Asymmetric Organozincate Additions to Ethyl 2,2,2-Trifluoropyruvate

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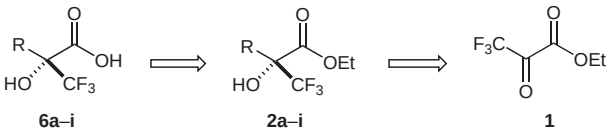
Abstract: A chromatography-free synthesis of enantiomerically enriched chiral α-trifluoromethyl α-hydroxy acids prepared via an asymmetric (*R*)-BINOL-mediated organozincate addition to ethyl 2,2,2-trifluoropyruvate (**1**) is reported.

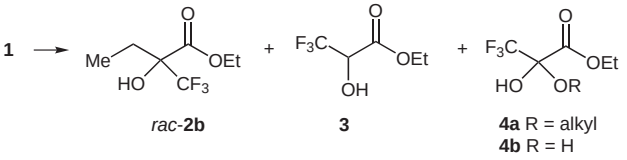
Key words: zincate, BINOL, α-keto ester, asymmetric organometallic addition, trifluoropyruvate

The preparation of chiral secondary alcohols by enantioselective addition of organometallics to aldehydes has received considerable attention.[1] A plethora of methods exist to catalyze the addition of organometallics to aldehydes. In contrast, there are relatively few reports on the synthesis of chiral tertiary alcohols by catalytic asymmetric organometallic additions to ketones[2] and α-keto esters.[3] This may be attributed, respectively, to poorly defined catalyst–substrate interaction and the increased electrophilic character of the carbonyl group that renders catalyzed additions more difficult. Introduction of an electron-withdrawing group such as a trifluoromethyl group is likely to worsen the situation. Recent examples from the literature confirm the increased difficulty faced in preparing chiral trifluoromethyl-substituted tertiary alcohol stereogenic centers.[4] As part of an on-going drug discovery program we required large quantities of enantiomerically enriched chiral α-trifluoromethyl α-hydroxy-acids **6a**–**i** (Scheme 1).[5,6] We report herein a novel procedure for the introduction of the chiral center found in **2a**–**i** from commercially available ethyl 2,2,2-trifluoropyruvate (**1**).



Scheme 1

Although asymmetric additions of organometallic reagents to pyruvate derivatives have been reported for the synthesis of chiral α-hydroxy acids, we found no examples of catalytic asymmetric organometallic additions to ethyl 2,2,2-trifluoropyruvate (**1**).[7] Perhaps not surprisingly, we found that **1** is a highly electrophilic species that reacts rapidly with Et_2Zn at –78 °C to afford a solvent-dependent mixture of ethyl addition product **2b** and reduction product **3**, which results from β-hydride transfer from Et_2Zn (Scheme 2). For example, in toluene, the reaction of **1** with Et_2Zn afforded α-hydroxy-ester **3** in yields of up to 95%, while reactions carried out in THF provided the ethyl adduct **2b** in ca. 70% yield. Based on these results, we evaluated various methodologies for catalyzing the asymmetric addition of either Et_2Zn or Et_3Al to ethyl 2,2,2-trifluoropyruvate (**1**). In general, these reactions were often complicated by a fast background reaction of **1** with the organometallic reagent and rapid formation of stable hemiketals (e.g. **4a**) with a variety of chiral alcohol catalysts (e.g., BINOL) or Lewis acid additives such as $Ti(O\textit{i}\text{-}Pr)_4$.[8]



Scheme 2

Interestingly, while we were unsuccessful in our attempts to effect a catalytic enantioselective addition of Et_2Zn to **1**, we found that the addition of Et_3Al to trifluoropyruvate could be catalyzed by chiral ligands (e.g. *N*-methylephedrine) affording high conversion into the ethyl adduct **2b**, albeit with only moderate levels of asymmetric induction (Table 1).

Although generally not perceived as competitive with catalytic methods, the use of a cheap and readily available stoichiometric chiral modifier for asymmetric reactions can provide a viable and practical option.[9] For example, the asymmetric acetylide addition to trifluoromethyl ketones, using a stoichiometric amount of chiral amino alcohol modifier, has been reported by others in our laboratories.[9a] Inspired by this finding we evaluated a number of stoichiometric chiral modifiers for the addition of organometallic reagents to ethyl 2,2,2-trifluoropyruvate (**1**). As illustrated in Table 2, use of the zincate reagent derived from either *N*-methylephedrine[6] or TADDOL[9b] afforded **2b** in low yield and enantioselectivity (entries 1 and 2). In contrast, commercially available and inexpensive (*R*)-(+)-1,1′-bi(2-naphthol) (BINOL)[10] emerged as a unique chiral modifier, and provided the *R*-α-hydroxy-

