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Self-organization of ligands in multi-component titanium catalysts for the enantioselective ene reaction of glyoxylates

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Abstract

Addition of conformationally flexible biphenols to (*R*)-BINOL–Ti(O^iPr)$_2$, forms a new catalytic species with which *ee*s are as high as 97.3% in the hetero-ene reaction of *n*-butyl glyoxylate to α-methyl styrene.

1. Introduction

In the course of a study on an enantioselective reaction catalyzed by complexes of 2,2′-binaphthol (BINOL, **1**), particularly a $BINOL_2Ti$ complex, we have considered the replacement of one of the chiral moieties by non-chiral equivalents. To this end we have developed a series of complexes containing BINOL and a 2,2′-biphenol (BIPOL) derivative.

2. Results and discussion

When two different chiral ligands are complexed to the same metal, the question of matching pairs of ligands immediately comes into play. Our principal hypothesis is that the conformationally flexible BIPOL ligand **2** would, upon reaction with the optically active BINOL–Ti(O^iPr)$_2$ precatalyst **3** (Scheme 1), preferentially adopt the most favorable conformation in the final complex, therefore the pair of ligands would automatically match.

In this study, we investigate the effects (electronic and steric) of substitution of the aromatic ligands around titanium. The use of a BIPOL ligand also facilitates this task greatly. A large number of *ortho*-substituted BIPOL derivatives are available by single-step literature procedures. For example

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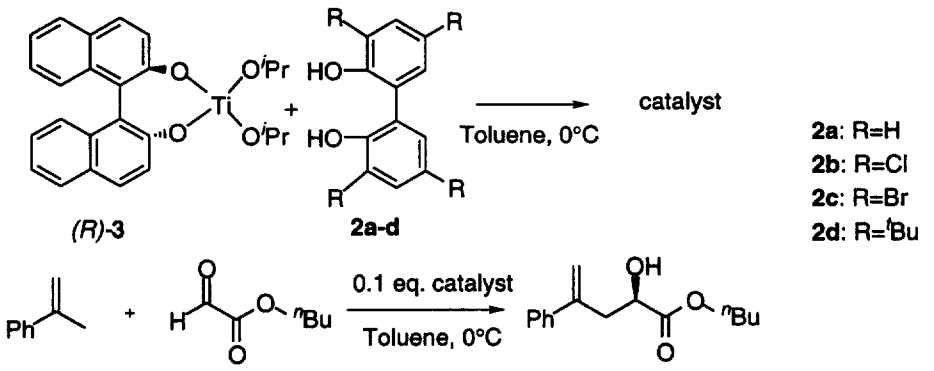


Scheme 1.

Table 1
Ene-reaction catalyzed by 2 + 4 complexes

Run	second ligand	Time (Hrs)	e.e., %
1	none	7	93.2
2	*(R)*-BINOL **1**	2	91.6
3	BIPOL **2a**	2	95.4
4	BIPOL **2a**	7	94.8
5	Cl_4BIPOL **2b**	2	96.7
6	Br_4BIPOL **2c**	2	96.3
7	$^t Bu_4$BIPOL **2d**	2	97.3

electrophilic substitution reactions of BIPOL cleanly lead to *ortho, para* derivatives, whereas a complex mixture of products is obtained in the case of BINOL.[1] Coupling of substituted phenol rings gives the non-chiral phenol derivative in high yield[2] and the task of deracemization of products is avoided.

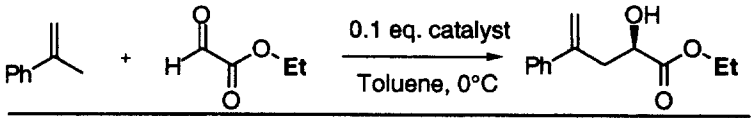
A well-studied example of the catalytic activity of $BINOL_2Ti$ complexes is the ene-reaction of α-methyl-styrene with *n*-butyl-glyoxylate, studied by Mikami et al.[3] They reported that an efficient enantioselective catalyst can be obtained by addition of optically active ligands to the BINOL–Ti(O^iPr)$_2$ precatalyst **3**. Dramatic increases in both rates of reaction and *ee*s were found when (*R*), (*S*) or racemic BINOL **1** was added to **3**, and the authors discussed this in terms of ligand-accelerated catalysis.[4] It was found that the absolute configuration of the activating ligand has little effect on the overall enantioselectivity of the reaction. The direction of selectivity is governed by the initial complex.

