Generation of Highly Enantioselective Catalysts from the Pseudoenatiomeric Assembly of BINOL, F_8BINOL, and Ti(O*i*Pr)$_4$

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The quest for new asymmetric catalysts continues to depend both on accidental discovery and on mechanistic understanding of the uncovered processes.[1] The development of new and improved chiral ligands is one of the most important research activities in this area. The derivatives of 2,2′-binaphthol (BINOL, **1**) are among the most widely used chiral ligands in asymmetric catalysis.[2−4] A number of modifications of the BINOL scaffold aimed at improving its catalytic performance have been documented.[5−14] We recently reported the synthesis and catalytic applications of F_8BINOL (**2**), an isostere of BINOL with modulated coordination preferences and stability toward racemization under a wide range of reaction conditions.[15,16] In this communication, we report on the "pseudoenantiomeric" relationship between the enantiomers of **1** and **2** (Figure 1) and its potential applications to asymmetric catalysis using the glyoxylate−ene reaction[17] as a model.

Many well-known asymmetric catalysts rely on the active species produced in equilibrating metal/ligand mixtures. Titanium is known to exhibit particularly convoluted behavior when several ligands are capable of entering its coordination sphere.[18,19] Some important breakthroughs in titanium chemistry are attributed to ligand-accelerated catalysis (LAC) which involves in situ selection of the active catalyst from many thermodynamically accessible complexes.[20] This powerful approach provides a means to direct a reaction toward the enantioselective pathway even though the catalytically active species may be present only in small amount relative to the more abundant, but less selective, species. Another important consequence of the agglomerate formation is nonlinear effect which enables one to use nonenantiopure ligands in asymmetric catalysis. When the minor ligand is converted into the less active, but generally more stable *meso* species, asymmetric amplification may take place.[21,22]

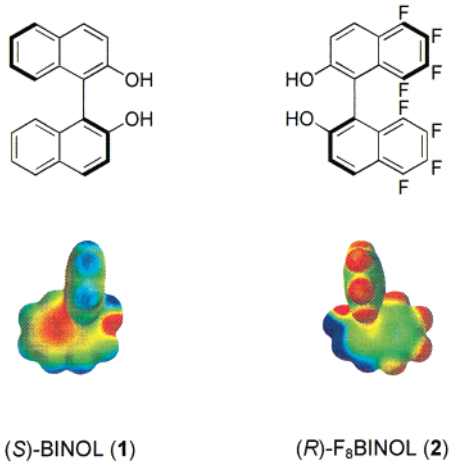

Figure 1. (*S*)-BINOL and (*R*)-F_8BINOL as pseudoenantiomers (AM1 electrostatic potential surfaces).

$$\mathrm{M} + \textit{rac}\text{-L} \rightarrow \underset{\mathbf{A}}{\mathrm{ML_RL_R}} + \underset{\mathbf{B}}{\mathrm{ML_SL_S}} + \underset{\mathbf{C}}{\mathrm{ML_RL_S}} \qquad (1)$$

$$\mathrm{M = Ti(IV);\ L = BINOL}$$

Both asymmetric amplification and enantiomer-selective activation of racemic catalysts were recently demonstrated for the glyoxylate−ene process.[23−25] A remarkable nonlinear effect in this system was attributed to the increase in activity of the homochiral BINOL/Ti adducts **A** an **B** (equation 1) compared to the more stable *meso*-adduct **C**.[23] It was established that the *meso* adduct, rather than a mixture of homochiral adducts, is preferentially formed between racemic BINOL and Ti. We reasoned that if one of the enantiomers of BINOL is replaced by its fluorinated analogue, a "pseudo-*meso*" aggregate may be formed for similar geometrical reasons that are responsible for the formation of the *meso* aggregate in the BINOL case.

We started by investigating the more acidic F_8BINOL ligand (F_8BINOL p*K*a′ 9.29; BINOL p*K*a′ 10.28) in titanium-catalyzed asymmetric glyoxylate−ene process using the literature conditions. With Ti(O*i*Pr)$_4$ as the source of Ti(IV), high levels of enantioselectivity were obtained. For example, the reaction between ethyl glyoxylate and α-methyl styrene in the presence of 10 mol % (*S*)-**2**/Ti(O*i*Pr)$_4$ (2:1 ratio) catalyst afforded ethyl (*S*)-2-hydroxy-4-phenylpent-3-enoate with 92% ee in 53% yield (Table 1, entry 1). Thus, the same sense of asymmetric induction is observed for both Ti/(*S*)-F_8BINOL and Ti/(*S*)-BINOL catalysts. Initial rate studies indicate that the catalyst derived from F_8BINOL ($k = 0.6 \times 10^{-3}$, see Supporting Information) is approximately 4 times slower than the catalyst derived from BINOL ($k = 2.7 \times 10^{-3}$, see Supporting Information). From these data, we expected