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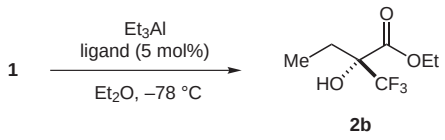
Table 1 Enantioselective Addition of Et_3Al to Ethyl 2,2,2-Trifluoropyruvate[a]



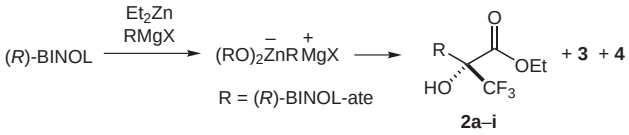
2b

Entry	Ligand	ee (%)[b]
1	*N*-Methylephedrine	35
2	*N*-Methylpseudoephedrine	55
3	(2*S*)-(–)-3-*exo*-(Dimethylamino)isoborneol (DAIB)	14
4	(*S*)-(–)-2,2′-Isopropylidene-bis(4-phenyl-2-oxazoline)	20

[a] Et_3Al (1 M in hexanes).
[b] Determined by chiral GC analysis of the crude reaction mixture.

ester **2b** in 50% conversion and 70–78% ee as determined by chiral GC analysis (entry 3). A subsequent solvent screen identified 1,2-dichloroethane (DCE) as the optimal solvent for this process, providing **2b** in high conversion (>95%) and acceptable enantioselectivity (entry 4). Optimal yields were obtained when ethyl 2,2,2-trifluoropyruvate (**1**) was added dropwise to the chiral (*R*)-BINOL–zincate reagent[11] over a period of 4–6 hours. This modified process minimized the competing reaction of **1** with the metal alkoxide from (*R*)-BINOL, which produces the hemiketal **4a** [R = (*R*)-BINOL], a stable species under the reaction conditions. Notably, the reagent obtained from a stoichiometric mixture of ethyllithium, Et_2Zn and (*R*)-BINOL gave **2b** with the opposite sense of stereoselectivity (entry 5).

Employing the optimized conditions discussed above, we evaluated the use of other organometallic nucleophiles in this methodology. The basic protocol for generating the chiral BINOL–organozincate reagent involved addition of a solution of Et_2Zn to a suspension of BINOL in 1,2-DCE–THF (4:1). This exothermic reaction proceeded with evolution of two equivalents of ethane to afford a BINOL–zinc complex. Subsequent addition of a suitable organomagnesium reagent led to the formation of a BINOL–organozincate reagent (Scheme 3). Importantly, while the use of THF as a co-solvent was essential for maintaining a homogeneous reaction, increasing the amount of THF above 25% by volume led to significant erosion in the enantioselectivity for this process.

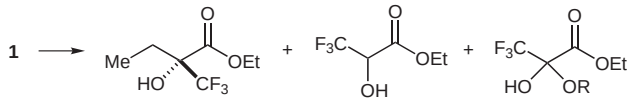


2a–i

Scheme 3 BINOL–zincate formation and addition to pyruvate **1**

The scope of the BINOL–organozincate asymmetric addition to ethyl 2,2,2-trifluoropyruvate (**1**) is summarized in Table 3. Although not optimized, these additions provided synthetically useful levels of asymmetric induction for the preparation of α-alkyl (entries 2–5) and α-phenyl α-trifluoromethyl α-hydroxy acids (entry 8). Unfortunately, in most cases the reaction was accompanied by competing hydride transfer and moderate levels of conversion, likely due to addition of BINOL alkoxides to **1**. In all cases, the reduction product **3** was found to be racemic as determined by chiral GC analysis. Residual alcohol **3**, (*R*)-BINOL and other byproducts were readily removed in the aqueous workup and concentration and the crude esters

Table 2 Chiral Modifiers for Organozincate Addition to Ethyl 2,2,2-Trifluoropyruvate[a]

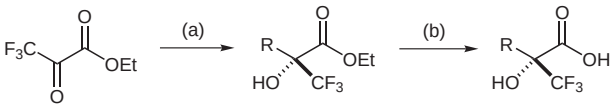


2b **3** **4a** R = alkyl
4b R = H

Entry	Ligand	Ethyl source	Solvent	Temp (°C)	Conv. (%),[b] ee (%)[c]
1	*N*-Methylephedrine	Et_2Zn, EtMgCl	Toluene	r.t.	20 (10)
2	TADDOL	Et_2Zn, EtMgCl	Toluene	r.t.	30 (<5)
3	(*R*)-BINOL	Et_2Zn, EtMgCl	Toluene	–40	50[d] (70–78)
4	(*R*)-BINOL	Et_2Zn, EtMgCl	DCE	–20	>95[e] (64–72)
5	(*R*)-BINOL	Et_2Zn, EtLi	DCE	–20	90 (–52)

[a] In all cases 1.0 equiv of Et_2Zn, chiral modifier, and a second ethyl source were employed.
[b] Determined by ^{19}F NMR spectroscopic analysis.
[c] Determined by chiral GC analysis.
[d] Pyruvate added over 30 min.
[e] Pyruvate added over 6 h.

