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Efficient Chiral Poisoning of Racemic Titanium Catalysts for the Asymmetric Chloral-Ene Reaction

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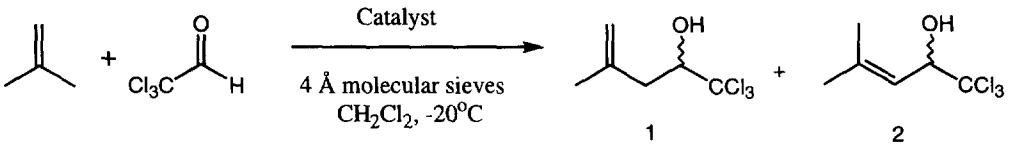
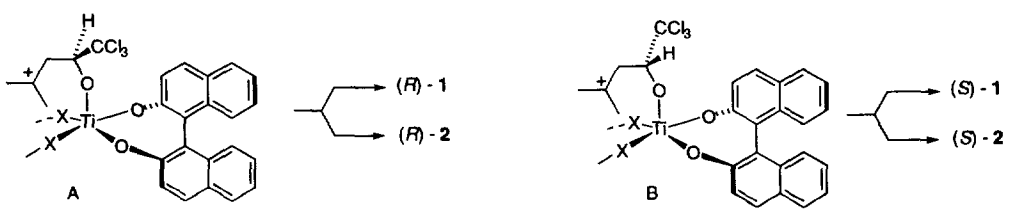
Abstract: A Ti(O-*i*-Pr)$_2$Cl$_2$ / *racemic* BINOL catalyst can be poisoned with an inactive enantiopure catalyst, diisopropyl D-tartrate/ Ti(O-*i*-Pr)$_2$Cl$_2$, to yield an effective catalyst for the asymmetric ene reaction with chloral. In some cases the ee's are greater than those observed with catalysts prepared from enantiopure BINOL.

A chiral poisoning strategy[1,2] has been successfully applied to the Ti(O-*i*-Pr)$_4$ / BINOL catalyst system for asymmetric allylation.[3] For the ene reaction between chloral and some selected olefins, we have found that a Ti(O-*i*-Pr)$_2$Cl$_2$ / *racemic* BINOL catalyst could be poisoned with an inactive diisopropyl D-tartrate/ Ti(O-*i*-Pr)$_2$Cl$_2$ and yield an effective catalyst for the asymmetric ene reaction.



The study was initiated by carrying out the reaction between chloral and isobutylene using Ti(O-*i*-Pr)$_2$Cl$_2$/ (*S*)-BINOL[4] as catalyst. Results similar to those observed by Mikami[4] for other olefins were obtained, i.e., homoallylic alcohol **1** and allylic alcohol **2** were formed in a ratio of ~2:1. Alcohol **1** was formed in 24% ee and a much higher enantiomeric purity (66%) was found for **2**, which is crystalline. Presumably any desired enantiomeric purity for **2** can be obtained by further recrystallizations, e.g., the ee can be improved to 88% by a single recrystallization from pentane.

The formation of the allylic alcohol is unusual for what might be expected to involve a typical ene mechanism, however, it is conceivable that the normal product, **1**, is initially formed but subsequently isomerizes to the internal olefin. The lower ee of **1** compared to **2** might make this seem a less likely path, but it could result from an enantioselective isomerization by a chiral catalyst. This isomerization under ene reaction conditions is unprecedented and furthermore, if **1** is treated with the catalyst, it does not isomerize to **2**. The formation of two products has been attributed to the competition between a traditional ene pathway and a pathway involving direct attack of a cation.[4] The results can also be accommodated by an alternative explanation for the difference in the enantiomeric purities of two products by considering only a direct cationic attack pathway.[5] If we assume that the



Ti-aldehyde complex adds to the ene like a carbonium ion with a given stereoselectivity, then the distribution of the two regioisomers, **1** and **2**, would be determined by the regioselective removal of protons from the intermediate. Since the base is presumably an oxygen atom within the complex (not necessarily that derived from chloral) and the complex is chiral, selective deprotonation could occur. The regioselectivity would differ for the diastereomeric intermediates. The initial selectivity of the attack on the ene by the carbonyl would not necessary be immediately reflected in the ee of the product. That is, the regioselectivity of the deprotonation of the initially formed intermediate could either enhance or reduce the ee of a given product. Even though the initial ratio of (*R*) to (*S*) at the carbon α to CCl_3 in the intermediate would not change, this selective deprotonation of either methyl or methylene could eventually lead to the observed enantiomeric purities of the final products (**1** and **2**) with one ee increasing and the other decreasing relative to that of the intermediate.[6] For example, **A** could preferentially form (*R*)-**1**, whereas **B** could preferentially form (*S*)-**2**. For convenience we define the stereoselectivity for this presumed intermediate as the *initial enantioselectivity* on carbonyl (%**B**-%**A** given as *iee* in the tables), which serves as a criteria to judge enantiofacial control of the asymmetric catalyst in directing attack on a diastereoface of the coordinated aldehyde. Based on this assumption, the initial enantioselectivity of reaction with the carbonyl can be calculated from the ratio and ee of final products.[7]

