Asymmetric Synthesis of 1-Alkoxy-2,2,2-trifluoroethanol Derivatives

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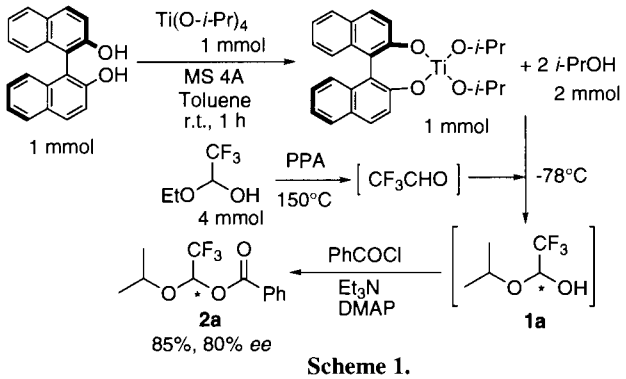
Reaction of trifluoroacetaldehyde with an alcohol in the presence of a catalytic amount of (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ gives optically active 1-alkoxy-2,2,2-trifluoroethanol with high *ee*.

Although trifluoroacetaldehyde and its derivatives are versatile CF_3-containing building blocks[1] for the synthesis of various fluorinated opto-electronic materials, pharmaceuticals and polymers, few synthetic methods are known which provide us with optically active CF_3-substituted compounds; the approach is, expect for resolution, limited to the carbonyl-ene reaction[2,3] and the aldol reaction[4] using trifluoroacetaldehyde and a chiral binaphthol-derived titanium complex. We envisaged that chiral hemiacetals $R^1OCH(CF_3)OH$ of trifluoroacetaldehyde, if available, would be a useful chiral building block for a variety of optically active CF_3-containing target molecules. Herein, we report the unprecedented asymmetric synthesis of such hemiacetals and the corresponding esters with good to high enantiomeric excess (*ee*).[5,6]

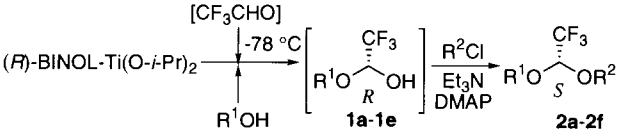
We first studied the reaction of trifluoroacetaldehyde with 2-propanol as shown in Scheme 1. Trifluoroacetaldehyde, generated from 1-ethoxy-2,2,2-trifluoroethanol (4 mmol) with polyphosphoric acid (PPA), was passed into a toluene solution of (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ (1 mmol) at -78 °C in the presence of 2-propanol (2 mmol) as coproduced during the preparation of the catalyst from Ti(O-*i*-Pr)$_4$ and (*R*)-binaphthol. The resulting hemiacetal **1a** was treated with benzoyl chloride, triethylamine and 4-dimethylaminopyridine (DMAP) at -78 °C to afford benzoate **2a** in 85% yield. *Ee* of **2a** was assayed by HPLC (Daicel, CHIRALPAK OT(+), hexane) and shown to be 80%. All attempts to decrease the catalyst amount met with limited success. When the esterification was carried out at higher temperatures, % *ee* of **2a** decreased considerably due probably to racemization of the hemiacetal **1a** at the higher temperature.

We next examined the rate and order of the addition of substrates and found that slow and simultaneous addition of 2-propanol and trifluoroacetaldehyde to a toluene solution of (*R*)-



Scheme 1.

