



## Highly Enantioselective Catalysis of the Mukaiyama Aldol Reaction by BINOL-Ti Perfluorophenoxide and Enoxysilacyclobutane

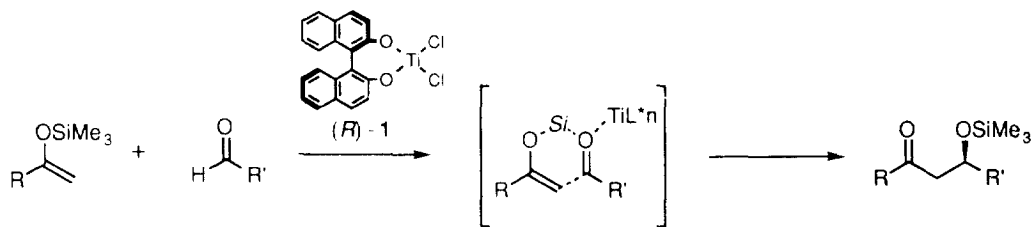
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**Abstract:** An extremely high level of enantioselectivity is established in the Mukaiyama aldol reaction using perfluorophenol as an effective achiral ligand for binaphthol (BINOL)-derived titanium (IV) catalyst. Enoxysilacyclobutane is more effective as the silyl nucleophile than the usual trimethylsilyl enol ether in the enantioselective catalysis of the Mukaiyama aldol reaction.

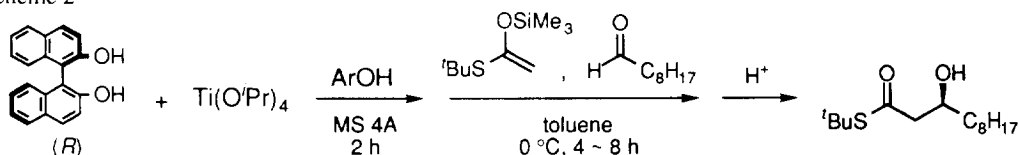
The aldol reaction constitutes one of the most fundamental carbon-carbon bond construction processes in organic synthesis.<sup>1</sup> Therefore, the detailed understanding of the reaction mechanisms of aldol process and asymmetric catalysis thereof<sup>2</sup> have attracted much attention. We have recently reported the enantioselective catalysis of the Mukaiyama aldol reaction with trimethylsilyl enol ethers by binaphthol-derived titanium (IV) complex (BINOL-TiCl<sub>2</sub>: **1**)<sup>3</sup>, and the possible intervention of pericyclic ("silatropic-ene") mechanism (Scheme 1).<sup>4</sup> Herein, we wish to report the highly enantioselective catalysis of the Mukaiyama aldol reaction by adjusting the Lewis acidity and steric effect of BINOL-Ti (IV) catalyst through the introduction of perfluorophenoxy ligand or by using silacyclobutane as a highly migrating silyl group (Schemes 2 and 3).

Scheme 1



First, we attempted the use of aromatic alcohols (ArOH) instead of the chloride ligand of the BINOL-Ti complex (**1**) in the reaction of a trimethylsilyl enol ether, in view of the electronic and steric advantage of ArOH as compared to aliphatic alcohols. The catalysts were prepared by stirring, first, (*R*)-BINOL and Ti(O<sup>*i*</sup>Pr)<sub>4</sub><sup>5</sup> in the ratio of 1 : 1 in the presence of MS 4A in toluene for 2 h, and then further addition of 1 or 2 equivalents of ArOH (Scheme 2). The aldol reactions were carried out *in situ* by adding thioester-derived trimethylsilyl enol ether and aldehyde at 0 °C to a toluene solution of the catalyst thus prepared. The reaction was monitored by TLC analysis. Careful hydrolytic workup followed by flash column chromatography afforded the aldol product. The enantiomeric purity of the product was determined by chiral HPLC (Daicel chiral OD column) analysis of the β-hydroxy thioester obtained on protodesilylation of the product.

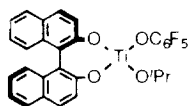
Scheme 2

Table 1. The Mukaiyama Aldol Reaction Catalyzed by BINOL-Ti Aryloxyde.<sup>a</sup>

entry	ArOH	eq of ArOH	yield (%)	% ee
1 <sup>b</sup>	none (BINOL-TiCl <sub>2</sub> )	-	60	91
2	none (BINOL-Ti(O <sup>i</sup> Pr) <sub>2</sub> )	-	53	91
3	(CF <sub>3</sub> ) <sub>2</sub> CHOH	2eq	56	92
4		2eq	55	93
5		2eq	40	97
6		1eq	62	97
7		1eq	61	96

<sup>a</sup> All reactions were carried out using 10 mol% of a catalyst. <sup>b</sup> Ref. 4.