We decided to check the validity of our hypothesis on the same reaction, in order to get further insight into the possible nature of the active species. Table 1 presents the results obtained when the ene-reaction of α-methyl-styrene with *n*-butyl-glyoxylate (Scheme 1) was catalyzed by complexes prepared from BINOL–Ti(O^iPr)$_2$ (**3**) and various biphenols **2a–d** or (*R*)-BINOL (**1**).

In runs 2 to 7, we did observe an acceleration of the reaction compared to run 1. In our hands, in all runs, polymerization of butyl-glyoxylate competed with the desired reaction, leading to poor isolated yields (18–33%).[5] The effect on enantioselectivity is more interesting. Non-substituted BIPOL **2a** (runs 3, 4) slightly improved the *ee*. Substitution in positions 3,3′ increased the enantioselectivity, equaling the best *ee* published for this reaction.[6]

Some assays were also performed with commercially available ethyl-glyoxylate and similar results

were obtained. Although the *ees* were globally lower, the same trends were observed (Scheme 2). It is particularly worth noting the increase in both isolated yield and selectivity when ligand **2b** was used.



Run	second ligand	Yield(%)	e.e. (%)
8	none	24	86.8
9	BIPOL **2a**	42	85.2
10	Cl_4BIPOL **2b**	62	92.1

Scheme 2.

We attempted to study the complex in solution by NMR spectroscopy. We prepared BINOL–Ti(O^iPr)$_2$ (**3**) in d_6-benzene, added 1 equiv. of tetrachloro-BINOL (**2b**) and obtained the ^{1}H-NMR (400 MHz, 20°C) spectrum of a single species (broad lines). To this solution were added gradually two more equivalents of **2b**, so that not every ligand could be bound to the metal. The NMR spectrum still showed one signal per nucleus, clearly indicating that rapid ligand exchange takes place at room temperature. Lines gradually become sharper and shift, as shown in Table 2. Spectra of 1:1 mixtures of (*R*)-**3** + (*R*)-BINOL (**1**) and (*R*)-**3** + **2a** were also coherent with single species or rapid equilibria. Interestingly, adding BIPOL **2a** to Ti(O^iPr)$_4$ led to a very complex spectrum.

We then turned our attention to the preparation of the catalyst, in particular the order of introduction of the ligands (Table 3).

We were surprised to find (run 11) that BIPOL **2a** reacts much more slowly with Ti(O^iPr)$_4$ than BINOL, so that at room temperature no active catalyst is formed: in repeated experiments, no homo allylic alcohol was obtained (this is coherent with the aforementioned NMR observation). It is necessary

Table 2
NMR chemical shifts of mixtures of **3** and **2b** (d_6-benzene, 20°C, 400 MHz)

