Catalytic Enantioselective Homoaldol Reactions Using Binol Titanium(IV) Fluoride Catalysts

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Abstract: Titanium (IV) fluoride catalysts, prepared by the combination of (*R*)-2,2′-binaphthol and TiF_4, are effective for promoting the homoaldol addition of 1-ethoxy-1-(trimethylsilyloxy)cyclopropane to aldehydes. The reactions proceed with ee's of up to 72% and are effective with a range of aldehyde substrates. The reactions show greatly improved enantioselectivity when compared to those catalyzed by titanium(IV) triflates. The increase in selectivity is presumed to result from the elimination of deleterious silicon co-catalysis.

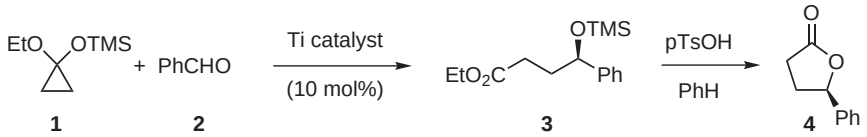
Key words: homoenolates, homoaldol additions, asymmetric catalysis, titanium(IV) fluorides

In the field of asymmetric catalysis, the aldol reaction features prominently because of its ability to simultaneously form a carbon-carbon bond and to set up to two new stereocenters. Catalytic asymmetric homoaldol reactions, in contrast, are virtually unknown. This reflects the greater difficulty both in forming homoenolates and in successfully executing their subsequent addition to aldehydes and ketones.[1] To date, the highest enantioselectivity attained in a catalytic enantioselective homoaldol reaction was 30% ee using a pre-formed titanium homoenolate and Seebach's Taddol-Ti(*i*-PrO)$_2$ catalyst.[2] In this letter, we report a greatly improved catalytic enantioselective homoaldol reaction based on titanium(IV) fluoride catalysts.

We previously reported a catalytic homoaldol reaction which employed titanium(IV) triflates as catalysts.[3] The advantage of this catalytic system is that it did not require the prior formation of a metal homoenolate. The desired reactive intermediate was instead formed in situ via ring-opening of commercially available 1-ethoxy-1-(trimethylsilyloxy)cyclopropane. Although the reaction was efficient, only low enantioselectivities were observed using (*R*)-2,2′-binaphthol as a ligand. The low enantioselectivity in this reaction was attributed to the formation of trimethylsilyl triflate, which served to activate the aldehyde towards homoenolate addition. Although this co-catalysis accelerated the reaction, it prevented the formation of a closed transition state, which is presumably a necessary requirement for high enantioselectivity.

In order to prevent the release of a highly Lewis acidic species during the catalytic process, we have explored the use of titanium(IV) fluorides as catalysts in this reaction. It was expected that any trimethylsilyl cation generated in this reaction would be trapped as the relatively non-acidic trimethylsilyl fluoride, thus precluding silicon co-catalysis. Alkoxytitanium(IV) fluorides have been developed by Carreira for the catalysis of allylsilane and trimethylaluminum additions to aldehydes.[4] The catalyst was prepared by combining (*R*)-2,2′-binapthol (20 mol%) and TiF_4 (10 mol%) in acetonitrile. After evaporation, the resulting red-brown solid was suspended in a mixture of $CDCl_3$–CD_3CN (3:1) and treated with a proton scavenger. Either allyltrimethylsilane or cyclopropane **1** may be used as the proton scavenger, with the former generally affording a more active catalyst. The homoaldol reaction was conducted by combining cyclopropane **1** and benzaldehyde with the catalyst in $CDCl_3$–CD_3CN (3:1) at room temperature. The reaction was monitored by ^1H NMR and over a period of 18 h, the silylated homoaldol adduct **3** was observed to form (Scheme 1). After work-up, the crude product was treated with *p*-TsOH in benzene to provide lactone **4**. Analysis of the product by chiral capillary GC analysis (Chirasil-dex column) indicated that the product had formed with 48% enantiomeric excess. Repeating the reaction in a series of solvents (Table 1) revealed that pure acetonitrile afforded the highest enantioselectivity (69% ee).[5,6]

Examining the reaction further, it was found that the highest enantioselectivities were observed at room temperature, with the use of either higher or lower temperatures leading to markedly lower selectivity (Table 2, entries



Scheme 1

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Table 1 Effect of Solvent on the Stereoselectivity of the Homoaldol Reaction (Equation 1).

Entry	Solvent[a]	ee[b] (%)
1	3:1 $CDCl_3/CD_3CN$	48
2	$CDCl_3$	0
3	**CH_3CN**	**69**
4	PhCN	35
5	Et_2O	17
6	THF	5
7	C_6H_6	0
8	CH_3NO_2	7
9	DMF	8

[a] All reactions were carried out using 10 mol% catalyst and 1.0 equiv silyloxycyclopropane in the indicated solvent.
[b] Determined by chiral GC analysis (Chirasil-dex column).

1–4). The yield of the reaction using a one to one ratio of **1** and benzaldehyde was only 36%, but this could be increased by employing a modest excess of cyclopropane **1** (entries 5 and 6) and by running the reaction at slightly higher concentrations. The optimum conditions utilized 1.5 equivalents of **1** and a reaction concentration of approximately 0.7 M.