Table 3 Asymmetric BINOL–Zincate Addition to Ethyl 2,2,2-Trifluoropyruvate[a]



1 **2a–i** **6a–i**

Entry	R = (**2a–i**)	Conv. (%)[b]	ee (%)[c]	**3** (%)[b]	**4a** (%)[b]	Yield **6a–i** (%), ee (%)[d]
1	Me (**2a**)	44	53	0	53	29 (50) **6a**
2	Et (**2b**)	90	70	1	8	74 (74) **6b**
3	*n*-Pr (**2c**)	48	76	16	24	34 (76) **6c**
4	*n*-Bu (**2d**)	49	84	15	22	35 (83) **6d**
5	*n*-C_5H_{11} (**2e**)	39	81	14	36	25 (83) **6e**
6	Vinyl (**2f**)	76	13[e]	1	18	29 (13) **6f**
7	Allyl (**2g**)	76	4[e]	0	19	37 (4) **6g**
8	Phenyl (**2h**)	75	69[f]	0	16	38 (69) **6h**
9	Benzyl (**2i**)	79	<5[g]	0	7	36 (<5) **6i**

[a] *Conditions*: (a) (*R*)-BINOL, Et_2Zn, RMgCl, DCE–THF (4:1), –40 °C; (b) KOH, H_2O.
[b] Determined by ^{19}F NMR spectroscopic analysis.
[c] Determined by chiral GC analysis of the crude reaction mixture.
[d] Determined by chiral GC analysis of the corresponding methyl ester.
[e] Determined after catalytic hydrogenation of the corresponding α-hydroxy acid and chiral GC analysis of the corresponding methyl ester.
[f] Determined by chiral SFC analysis.
[g] Determined by HPLC analysis after conversion into the corresponding (*S*)-α-methylbenzylamide.

2a–i were directly hydrolyzed with aqueous KOH to afford the enantiomerically enriched α-hydroxy acids **6a–i** in up to 74% yield over 2 steps and up to 83% ee, without chromatographic purification.[12]

In summary, we have developed a novel and preparatively useful asymmetric synthesis of enantiomerically enriched α-trifluoromethyl α-hydroxy acids based on the addition of (*R*)-BINOL–organozincates to ethyl 2,2,2-trifluoropyruvate.

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(12) **Experimental Procedure**
(*R*)-(+)-1,1′-Bi(2-naphthol) (5.1 g, 17.6 mmol, 120 mol%) was dissolved in anhyd 1,2-dichloroethane (35 mL) and THF (8.75 mL) and the solution was cooled to –40 °C. A solution of Et_2Zn (13.4 mL, 14.7 mmol, 100 mol%, 1.1 M in toluene) was added over 30 min. *Caution: gas evolution! Proper venting required!* The mixture was stirred at r.t. for 1 h, cooled to –40 °C and a solution of EtMgCl (8.8 mL, 17.6 mmol, 120 mol%, 2 M in THF) was added over 15 min. The solution was warmed to r.t. for 1 h and then cooled to –40 °C. Ethyl 2,2,2-trifluoropyruvate (1.95 mL, 2.50 g, 14.7 mmol) was added dropwise via syringe pump over 6 h. The mixture was let stir 18 h and then quenched with 2 N aq HCl (25 mL). The organic layer was washed with 1 N aq NaOH (3 × 20 mL). The organic layer was then treated with 8 N KOH (200 mol%) at reflux for 2 h. The solution was cooled to r.t. and the layers were separated. The aqueous layer was washed with MTBE (20 mL) and then acidified to pH 1 with 6 N HCl. The aqueous layer was extracted with MTBE (20 mL), dried with $MgSO_4$, and concentrated under vacuum to afford (2*R*)-2-hydroxy-2-(trifluoromethyl)butanoic acid (**2b**) as a white solid in 74% yield and 74% ee; mp 120–122 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.96 (m, 1 H), 1.81 (m, 1 H), 0.88 (t, 3 H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, acetone-d_6): δ = 170.4, 123.6 (q, *J* = 284 Hz), 77.6 (q, *J* = 28.5 Hz), 24.7, 6.4. ^{19}F NMR (470 MHz, $CDCl_3$, internal standard $PhCF_3$ at –61.5 ppm): δ = –77.3. Chiral GC analysis (methyl ester): Cyclodex-B column, 50 °C for 1 min, 5 °C/min to 95 °C, hold at 95 °C for 1 min, 20 °C/min to 200 °C, injector 180 °C, detector 250 °C, split 10:1, 13.5 psi He, *S*-enantiomer at 6.10 min, *R*-enantiomer at 6.83 min.