Table 1. Asymmetric Catalysis of the Reaction of Chloral with Isobutylene

entry	catalyst (mmol)		poison (mmol)		time	%yield [a]	ratio	ee (%) [b]		*iee* [c]	config.[d]
	$Ti(OR)_2Cl_2$ /BINOL		$Ti(OR)_2Cl_2$/*D*-DIPT				(**1**:**2**)	**1**	**2**		
1	0.10	0.1 (*S*)	0.00	0.00	16 h	87	67:33	24	66	*38%*	*S*
2	0.20	0.2 (*rac*)	0.10	0.10	16 h	66	83:17	14	14	*14%*	*S*
3	0.20	0.2 (*rac*)	0.10	0.20	16 h	53	88:12	30	20	*29%*	*S*
4	0.20	0.2 (*rac*)	0.10	0.30	16 h	43	87:13	48	35	*46%*	*S*
5	0.20	0.2 (*rac*)	0.10	0.30	72 h	58	94:6	48	25	*46%*	*S*
6	0.0	0.0	0.10	0.30	72 h	0					
7	0.10	0.1 (*S*)	0.05	0.15	16 h	40	90:10	33	9	30%	*S*
8	0.10	0.1 (*S*)	0.10	0.30[e]	16 h	98	82:18	4	9	5%	*S*

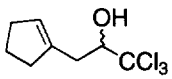
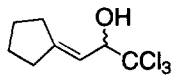
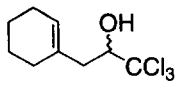
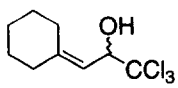
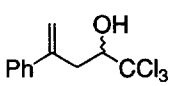
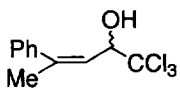
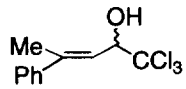
[a] Determined by ^1H NMR measurement on crude reaction mixture. [b] Measured by GC using a cyclodex-B chiral column. [c] Initial enantioselectivity, which is defined in text. [d] Determined by GC retention time. [e]Ethylene glycol.

Catalysts prepared *in situ*[8] by mixing $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ / racemic BINOL and poison $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ / diisopropyl-D- tartrate were used (entry 2 - 4, Table 1) and yielded homoallylic alcohol **1** as the major product in modest ee. With the use of ratios of 1:2 to 1:3 of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$:diisopropyl *D*-tartrate as poison (entry 4 and 5, Table 1), alcohols were produced in the same or slightly higher initial enantioselectivity[9,10] compared to those from (*S*)-BINOL and $Ti(O\text{-}i\text{-}Pr)_2Cl_2$. More importantly, a greater fraction of **1** was produced and it was formed in higher enantiomeric purity. Entry 6 shows that the titanium-tartrate complex displays no catalytic activity on its own. The yield also increases by extending the reaction time. Comparison of entries 7 and 8 demonstrate that the addition of a diol other than BINOL to the original $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ / (*S*)-BINOL catalyst can significantly affect the regiochemistry.

These results are consistent with some previous suggestions that dimers are the active species[9] and suggests that a Ti/(*R*)-BINOL moiety has been effectively deactivated upon forming a Ti_2/(*R*)-BINOL/(D)-DIPT) complex. It also suggests that the reactivity of one half of a dimer is significantly affected by the nature of the other half. Thus in heterodimers, it appears that the enantioselectivity and regioselectivity can be enhanced over that of a pure homodimer. Hence, one moiety in a heterodimer may either act as a chiral auxilliary to enhance selectivity of the other or deactivate it.

Table 2 summarizes the results from the reaction of chloral with other olefins at 0 °C employing this chiral poisoning protocol. In entry 2 and 3, a slight modification[11] in preparing catalyst A affords a solvent of only dichloromethane, consequently the distribution and optical purity pattern of products may not be directly comparable to those in entry 1. Note that these products have the potential for conversion to amino acids and subsequent enrichment to enantiomeric purity via recrystallization.[12]

Table 2. A Comparison of Enantiopure and Poisoned Catalysts for Selected Olefins

Entry	olefin	*cat*[a]	time	yield[b] (%)	Product ratio (%) (ee)[c]		Config[d]	*iee*[e]
								
