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Asymmetric Mukaiyama aldol reaction of a ketene silyl acetal of thioester catalyzed by a binaphthol–titanium complex in supercritical fluorofrom

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Abstract

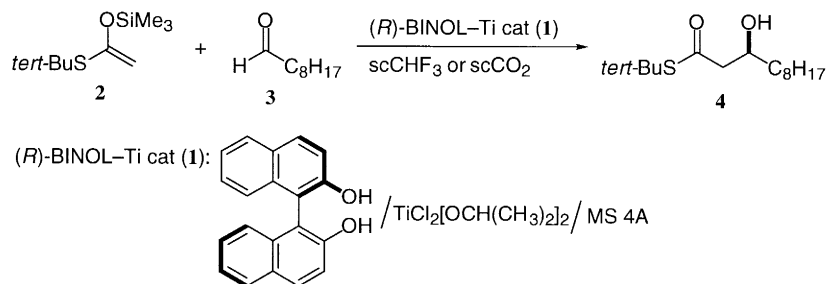
The Mukaiyama aldol reaction catalyzed by a binaphthol-derived chiral titanium(IV) complex proceeds smoothly in an unorthodox reaction medium, supercritical fluid (SCF) such as fluorofrom (scCHF₃). The chemical yield and enantioselectivity of the reaction in SCFs are found to be tuned by changing the supercritical fluids, scCHF₃ versus carbon dioxide (scCO₂), and adjusting the matched polarities by varying the pressure of CHF₃. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Mukaiyama aldol reaction; chiral Ti catalyst; asymmetric catalysis; supercritical fluids.

Homogeneous asymmetric catalysis of organic reactions has evolved into a rapidly growing and prominent area in contemporary chemistry.¹ The replacement of conventional liquid solvents by supercritical fluids as reaction media for homogeneous asymmetric catalysis offers the opportunity to control the reaction performance in terms of the reactivity and selectivity because of high gas miscibilities, greater diffusivities, clustering effects, and tunable solvent power by adjusting their densities along with the pressure.^{2,3} However, examples of asymmetric catalysis in SCFs are quite rare and thus far reported on hydrogenation reactions^{2a,3} and vinylation and hydroformylation of olefins⁴ in less polar scCO₂, wherein the enantioselectivities are comparable to those achieved in conventional solvents. Herein reported is the first example of asymmetric Lewis acid-catalyzed⁵ carbon–carbon bond formation, Mukaiyama aldol reaction, in SCFs such as polar fluorofrom (Scheme 1).

The Mukaiyama aldol reaction catalyzed by a chiral binaphthol–titanium(IV) catalyst⁶ in an SCF containing a ketene silyl acetal of thioester (**2**)⁷ and an aldehyde (**3**) (**1**:**2**:**3**=1:20–40:20 molar ratio) proceeded smoothly to give a trimethylsilyl ether of the aldol product (**4**) in moderate yields. The outcome of the reaction was found to be influenced by tuning SCFs (scCO₂: *T*_c=31.0°C, *P*_c=72.8 atm, the

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Kamlet–Taft solvatochromic π^* parameter⁸ -0.1 at 160 atm and 40°C; CHF₃: $T_c=25.9^\circ\text{C}$, $P_c=48.1$ atm, $\pi^*=3.50$ at the critical point⁹) and adjusting the matched polarities by varying the pressure of CHF₃.

The typical experimental procedure is illustrated in Fig. 1: The isolated (*R*)-binaphthol–titanium (BINOL–Ti) catalyst (**1**) (5 mol%) preformed from (*R*)-binaphthol (BINOL) and diisopropoxytitanium dichloride in the presence of molecular sieves 4 Å,¹⁰ and a small vial for the substrates **2** and **3** were placed in a 50 mL stainless steel autoclave under an argon atmosphere at 34°C for 2 h. Separating the catalyst from the substrates by use of the small container can prevent reactions in the liquid phase before charging supercritical fluids (Fig. 1, vide infra). An SCF was introduced with an HPLC pump and then the pressure was increased to the pressure tested. After 14 h, the reactor was cooled with a methanol/dry ice mixture and then after releasing the pressure, hydrolytic workup followed by flash column chromatography afforded the aldol product (**4**). The enantiomeric excess (% ee) of **4** was determined on the basis of chiral HPLC (Daicel chiral OD column) analysis and ¹H NMR (300 MHz) spectral analysis of the (*S*)- and (*R*)-MTPA ester derivatives.⁶ Visual inspection of the reaction mixture in a 50 mL autoclave equipped with sapphire windows showed that the reactants **2** and **3** were all soluble in scCO₂ or scCHF₃ under the reaction conditions and that the chiral Ti complex was partially soluble in SCFs although the solubility could not be determined. Therefore, the reaction takes place in the homogenous supercritical phase. The results thus obtained are summarized in Table 1.