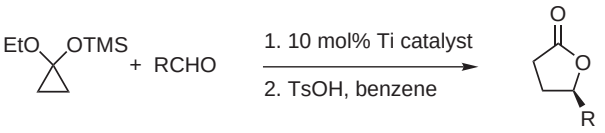
Table 2 Optimization of Temperature and Concentration (Scheme 1).[a]

Entry	T (°C)	**1**:PhCHO	[PhCHO] (M)	ee[b] (%)	Yield (%)
1	–30	1: 1	0.55	0	ND
2	0	1: 1	0.55	31	ND
3	25	1: 1	0.55	66	36
4	50	1: 1	0.55	57	ND
5[c]	25	1.5: 1	0.52	72	66[d]
6	25	1.5: 1	0.69	65	80[d]

[a] Reactions were conducted over a 24 h period with a catalyst aging time of 1 h prior to addition of **1** and PhCHO, except as noted.
[b] Determined by Chiral GC analysis (Chirasil-Dex column).
[c] The catalyst was aged for 2.5 hours rather than one hour prior to addition of **1** and PhCHO.
[d] Reaction time 3 d.

A series of aromatic and acetylenic aldehydes were surveyed under the optimized reaction conditions.[7] As can be seen from the results in Table 3, good yields and modest selectivities were observed with simple aromatic aldehydes and those containing electron withdrawing groups at the 4-position. In contrast, electron donating groups at the 4-position (entries 7 and 8) significantly reduce the enantioselectivity of the reaction. As with the titanium(IV) triflate catalysts,[3] aliphatic and α,β-unsaturated aldehydes were not useful substrates for the reaction.

Table 3 Homoaldol Reactions of Aromatic and Acetylenic Aldehydes[a]



Entry	R	ee[b] (%)	yield (%)
1	C_6H_5-	65	80
2	1-$C_{10}H_9$-	55	59[c]
3	2-$C_{10}H_9$-[d]	61[e]	85
4	4-ClC_6H_4-	45	62
5	4-BrC_6H_4-	43	69
6	4-$CF_3C_6H_4$-	40	69
7	4-$CH_3C_6H_4$-	18	59
8	4-$CH_3OC_6H_4$-	0	ND
9	$C_6H_5C{\equiv}C$-	61[e]	41

[a] Reactions were allowed to proceed for 7 d under conditions cited in Table 2, entry 5 for a period of 168 h.
[b] Determined by chiral GC analysis (Chirasil-Dex column).
[c] Based on recovered starting material.
[d] The catalyst was aged for 2.5 h for this example.
[e] Determined by Chiral HPLC analysis [Pirkle covalent (S,S) Whelk –0 1].

Details regarding the catalytic cycle of this process remain to be elucidated. Although the intermediacy of a metal homoenolate seems likely, as with the titanium(IV) triflate catalyzed reaction, it was not possible to observe homoenolate formation by ^1H NMR. The products are invariably isolated as the trimethylsilyl ethers. Given the low probability of silylation by trimethylsilyl fluoride, there seems to be two likely mechanisms for homoaldolate silylation. The first would be direct silicon transfer during the ring opening of **1** by a product homoenolate titanium complex, simultaneously forming **3** and a new homoenolate. Alternatively, the binaphthol ligand might play a part as a silicon shuttle. In this regard, it is important to note that the optimum reaction conditions require a 2:1 ratio of 2,2′-binaphthol to TiF_4. The use of a 1:1 ratio results not only in lower yields and ee's, but also results in formation of a significant amount of lactone **4**, indicating that silicon transfer is a problem under these conditions.

In conclusion, we have developed a catalytic asymmetric homoaldol reaction, which utilizes an alkoxytitanium(IV) fluoride catalyst. The enantioselectivities, while modest, are the highest reported for this class of reactions. The method works well for a series of aromatic and acetylenic aldehydes and gives the highest enantioselectivities for electron-neutral and electron-poor aromatic aldehydes.

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(5) The absolute stereochemistry was established as *R* by comparison of the optical rotation of **4** with literature values: Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.
(6) A survey of other ligands, including 3,3′-disubstituted binaphthols, F_8-Binol and TADDOL did not afford any increase in enantioselectivity.
(7) **Sample Experimental Procedure**. A solution of titanium(IV) fluoride (12 mg, 0.095 mmol, 0.1 equiv) in acetonitrile (1.5 mL) was added to a solution of (*R*)-2,2′-binaphthol (56 mg, 0.195 mmol, 0.2 equiv) in acetonitrile (1.5 mL) in a flame dried Schlenk flask. The resulting red mixture was stirred at 21 °C for 1 h and then the solvent was removed in vacuo. The resulting oil was redissolved in acetonitrile (1.5 mL), allyltrimethylsilane (62 μL, 0.392 mmol, 0.4 equiv) was added and the resulting solution was allowed to stir for 3 h during which time a precipitate was observed to form. To this mixture was added 1-ethoxy-1-(trimethylsilyloxy)cyclopropane (300 μL, 1.50 mmol, 1.5 equiv), and after 10 min, benzaldehyde (100 μL, 0.99 mmol, 1 equiv) was added. This final solution was continuously stirred over 4 days. The reaction was quenched by addition of 1 M HCl (30 mL) and the products were extracted into ethyl acetate (2 × 30 mL). The organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was dissolved in benzene (6 mL) and *p*-TsOH(cat) was added. The reaction mixture was stirred overnight. The reaction was quenched by addition of saturated $NaHCO_3$ (30 mL) and the product was extracted into ethyl acetate (2 × 30 mL). The organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 % hexanes in methylene chloride as eluent afforded 128 mg of the lactone (66% yield, 72% ee). ^{1}H NMR ($CDCl_3$) δ 7.24–7.39 (m, 5 H), 5.46 (dd, 1 H, *J* = 7.9 Hz, 6.2 Hz), 2.54–2.67 (m, 3 H), 2.04–2.22 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.8, 139.2, 128.5, 125.1, 81.0, 30.7, 28.7. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.73; H, 6.02.