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Importance of chiral activators in the asymmetric catalysis of Diels–Alder reactions by chiral titanium(IV) complexes

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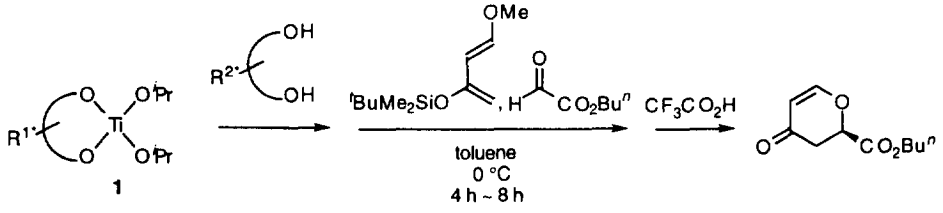
Abstract: Asymmetric activation of chiral titanium(IV) complexes is found to be essential to provide higher levels of enantioselectivity than that attained by enantiopure catalysts in Diels–Alder reactions of the Danishefsky diene and glyoxylate. © 1997 Elsevier Science Ltd. All rights reserved.

Asymmetric catalysis of organic reactions has evolved into a rapidly growing, prominent area in contemporary chemistry.[1–4] Although racemic catalysts inherently provide racemic products, an enantiomer-selective *de-activation* strategy of racemic catalysis has recently been reported to provide a certain level of asymmetric induction that does not, however, exceed the level attained by the enantiopure catalyst.[5–7] In contrast, a *chiral activator* may selectively activate one enantiomer of a chiral catalyst to attain higher enantioselectivity than that achieved by an enantio-pure catalyst (% $ee_{activated}$ » % $ee_{enantiopure}$?), in addition to a higher level of catalytic efficiency ($k_{activated}$ » $k_{enantiopure}$?). The present paper describes the critical importance of the chiral activators for the titanium(IV) catalysis of Diels–Alder reactions of the Danishefsky diene and glyoxylate. In fact, the enantiopure binaphthol-derived titanium diisopropoxide catalyst **1**[8–11] provides only low (5% ee) enantioselectivity in the D–A reaction without any chiral activator (Scheme 1, Table 1).



Scheme 1.

The catalyst was prepared by mixing chiral diols such as binaphthol (BINOL) or α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) and $Ti(OPr^i)_4$ at a ratio of 1:1 in toluene for 20 min,[7] and then adding 1.0 equivalent of chiral activators such as 5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol (5-Cl-BIPOL) or BINOL. The D–A reaction was carried out *in situ* through the further addition of the Danishefsky diene and glyoxylate at 0°C to a toluene solution of the BINOLate–Ti catalyst/BINOL complex, for example. The reaction was monitored by TLC analysis. Standard workup with CF_3CO_2H followed by flash chromatography afforded the D–A product. Enantiomer excess of the D–A product was determined by chiral HPLC (Daicel chiral AD column) analyses.

The critical importance of asymmetric activation was examined by adding chiral activators (R^{2*}-$(OH)_2$) to the catalyst **1** (Table 1). Significantly, high enantioselectivities (84% ee, *R*) were established using (R^2)-BINOL activator (run 3). The reaction proceeded smoothly to provide the D–A product in an increased chemical yield (50%) along with an enhanced level of enantioselectivity (84% ee)

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Table 1. Asymmetric catalytic Diels–Alder reaction[a]

run	R^{1*}-$(OH)_2$	R^{2*}-$(OH)_2$	yield (%)	% ee[b]
1	(R^1)-BINOL	none	40	5
2		(R^2)-5-Cl-BIPOL	53	26
3		**(R^2)-BINOL**	**50**	**84**
4		(R^2)-6-Br-BINOL	25	43
5	(R^1)-TADDOL	none	32	3
6		(R^2)-5-Cl-BIPOL	50	25
7		(R^2)-BINOL	60	5

[a] Conditions as in text. [b] Determined by chiral HPLC (Daicel chiral AD column) analysis.

compared to the values obtained using the (R^1)-BINOLate–Ti(IV) catalyst **1** without additional diols (40%, 5% ee) (run 1). Thus, the (R^1)-BINOLate–Ti(IV) catalyst **1** is activated by the addition of another 1 molar amount of (R^2)-BINOL, as is evidenced by the enantiomeric excesses and chemical yields. Sharpless *et al.* have emphasized the importance of 'chiral ligand acceleration',[12] however, in the construction stage of a chiral catalyst from an *achiral pre-catalyst.*

In summary, this paper reports an asymmetric activation to provide enhanced levels of catalyst efficiency and enantioselectivity than those attained by an enantiopure catalyst. Thus, the asymmetric activation strategy provides a more practical advantage than the de-activation strategy.

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References

1. *Advances in Catalytic Processes: Asymmetric Chemical Transformations* Doyle, M. P., Ed.; JAI Press: Greenwich, Connecticut, Vol. 1 (1995).
2. Noyori, R. *Asymmetric Catalysis in Organic Synthesis* Wiley: New York (1994).
3. *Catalytic Asymmetric Synthesis* Ojima, I., Ed.; VCH: New York (1993).
4. Kagan, H. B. *Comprehensive Organic Chemistry* Pergamon: Oxford, Vol. 8 (1992).
5. Alcock, N. W., Brown, J. M., Maddox, P. J. *J. Chem. Soc., Chem. Commun.* 1532–1533 (1986). Brown, J. M., Maddox, P. J. *Chirality* **3**, 345–351 (1991).
6. Maruoka, K., Yamamoto, H. *J. Am. Chem. Soc.* **111**, 789–790 (1989).
7. Faller, J. W., Parr, J. *J. Am. Chem. Soc.* **115**, 804–805 (1993).
8. Private communication from Prof. K. B. Sharpless: Martin, C. A. Ph.D. thesis, MIT (1988).
9. Wang, J. T., Fan, X., Feng, X., Qian, Y. M. *Synthesis* 291–292 (1989).
10. Keck, G. E., Li, X.-Y., Krishnamurthy, D. *J. Org. Chem.* **60**, 5998–5999 (1996). In their method, the catalyst is prepared using 1:1 stoichiometry of BINOL and $Ti(OPr^i)_4$. In the modified method, the catalyst is prepared using the 2:1 ratio. In both cases, oven dried MS 4A is used to generate the catalyst under refluxing conditions.
11. Faller, J. W., Sams, D. W., Liu, X. *J. Am. Chem. Soc.* **118**, 1217–1218 (1996).
12. Berrisford, D. J., Bolm, C., Sharpless, K. B. *Angew. Chem. Int. Ed Engl.* **34**, 1059–1070 (1995).
13. Mitsuda, M., Hasegawa, J., Ohashi, T. Ann. Meeting of Chem. Soc. Jpn. 2H439, Tokyo, 1996.

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