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(1) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.
(2) Rosini, C.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517.
(3) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(4) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494.
(5) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310−312.
(6) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693−6696.
(7) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343−344.
(8) Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273.
(9) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080−4081.
(10) Morita, T.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1445−1450.
(11) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223−2226.
(12) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220−4221.
(13) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351−356.
(14) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403−5404.
(15) (a) Yudin, A. K.; Martyn, L. J. P.; Pandiaraju, S.; Zheng, J.; Lough, A. *Org. Lett.* **2000**, *2*, 41−44. (b) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433.
(16) Martyn, L. J. P.; Pandiaraju, S.; Yudin, A. K. *J. Organomet. Chem.* **2000**, *603*, 98.
(17) For a recent review, see: Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305−342.
(18) Clark, R. J. H. *The Chemistry of Titanium and Vanadium*; Elsevier: Amsterdam, 1968.
(19) Sharpless, K. B. *Chem. Scr.* **1987**, *27*, 521−524.
(20) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.
(21) Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345−352.
(22) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411.
(23) Mikami, K. *Tetrahedron* **1992**, *48*, 5671−5680.
(24) (a) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613−615. (b) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Matsukawa, S. *Acc. Chem. Res.* **2000**, *33*, 391−401.
(25) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Pardillos-Guindet, J.; Vallée, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3889−3894.

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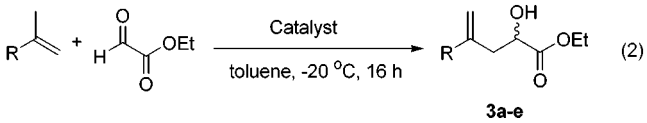
Table 1. Use of F_8BINOL and Mixed F_8BINOL/BINOL Catalysts in the Glyoxylate−Ene Reaction

entry	R	catalyst	yield (%)*	ee (%)
1	phenyl	(*S*)-**2** (10 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	53	92 (*S*)
2	phenyl	(*R*)-**2** (5 mol %), (*S*)-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	95	99 (*S*)
3	methyl	(*R*)-**2** (5 mol %), (*S*)-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	57	99 (*S*)
4	ethyl	(*R*)-**2** (5 mol %), (*S*)-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	71	99 (*S*)
5	cyclohexyl	(*R*)-**2** (5 mol %), (*S*)-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	47	99 (*S*)
6	cyclopentyl	(*R*)-**2** (5 mol %), (*S*)-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	59	99 (*S*)
7	phenyl	(*R*)-**2** (5 mol %), *rac*-**1** (5 mol %), Ti(O*i*Pr)$_4$ (5 mol %)	65	78 (*R*)

*Isolated yield based on olefin.

only moderate enantioselectivity (around 60%ee) for the catalyst produced in the (*R*)-F_8BINOL/(*S*)-BINOL/Ti(O*i*Pr)$_4$ mixture (1:1:1 ratio). However, the reaction between ethyl glyoxylate and α-methyl styrene proceeded with excellent enantioselectivity (Table 1, entry 2). Most intriguing was a significant yield improvement in the "mixed" case compared to either **1** or **2** alone. Analysis of the conversion/time characteristics confirmed the unexpected higher activity of the catalyst produced in the pseudoracemic mixture (see Supporting Material). In addition, the reaction between ethyl glyoxylate and aliphatic olefins in the presence of the mixed catalyst led to the desired α-hydroxy esters with >99% ee (Table 1, entries 3−6). In our hands, neither **1**/Ti nor **2**/Ti alone gave any conversion with aliphatic olefins.



(2)

3a-e

To clarify this synergistic behavior, we carried out structural work. Upon mixing (*R*)-**2** and (*S*)-**1** with Ti(O*i*Pr)$_4$ in toluene, we were able to isolate crystals of a new species **4**[26] incorporating *both* **1** and **2**, rather than an equimolar mixture of **2**/Ti and **1**/Ti complexes. The molecule of **4** (Figure 2) contains a pseudocrystallographic inversion symmetry which is broken by fluorine substitution. The stabilizing stacking interactions between the proximal aromatic planes in **4** were identified through the corresponding intraplanar distances in the region of 3.5 Å. The central core in this structure is composed of six titanium centers surrounded by the BINOL- and F_8BINOL halves. The source of the oxo bridges, which serve as links between the initially formed Ti/F_8BINOL dimers, is under investigation.