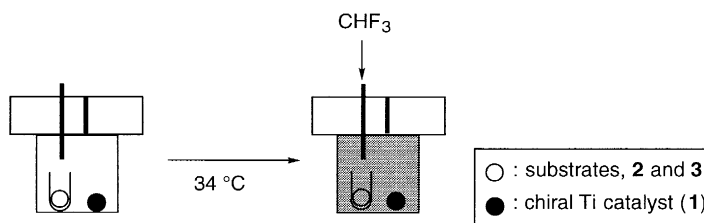


Fig. 1. Standard procedure for the Mukaiyama aldol reaction in SCFs

Inspection of Table 1 reveals the characteristic features of the present asymmetric reaction catalyzed by the Ti complex (**1**) in SCFs. The sense of enantioselectivity of the aldol reaction catalyzed by **1** in the SCFs is exactly the same as that observed in liquid solvents such as toluene and dichloromethane. The (*R*)-BINOL–Ti catalyst provides the (*S*)-aldol product. As reported previously, the outcome of this aldol condensation is strongly affected by the properties of the solvents.⁶ In toluene ($\pi^*=0.535$),^{11a} for example, the ee values of the products attained at high concentration was higher than that observed in polar solvent such as dichloromethane (dielectric constant $\epsilon=9.1$ at 20°C; $\pi^*=0.802$) and reached 92% ee at 0°C in toluene (entries 1, 2 and 5), while the reaction did not proceed under high dilution conditions, the catalyst (0.2 mM) and the aldehyde (4.0 mM) in toluene and dichloromethane at 34°C (entries 1–3).

Table 1
Asymmetric catalytic Mukaiyama aldol reactions of **2** and **3** in SCFs^a

entry	solvent	pressure [atm]	concentration [mM]		temp. [°C]	yield [%]	<i>S</i> : <i>R</i> ^b
			catalyst	substrate			
1	toluene	1	16.7	333	0	60	96 : 4
2		1	16.7	333	34	49	86 : 14
3		1	0.2	4.0	34	0	–
4	CH ₂ Cl ₂	1	0.2	4.0	34	0	–
5 ^c		1	16.7	333	0	60	80 : 20
6	scCHF ₃	100	0.2	4.0	34	46	94 : 6
7		200	0.2	4.0	34	22	94 : 6
8 ^d		200	0.2	4.0	24	20	86 : 14
9 ^d		50	0.2	4.0	34	23	85 : 15
10	scCO ₂	200	0.2	4.0	34	8	86 : 14

^a Conditions as in the text. ^b An enantiomer ratio was determined by chiral HPLC (Daicel chiral OD column) analysis and ¹H NMR (300 MHz) spectral analysis of the (*S*)- and (*R*)-MTPA ester derivatives.

^c *S*-Ethyl thioacetate-derived ketene trimethylsilyl acetal was used instead of the *S*-*tert*-butyl counterpart.

^d The catalyst was not separated from the substrates.

In scCHF₃ of 100 atm and at 34°C, the reaction proceeded to give the product with a relatively high ee in moderate yield.

The enantioselectivity is increased from 72% ee in toluene to 88% ee in scCHF₃ (entry 2 versus 6). The ee values of the product did not change much with an increase in the pressure from 100 to 200 atm probably because of no significant change in the dielectric constants at 34°C: 6.1 at 100 atm and 6.5 at 200 atm⁹ (entry 4 versus 5). Increasing the pressure of CHF₃ to 200 atm led to the decrease in chemical yield, probably due to an increase in the density, as observed in dichloromethane (entry 3 versus 7). Similarly, CHF₃ liquid phase reaction gave the product with lower ees and in low yields (entries 8 and 9). On the other hand, in scCO₂ which is less polar than toluene ($\epsilon=1.6$, liq. CO₂ at 0°C, 50 atm; 2.6, toluene at 20°C), the reaction proceeded only slightly to give a very low yield of the aldol product, presumably because of low solubility of the Lewis acid catalyst in this medium.

In summary, we have disclosed the first example of asymmetric Lewis acid, BINOL–Ti complex (**1**) catalyzed carbon–carbon bond forming reactions in SCFs. The outcome of the reaction can be controlled by tuning supercritical fluids and by adjusting their polarities with pressure.

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