BINOL-Ti(O-*i*-Pr)$_2$ gave better results. To extend the reaction to various alcohols, it was necessary to prepare the chiral catalyst free of 2-propanol. Thus, we prepared the catalyst by treatment of dilithium (*R*)-binolate with Ti(O-*i*-Pr)$_2$Cl$_2$[2] in toluene at room temperature for 2 h. The catalyst solution was then cooled to -78 °C, and a toluene solution of 2-propanol (2 mmol) was added slowly by a syringe pump over 20 min while simultaneously passing trifluoroacetaldehyde (4 mmol) as illustrated in Scheme 2. This procedure improved *ee* of **2a** to 85% or 82% using 50 or 10 mol% of (*R*)-BINOL-Ti(O-*i*-Pr)$_2$, respectively. The results are listed in entries 1 and 2, respectively, of Table 1.



a: R^1 = *i*-Pr, R^2 = COPh; **b**: R^1 = $PhCH_2$, R^2 = COPh; **c**: R^1 = $PhCH_2CH_2$, R^2 = COPh; **d**: R^1 = Bu, R^2 = COPh; **e**: R^1 = Et_2CH, R^2 = COPh; **f**: R^1 = $PhCH_2$, R^2 = SO_2CH_3

Scheme 2.

Table 1. Asymmetric synthesis of benzoates and mesylates of optically active 1-alkoxy-2,2,2-trifluoroethanols

Entry	(R)-BINOL-Ti(O-i-Pr)$_2$	$CF_3CH(OEt)OH$	R^1OH (2.0 mmol)	R^2Cl	Yield	*ee*	Products
1	1.0 (mmol)	4.0 (mmol)	*i*-PrOH	PhCOCl	85 (%)	85 (%)	(+)-**2a**
2	0.2	4.0	*i*-PrOH	PhCOCl	81	82	(+)-**2a**
3	0.2	4.0	$PhCH_2OH$	PhCOCl	61	25	(*S*)-(+)-**2b**
4	0.2	2.2	$PhCH_2OH$	PhCOCl	48	74	(*S*)-(+)-**2b**
5	0.4	2.2	$PhCH_2OH$	PhCOCl	54	91	(*S*)-(+)-**2b**
6	0.4	2.2	$PhCH_2CH_2OH$	PhCOCl	57	78	(+)-**2c**
7	0.4	2.2	*n*-BuOH	PhCOCl	65	65	(+)-**2d**
8	0.4	4.0	Et_2CHOH	PhCOCl	54	73	(+)-**2e**
9	0.4	2.2	$PhCH_2OH$	$MeSO_2Cl$[a]	35	79	(*S*)-(+)-**2f**

[a]Methanesulfonyl chloride was added at -78 °C and stirred for 5 h at 0 °C.

The hemiacetal formation using benzyl alcohol resulted in considerably lower *ee*'s due probably to less steric influence. The best *ee* of benzoate **2b** was 25% using 10 mol% of the (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ catalyst (entry 3). By decreasing the amount of trifluoraldehyde under the same conditions, we attained 74% *ee* (entry 4). *Ee* was further improved to 91% by use of 20 mol% of the chiral BINOL-Ti catalyst (entry 5). According to this procedure, various alcohols were allowed to react with trifluoroacetaldehyde in the presence of (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ (20 mol%). The results are listed in entries 6-8 of Table 1. We also undertook the synthesis of sulfonates, because they could easily be substituted by a nucleophile. Methanesulfonyl chloride turned out to be less reactive than benzoyl chloride and needed temperatures above 0 °C for the esterification. As in the case of the synthesis of **2b**, use of $CF_3CH(OEt)OH$ (2.2 mmol) and the titanium catalyst (0.4 mmol) gave (*S*)-(+)-**2f** in 35% yield with the highest *ee* of 79% (entry 9). The lower *ee* as compared with the benzoate (entry 5) may be attributed to a partial racemization of the corresponding hemiacetal at 0 °C required for the mesylation. To demonstrate the substitution reaction, optically active sulfonate (*S*)-(+)-**2f** of 83% *ee* allowed to react with $LiAlEt_4$ to give (*R*)-(+)-2-benzyloxy-1,1,1-trifluorobutane of 83% *ee*.[7]

