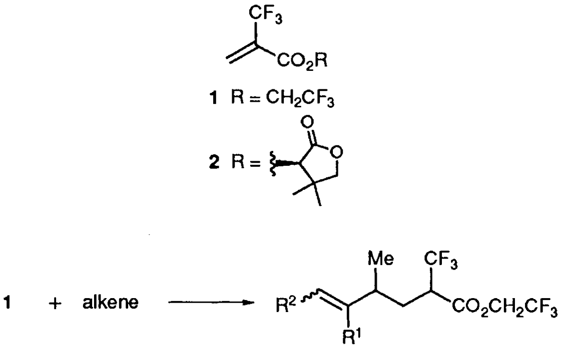
Lewis Acid-catalysed Ene Reactions of Esters of 2-Trifluoromethylpropenoic Acid

Yuji Hanzawa, Makoto Suzuki, Takeshi Sekine, Tetsu Murayama and Takeo Taguchi*
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

In Lewis acid-catalysed ene reactions of esters (**1** and **2**) of 2-trifluoromethylpropenoic acid, the high reactivity of **1** and **2** and preparation of an optically active trifluoromethylated tertiary carbon (*S*-configuration, >80% diastereoisomeric excess) by $TiCl_4$-catalysed ene reactions of **2** are reported.

The Diels–Alder reactions of esters (**1** and **2**) of 2-trifluoromethylpropenoic acid and application to the synthesis of fluorinated retinal were considered in a previous study.[1] Of particular importance is the fact that excellent optical induction (>95% enantiomeric excess, e.e.) at the trifluoromethylated quaternary carbon atom can be obtained *via* $TiCl_4$-catalysed Diels–Alder reaction of the 2-trifluoromethylpropenoate **2** of D-pantolactone. Recently, the ester **1** was shown to react with an ynamine derivative in a concerted way to give a [2 + 2] adduct in high yield.[2] It was thus considered pertinent to examine the Lewis acid-catalysed ene reactions of **1** and **2** for constructing trifluoromethylated tertiary carbon atoms in an optically active form, since the ene reaction may possibly proceed in a concerted manner.[3] Concerted reactions should be effective for producing carbon–carbon bonds using **1** and **2**, since organocuprate and Lewis acid-catalysed addition of trimethylsilyl enol ethers to esters of 2-trifluoromethylpropenoic acid causes elimination of fluoride ion.[4]

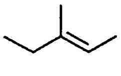
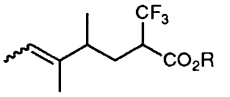
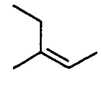
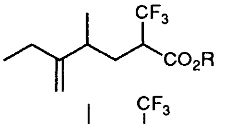
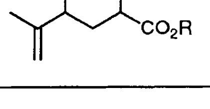


Scheme 1 *Reagents and conditions*: alkene (1 equiv.; 0.5 mmol dm^{-3} benzene solution), **1** (0.9 equiv.), $EtAlCl_2$ (0.8 equiv.) at 0 °C

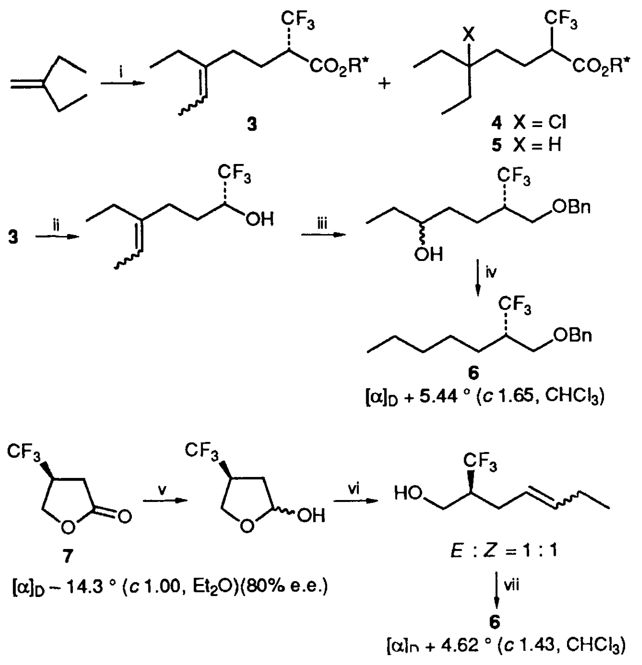
We now report the ene reactions of **1** and **2** in the presence of a Lewis acid and determination of the absolute configuration of the product obtained from **2**. The ene reaction of **1** with alkenes in the presence of $EtAlCl_2$ (0.8 equiv.) in benzene at 0 °C gave a 1 : 1 mixture of *syn*- and *anti*-isomers (Table 1). The absence of 1,3-selectivity in the reaction of **1** is in contrast with the results of the ene reactions of 2-chloropropenoate which have been reported to give mainly the 1,3-*syn*-isomer.[3] In the absence of the Lewis acid, no reaction except the polymerization of **1** could be detected on heating at 170 °C in a sealed tube.