1		A	3 hrs	87	91 (64%ee)	9 (24%ee)	*S*	60%ee
		B[f]			*55 (26%ee)*	*45 (75%ee)*	*R*	*48%ee*
								
2		A	24hrs	50	74 (47%ee)	26 (70%ee)	*S*	53%ee
		B[f]			*52 (34%ee)*	*48 (66%ee)*	*R*	*49%ee*
						 		
3[g]		A	24hrs	90	43 (54%ee)	32 (88%ee) 25 (68%ee)		68%ee[h]

[a]Method A: $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (0.3 mmol)/ rac-BINOL(0.2 mmol)/Diisopropyl D-tartrate (0.3 mmol)
Method B: $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (0.1 mmol)/ (*R*)-BINOL(0.1 mmol)
[b]Determined by ^1H NMR measurement of the crude reaction mixture. [c]Entry 1 determined by GC using a cyclodex-B chiral column. Entry 2 and 3 determined by ^1H NMR and ^{19}F NMR analysis of Mosher's ester derivatives. [d]Determined by GC retention time and ^1H NMR of Mosher's ester derivatives compared to samples using catalyst B. [e]Initial facial selectivity as defined in the text. [f]Data from ref 4b. [g]Olefin isomers distinguished by NOE in ^1H NMR. [h] Configuration not determined.

In conclusion, using chiral poisoning of racemic titanium BINOL complexes, comparable or enhanced enantioselectivity can be achieved relative to catalysts from enantiopure titanium (*S*)-BINOL complexes in the

catalyzed reaction between chloral and olefins. In addition, the poisoning protocol improves the regioselectivity and enantioselectivity in some cases and thereby produces new catalysts which may be more useful than those of the enantiopure catalyst itself (e.g., Table 2, entry 1). These results suggest that chiral poisoning can be a practical alternative and perhaps even a better route for asymmetric reactions[4] in which enantiomerically pure titanium BINOL reagents are appropriate, but not cost effective.

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2. (a) Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789. (b) Brown, J. M.; Maddox, P. J. *Chirality* **1991**, *3*, 345.
3. Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.*, **1996**, *118*, 1217.
4. $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ \ (*S*)-BINOL is highly effective in the asymmetric catalysis of some types of ene reaction. Examples are: (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (b) Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591. The preparation of catalyst and typical reaction procedure are described in (a).
5. An acid-activated aldehyde is sufficiently nucleophilic to add to benzene, see Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211.
6. A prior example where partitioning within diastereomers occurs after an initial irreversible enantioselective step has been observed by Zhang, W.; Lee, N. H.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1994**, *116*, 425.
7. For example, the initial enantioselectivity on C=O (entry 1, Table 1) is:
   67% × 24%ee + 33% × 66%ee = 38%ee
8. A typical catalysis procedure is described. In a predried 3-neck flask being flushed with N_2, 4 Å molecular sieves (500 mg for entry 2 and 3, Table 1; 200 mg for entry 4-6, Table 1) and racemic BINOL (57 mg, 0.2 mmol) were added. Subsequently CH_2Cl_2 (4.3 mL for entry 2 and 3, Table 1; 0.3 mL for entry 4 - 6, Table 1) and diisopropyl *D*-tartrate (1.44 M CH_2Cl_2 solution, 0.21 mL, 0.3 mmol). After 10 min, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (0.6 M toluene solution, 0.50 mL, 0.3 mmol) was also added. The mixture was stirred for 1h before the addition of chloral (0.098mL, 1 mmol). Then the mixture was cooled to -78 °C (dry ice/acetone bath) and isobutylene (~2 mmol) was condensed into the flask. Finally the reaction vessel was placed in a freezer (-23 °C). The work up followed the published procedures.[4a]
9. If poisoning only involves deactivation of one hand of a racemic catalyst, the highest enantioselectivity achievable would be that observed for the enantiomerically pure catalyst. The change of regioselectivity also magnifies the variation in ee. There is evidence (including kinetics) in analogous cases that the intact dimers are the active species (Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; and Takusagawa, F., *Organometallics*, **1994**, *13*, 2218 and references therein). Our results suggest that the enantioselectivity of a heterodimer is different and may even be greater than that of the homodimer. There are, however, proponents of a monomeric active species (Mikami, K.; Terada, M. *Tetrahedron* **1992**, *48*, 5671.)
10. (*S*)-**1** can be obtained >95% ee by reaction of (+)-CpMo(NO)I(methallyl) and chloral. Nguyen, J. T.; Faller, J. W., unpublished (J.T. Nguyen, dissertation, Yale University, 1995).
11. After stirring the catalyst for 1 h, the solvent (i.e., toluene, dichloromethane and some *i*-PrOH) was removed *in vacuo* for 2 h, subsequently 1 mL dichloromethane was added as solvent.
12. Secondary trichloromethyl carbinols can be converted in two steps to α-amino acids which can be crystallized to enantiomerically pure form, see Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.*, **1992**, *114*, 1906.

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