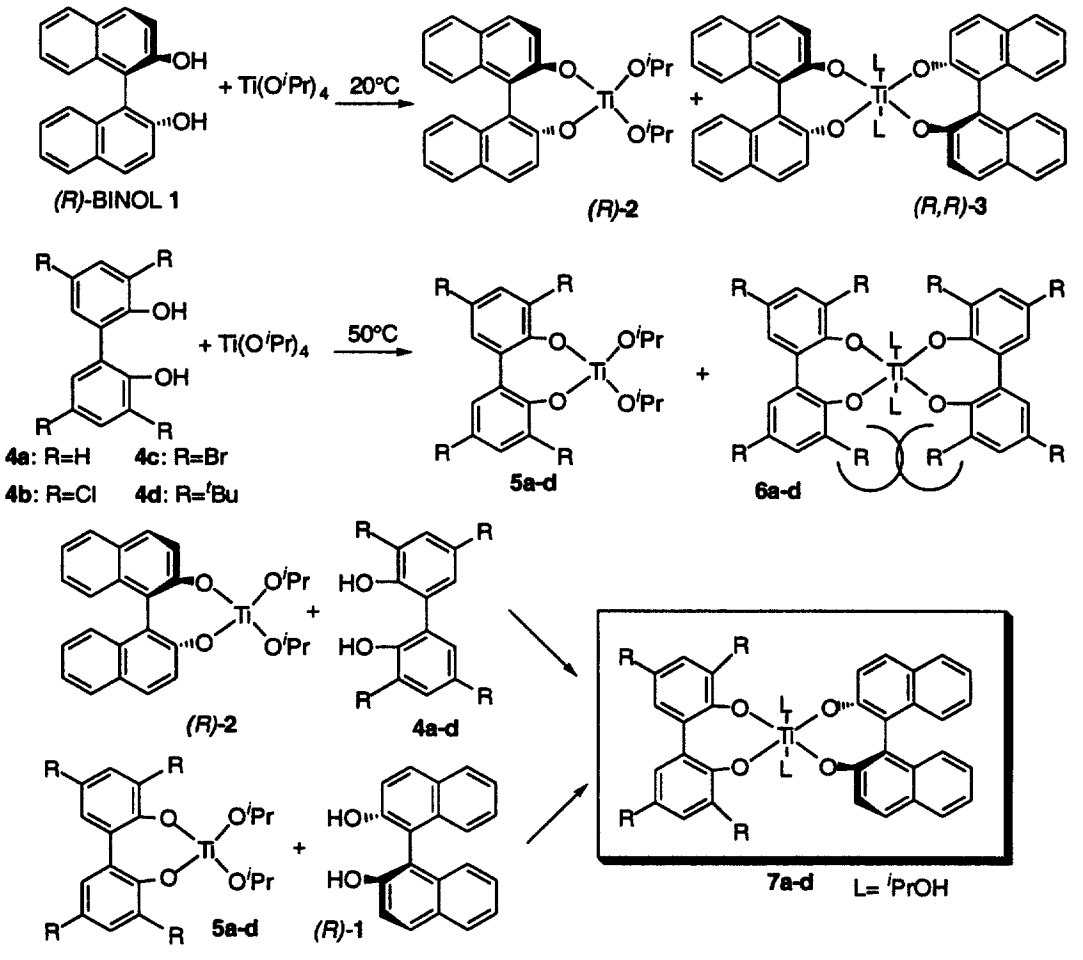
2b/1 molar ratio	BINOL, H_3 (d)	**2b**, H_6(d)
1	7.3(broad)	6.80
1.6	7.30	6.78
2.3	7.29	6.77
3	7.28	6.76
free ligands	7.23	6.73

Table 3
Influence of the order of introduction of the ligands

Run	Procedure	e.e., %
3	(*R*)-BINOL+Ti(O^iPr)4, 20°C, 30mn; then **2a**, 0°C,1mn; then reactants	95.4
11	(*R*)-BINOL+**2a**+Ti(O^iPr)4, 20°C, 30mn; then 0°C, reactants	73
12	**2a**+Ti(O^iPr)4,20°C, 30mn; then (*R*)-BINOL, 0°C, 1mn; then reactants	no reaction
13	**2a**+Ti(O^iPr)4,50°C, 1hr; then (*R*)-BINOL, 0°C, 1mn; then reactants	79
14	**2b**+Ti(O^iPr)4, 50°C, 1hr; then (*R*)-BINOL, 0°C, 1mn; then reactants	3
15	**2d**+Ti(O^iPr)4,50°C, 1hr; then (*R*)-BINOL, 0°C, 1mn; then reactants	96.5

to raise the temperature to 50°C (runs 13–15) to obtain a complex that then reacts rapidly with (*R*)-BINOL (**1**) to form an active catalyst.

