1 mmol scale.

Substrates with acid labile groups such as diethoxymethyl or cyano are stable under the reaction conditions. Stability of substrates having base sensitive groups was tested on alkylhaloesters. No side reaction due to base-catalyzed lactonisation was detected using menthyl 5-bromovalerate. When treated with menthol in the presence of titanium (IV) ethoxide, methyl 3-bromopropionate afforded tranesterification product in 80% yield, only traces of elimination products were detected in the reaction mixture.

In conclusion, we demonstrated that titanium (IV) ethoxide can be used as transesterification catalyst to synthesize sterically hindered esters in high yields. This method can be added to the existing methodologies to prepare hindered esters.

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12. In a typical run, an ester (1 eq), chiral alcohol (1.4 eq) and titanium (IV) ethoxide (10 mol %) were heated overnight at 80 °C (140 mm Hg vacuum). Subsequently, the titanium alkoxide was hydrolyzed by adding a small amount of water and the reaction mixture was purified using flash chromatography.