The outlined experiments strongly suggest a synergystic relationship between the opposite enantiomers of **1** and **2** in the asymmetric ene process. We designed additional experiments to further prove that BINOL and F_8BINOL are linked within the catalyst. An important insight was obtained when (*R*)-**2** was combined with *rac*-**1** at the catalyst preparation stage (Table 1, entry 7). The conversion/time study (see Supporting Information) indicates that the *rac*-**1**/Ti is more active than the (*R*)-**2**/Ti catalyst. Therefore, the racemic product would have been dominant had **1** and **2** acted independently. However, this process afforded the (*R*)-α-hydroxyester in good enantioselectivity (78% ee) indicating apparent competition between the mixed diastereomeric catalysts. It is possible that fluorine atoms break the *meso* symmetry of the catalytically active ligand/Ti(IV) assembly resulting in the observed enantioselective outcome of the catalytic process. The structurally characterized higher order aggregate **4** is significant as it captures the complimentarity between **1** and **2** and confirms the driving force to form the *meso*-aggregate in the mixture of pseudoenantiomers. Mikami and co-workers established that the oxygen-bridged cluster acts as an asymmetric catalyst in the glyoxylate ene reaction.[27] We have observed almost no catalytic activity for the mixed cluster **4**, which is not surprising. As opposed to Mikami's example, all titanium centers in the thermodynamically controlled aggregate **4** are octahedral which prevents **4** from acting as the Lewis acid.[28] We are currently trying to "intercept" mixed complexes that contain more reactive titanium centers.

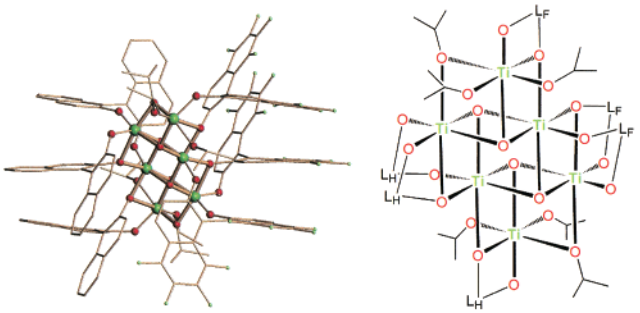


Figure 2. Molecular structure of the pseudoracemic Ti/(*R*)-F_8BINOL/(*S*)-BINOL adduct **4** and its schematic representation (L_H = BINOL; L_F = F_8BINOL).

In summary, highly enantioselective catalysts of increased activity are generated in the mixture of opposite enantiomers of BINOL and its electron-poor isostere, F_8BINOL. An important point is that the pseudoracemic system not only gives higher enantioselectivity but also affords much better yield indicating high stability of the catalyst. Structural evidence for the ligand synergy has been obtained. Investigations are currently underway to define the scope and limitations of the pseudoenantiomeric metal complexes in asymmetric catalysis. The key goal now is to identify other cases where better catalysts are produced in the "pseudo-*meso*" mixtures. In this regard, finding ligand-accelerated versions of the corresponding catalytic reactions will be most rewarding.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3a**−**e**, **4**, conversion/time diagrams, and kinetic plots are available (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Crystal structure analysis: The data were collected on a Nonius Kappa-CCD diffractometer with Mo Kα using ϕ scans and ω scans with κ offsets. Data were integrated and scaled using the Denzo-SMN package. The structure was solved and refined using the SHELXTL V5.1 package. **3**: $C_{138}H_{90}F_{24}O_{22}Ti_6 \cdot 6(C_7H_8)$, M_r = 3396.3, triclinic, space group *P*1, a = 14.3920(4) Å, b = 15.8740(3) Å, c = 18.2460(6) Å, α = 87.342(2)°, β = 73.951(1)°, γ = 75.966(1)°, V = 3885.47(18) Å^3, Z = 1, ρ_{calcd} = 1.451 Mg m^{-3}, $F(000)$ = 1742, λ = 0.71073 Å, μ(Mo Kα) = 0.393 mm^{-1}, T = −123 °C, crystal size 0.35 × 0.32 × 0.13 mm. Of the 49717 reflections collected (5.18 < 2θ < 50.16°), 22937 were independent; max/min residual electron density 0.37/-0.38 eÅ^{-3}, R1 = 0.0493 (I >2σ(I)) and wR2 = 0.1218(all data). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication no. CCDC-146925. Copies of the data can be obtained free of charge on application to CCDC, 12 union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

(27) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267−272.

(28) Corey, E. J.; BarnesSeeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513−6516.