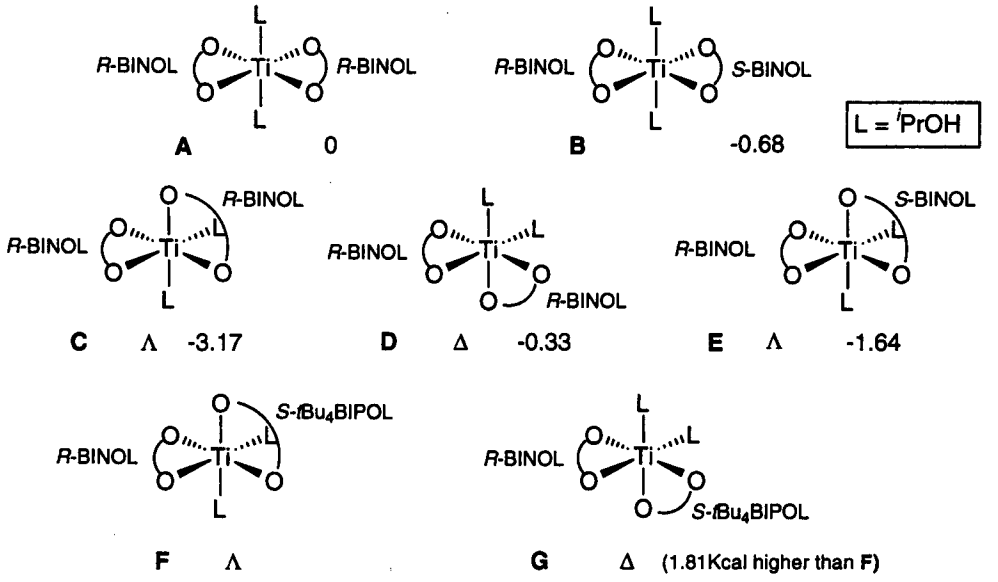
Scheme 3 summarizes our hypothesis about the stoichiometric nature of the catalysts or pre-catalysts involved in the system. To explain the results of Table 1, we propose that **7a–d** is the main catalyst. If R=H (runs 3–4), **7a** is sterically very close to (*R,R*)-**4**, and leads to comparable *ee*. If R=^{t}Bu (run 7), the bulky groups more readily orientate the complexed carbonyl group.



Scheme 3.

To explain the results of Table 3, we propose that the first step, reaction of (*R*)-BINOL (**1**) with Ti(O^{i}Pr)$_4$, leads mainly to (*R*)-**3**, together with a small amount of (*R,R*)-**4**. On addition of **2a–d**, a rapid reaction with (*R*)-**3** produces **7a–d**, contaminated with (*R,R*)-**4**. Both **7** and **4** are efficient and selective, thus high *ee*s are achieved. In runs 12–15, in the first step, **5** is produced with small amounts of **6**. Rapid reaction with (*R*)-BINOL (**1**) leads again to **7**, but in these cases contaminated by a chiral **6a–d**. **6a** (R=H) is as active as **7**, so the loss of selectivity due to a small amount of **6a** is limited: runs 11 and 13 (from 95 to 73–79% *ee*). In run 14, **6b** (eight Cl atoms!) is a much more active catalyst than **7**. Thus it has a deleterious effect on the selectivity. In contrast, not only is **6d** (R=^{t}Bu) too hindered to be a good catalyst, but it is probably present in lesser amounts. In this case (run 15), the *ee* is barely decreased (97.3 to 96.5%) upon changing the order of ligand introduction.

To discuss the geometry of the active species, some molecular modeling[7] was performed. Considering a hexacoordinated titanium atom bearing two different bidentate ligands and two isopropanol groups (Scheme 4), the latter groups can be *trans* (structures **A** and **B**) or *cis*. In the latter case, the hexacoordination of the titanium atom will make it a center of chirality. Since the ligands are also chiral, diastereoisomeric forms **C**, **D**, **E**, **F**, **G** can co-exist. We calculated the energy differences for the most stable conformer of each diastereoisomer; the values (in kcal) appear on Scheme 4. The most important point is that, in the case of two (*R*)-BINOL ligands, the Λ isomer **C** is clearly more favorable than the Δ isomer **D**.