The $TiCl_4$-catalysed ene reaction of **2** is expected to lead to high enantiomeric purity at the trifluoromethylated tertiary carbon atom by analogy with the established transition state for the $TiCl_4$-catalysed Diels–Alder reactions of **2**.[1] The ene

Table 1 $EtAlCl_2$-catalysed ene reaction of **1**

Alkene	Reaction time / min	Adduct	Yield (%)	Diastereoisomer ratio (*syn* / *anti*)[a]
	40		67[b]	1:1
	20		54	1:1
	40		47	1:1

[a] Determined by ^{19}F NMR and GLC analysis (OV-101, 25 m).
[b] *cis–trans*-Mixture; stereochemistry was not determined.



Scheme 2 *Reagents and conditions*: i, **2**, $TiCl_4$, 4 Å molecular sieves, CH_2Cl_2–hexane; ii, $LiBH_4$, Et_2O–MeOH; iii, $PhCH_2Br$, NaH, then O_3, then $NaBH_4$; iv, $MeSO_2Cl$, base, then $LiAlH_4$; v, Bu^i_2AlH; vi, $Ph_3P^+Pr^n$ Br^-, Bu^nLi; vii, H_2, Pd–C, then $PhCH_2Br$, NaH

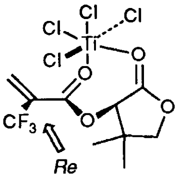


Fig. 1 $TiCl_4$-complexed *syn*-planar enophile **2**

reaction of **2** with 2-ethylbut-1-ene in the presence of $TiCl_4$† gave a mixture of the ene product **3** (mixture of *cis*- and *trans*-isomers, 54% yield) and the hydrogen chloride adduct **4** {28% yield; 84% diastereoisomeric excess, d.e., by ^{1}H NMR; $[\alpha]_D$ +9.47° (*c* 0.612, $CHCl_3$)}. The d.e. of **3** was determined by its conversion to the saturated compound **5** (Pd–C, H_2, quantitative yield) and the NMR spectra (^{1}H and ^{19}F) of **5** {81%, d.e.; $[\alpha]_D$ +15.4° (*c* 1.10, $CHCl_3$)}. The product was determined to have the (*S*)-configuration at the optical rotation centre by comparison with the benzyl ether **6**, derived separately from **3** and from the trifluoromethylated (*S*)-lactone **7**[5] (Scheme 2).

It is clear that the $TiCl_4$-catalysed ene reactions of **2** with alkenes proceed through a similar transition state to that of Diels–Alder reactions as expected. That is, the alkene approaches the *Re*-face of the $TiCl_4$-complexed *syn*-planar enophile (Fig.1).

The efficient formation of carbon–carbon bonds and construction of trifluoromethylated tertiary carbon centres *via* a Lewis acid-catalysed ene reaction of **1** and **2** were successfully conducted. In the $TiCl_4$-catalysed ene reactions of **2**, an optically active trifluoromethylated tertiary carbon centre (*S*-configuration, >80% d.e.) was obtained without loss of fluoride ion.

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† Typical experimental procedure: to a mixture of molecular sieves (4 Å; 1 g) and **2** (1 g; 3.97 mmol) in CH_2Cl_2–hexane (1.5 : 1) (10 ml) were added $TiCl_4$ (0.1 ml; 0.72 mmol) and 2-ethylbut-1-ene (0.5 mmol) at −20 °C. The mixture was stirred for 0.5 h at the same temperature. After further addition of $TiCl_4$ (0.25 equiv.) and 2-ethylbut-1-ene (0.7 equiv.) at −20 °C twice in every 0.5 h, the reaction was terminated by adding powdered $Na_2CO_3{\cdot}H_2O$. The mixture was filtered, the filtrate diluted with diethyl ether and the diethyl ether solution washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). Filtration and concentration of the solution gave a crude oil, which was purified by silica gel chromatography (hexane–EtOAc, 10 : 1) to give **3** (54%) as a *cis–trans*-mixture and **4** (28%).

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