The absolute configurations of **1b** and **2b** were determined by the Mosher method.[8] Esterification of the racemic hemiacetal with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPCl) gave a diastereoisomeric mixture of **3** which was separated by preparative HPLC to give (*S*,*R*)-**3** and (*R*,*R*)-**3**. The Newman projection of (*S*,*R*)-**3** and (*R*,*R*)-**3** is shown in Figure 1. Based upon this model, the benzylic protons of **3** whose configuration of the acetal carbon is (*S*) are shielded by the phenyl ring. Thus, comparison of the chemical shift at the benzylic protons of each diastereomer using ^{1}H NMR suggests the illustrated configuration. This (*S*,*R*)-**3** sample was derivatized to **2b** by treatment with HAl(*i*-Bu)$_2$ followed by benzoylation (Scheme 3). Compound **3** prepared from CF_3CHO with benzyl alcohol using the (*R*)-BINOL-Ti catalyst

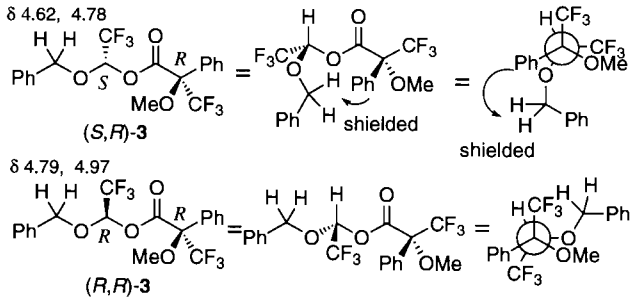
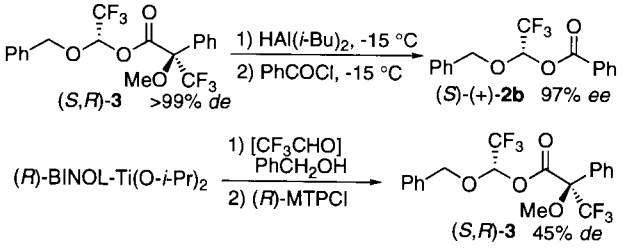


Figure 1.



Scheme 3.

corresponded to the (*S*,*R*)-**3** diastereomer. Thus, **2b** is shown to be (*S*). The Trost method using (*S*)-(+)-α-methoxyphenylacetic acid[9] also led to the same assignment.

Since the modification of the chiral diol in our titanium complex affected the enantioselectivity, we studied the effect of the alkoxide ligand in (*R*)-BINOL-Ti(OR)$_2$. We prepared several complexes treating lithium (*R*)-binolate with $TiCl_2(OR)_2$ and studied the enantioselectivity of **2a** using 10 mol% of the catalyst. The results are summarized in Table 2.

Table 2. Synthesis of (*S*)-(+)-1-benzyloxy-2,2,2-trifluoroethyl benzoate (**2b**) using 10 mol % of (*R*)-BINOL-Ti(OR)$_2$

Entry	(OR)$_2$	Yield (%)	*ee* (%)
1	(O-*n*-Bu)$_2$	42	0
2	$(OCH_2Ph)_2$	63	8
3	(O-*i*-Pr)$_2$	48	74
4	$[OCH(CF_3)_2]_2$	65	77
5	(O-*c*-C_6H_{11})$_2$	50	79
6	(O-*t*-Bu)$_2$	49	32
7	(*R*)-BINOLATE	41	3

When a primary alkoxide ligand was employed, there was no detectable asymmetric induction (entries 1 and 2), whereas a secondary alkoxide induced *ee* significantly (entries 3-5). However, by use of a tertiary butoxide or binolate ligand, the enantioselectivity decreased considerably (entries 6 and 7). The bulk of the alkoxide ligand on the titanium complex is extremely important to create an appropriate size of the reaction site: a secondary alkoxide is better than a tertiary alkoxide that generates an overly congested space.

The first asymmetric synthesis of 1-alkoxy-2,2,2-trifluoroethanol using a chiral titanium complex is achieved with a high degree of *ee*. The resulting hemiacetals were esterified to give the corresponding esters with good to high *ee*. These esters are convenient chiral intermediates for CF_3-containing chiral molecules.

References and Notes

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