Scheme 4.

In the case of (*R*)-BINOL–^{t}Bu$_4$BIPOL complexes **F** and **G**, the BIPOL moiety adopts an (*S*) conformation in the models. Again, the Λ diastereoisomer is more stable (−1.81 kcal) than the Δ one. We then replaced one isopropanol ligand in the complexes by the carbonyl substrate, and visually examined the possible hindrances of the approach of the nucleophile. In the case of the *trans* complex **A**, a clear difference can be seen, but the model predicts an (*S*) configuration for the adduct,[8] whereas the experimental result is (*R*). This rules out **A** as the active catalyst. A much better clue for eliminating *trans* isomers for the active catalyst is an experiment of Mikami et al.:[3b] when a catalyst is prepared from (*R*)-**3** and (*S*)-BINOL, and thus could be the *meso* structure **B**, the (*R*) isomer of the product is still obtained with a good *ee* (86%). This result is better explained by assuming that **E** is the active isomer in this case.

In our hypothesis, on reacting the second ligand with the precatalyst **3**, a *cis* complex would be formed. Also, the complexation of the second ligand would be diastereoselective: the Λ form of the complex (**C**, **E** or **F**), would be preferentially obtained from (*R*)-**3**. This form would be the most active catalyst for the reaction.

Thus, we found that addition of very simple, cheap and easily available biphenol derivatives, to the complex **3** obtained from BINOL and titanium tetraisopropoiyde leads to a highly enantioselective catalyst for the above ene-reaction, providing *ee*s equal or superior to the best literature data. Extensions of these activators to other catalytic systems are currently in progress.

3. Experimental section

2b (R=Cl)[1a] and **2c** (R=Br)[1b] were prepared according to literature procedures.

3.1. 3,3′,5,5′Tetraterbutyl-2,2′-biphenol,[8] 2d

Under an inert atmosphere, BIPOL (3 g) was dissolved in 100 ml of *tert*-butyl-methylether. $SnCl_4$ (20 ml) was added, and the solution was stirred at 20°C for 50 h. Water (50 ml) was added to quench the reaction, and the product was extracted with dichloromethane (2×100 ml). The product **4d** was obtained in pure form after recrystallization first from ethanol–water, then from toluene (1.5g, 25% yield).

3.2. Ene-reaction, general procedure

Under an atmosphere of argon, (*R*)-BINOL **1** (0.05 mmol) and $Ti(O^iPrO)_4$ (0.05 mmol) were stirred in dry toluene (2 ml) at 20°C for 30 min. At 0°C, **2** (0.05 mmol) was added, immediately followed by a mixture of α-methyl-styrene (0.5 mmol) and the alkyl glyoxylate (0.5 mmol, distilled immediately before use), in 2 ml of toluene. After stirring at 0°C for the indicated time, and standard aqueous work-up (brine, extraction in ethyl acetate, acidic washing), the adduct was isolated by chromatography on silica (ethyl acetate:pentane=15:85).

Enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak AD, cyclohexane:^{i}PrOH=99:1). The absolute configuration of the homoallylic alcohol is (*R*), based on literature data.[1e] We checked the optical rotation for run 6, $[\alpha]_D^{20}=-22.2$ (c=1.9, chloroform).

Acknowledgements

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4. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *36*, 1059–1070.
5. We could not improve the yields, either by use of 10 equivalents of α-methyl-styrene or by slow introduction of the *n*-butyl-glyoxylate.
6. Catalyst BINOL–$TiCl_2$, Ref. 3d.
7. Program Insight II® 97.0, force field esff, ε=1 (vacuum).
8. Models of the complexes of butyl glyoxylates and the other isomers **A–G** were also minimized. The structure **F** seems to favor the formation of the (*R*)-homoallylic alcohol. All 3D models are available on the Web: http//www-ledss.ujf-grenoble.fr/WebSrv/poster.html