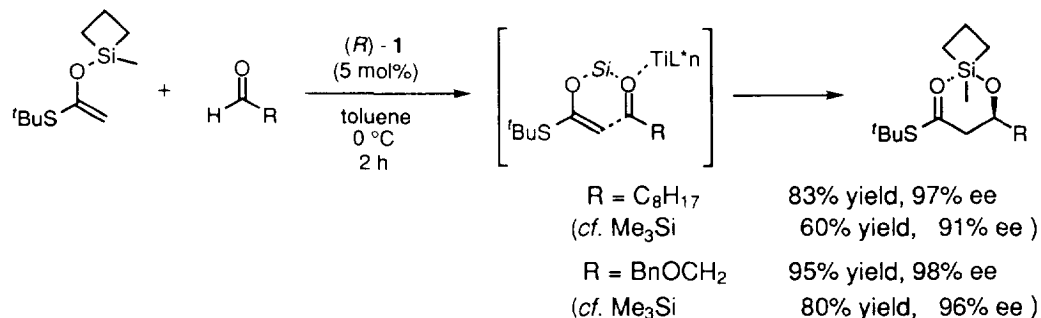
Representative results are summarized in Table 1. A similar level of enantioselectivity was obtained with diisopropoxy titanium complex, however, in lower chemical yield (entry 2) as compared with the dichloride catalyst **1** (entry 1), presumably because of the lower Lewis acidity of the diisopropoxy complex. Hexafluoroisopropoxy complex (entry 3) provided a slightly enhanced level of enantioselectivity and chemical yield presumably because of the electronic and steric advantages of polyfluoroalcohol.  $\beta$ -Naphthol gave a similar level of enantioselectivity (entry 4).<sup>6</sup> Highest enantioselectivity is obtained by perfluorophenol<sup>7</sup>, however, with low chemical yield in the 2 equivalents use (entry 5). Chemical yield was remarkably improved with no loss of high enantioselectivity, by using only 1 equivalent of perfluorophenol (entry 6).<sup>8</sup> These results may imply that only 1 equivalent of perfluorophenol can exchange to give the mono-perfluorophenoxy titanium complex (**2**).

**2**

Next, we examined the asymmetric catalysis of the aldol reaction with enoxysilacyclobutane (Scheme 3) which had been reported to proceed through a cyclic transition state, however, *in the absence of* the Lewis acid catalyst<sup>9</sup>. We thought that silacyclobutane could be more suitable as a silyl migrating group than the usual trimethylsilyl group even in the presence of chiral Lewis acid catalysts. The aldol reactions were carried out as described above except for the use of the enoxysilacyclobutane and the catalyst (**1**). The reaction was found to proceed quite smoothly to provide the aldol product in relatively high chemical yield along with extremely high level of enantioselectivity as compared to those obtained with trimethylsilyl counterpart.

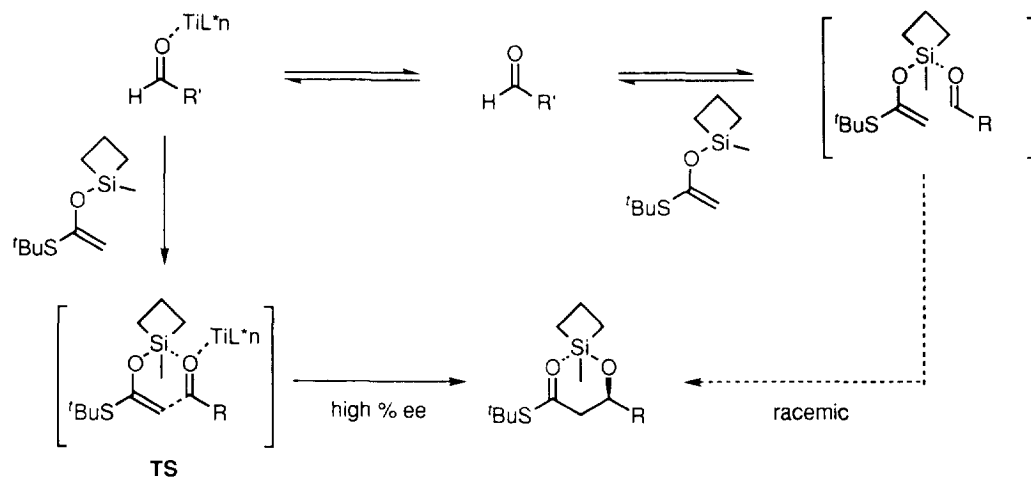
Particularly with  $\alpha$ -benzyloxyaldehyde, virtually complete level of enantioselectivity was observed along with almost quantitative yields.<sup>10</sup>

Scheme 3



The significantly enhanced enantioselectivity by enoxysilacyclobutane indicates that the BINOL-Ti catalyst is much more Lewis acidic than the enoxysilacyclobutane, in other words, the silacyclobutane acts as the migrating group rather than the Lewis acid<sup>9</sup> in the presence of BINOL-Ti catalyst (Scheme 4). Since the silacyclobutane is considered to migrate in synchronous fashion,<sup>9c</sup> the six-membered ring transition state (TS) becomes more rigid than the trimethylsilyl transition state. As the result, the extremely high enantiomeric excess and high chemical yield can be attained.

Scheme 4



In summary, we have disclosed that enoxysilacyclobutane is more suitable silyl nucleophile than the usual trimethylsilyl enol ether in the asymmetric catalytic Mukaiyama aldol reaction and that perfluorophenol acts as an effective ligand for binaphthol-derived titanium catalysts. Further studies along these lines are now underway in our laboratory.

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