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Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Titanate Complexes with a Tetradentate Ligand

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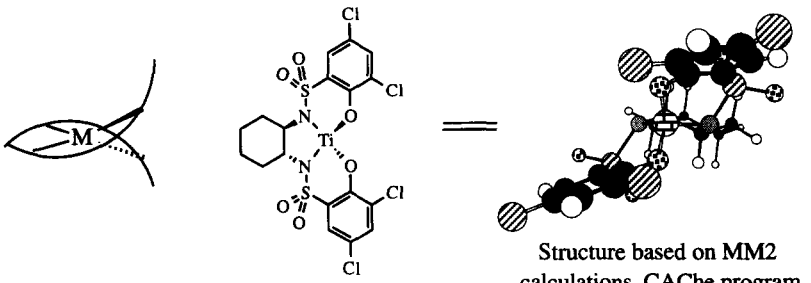
Abstract: *Enantioselective alkylation of aldehydes with Et_2Zn has been studied. This catalytic system employs titanate complexes with a tetradentate helical ligand to facilitate the transformation.*

Many highly enantioselective enzymatic reactions occur in a deeply embedded active site. Substrates enter into this deep chiral pocket and interact with the asymmetric catalytic center through multipoint interactions. In contrast, most synthetic chiral ligands bind through a metal atom, and the chiral environment created in these complexes can be distant from the substrates. To design efficient asymmetric catalysts, we would like to develop metal-ligand systems featuring a deep chiral pocket. Inspired by the helical structure of DNA and α-helical polypeptides, chiral Lewis acid catalysts with a similar helical ligand structure have been designed to facilitate asymmetric carbon-carbon bond formation (Scheme 1).[1] Analogous systems have been investigated for various asymmetric catalytic reactions (e.g., Yamamoto's substituted binaphthol systems,[2] Wulff's vaulted biaryl system[3]). Herein, we introduce a much simpler and readily available ligand system for asymmetric synthesis of carbon-carbon bonds.

Scheme 1

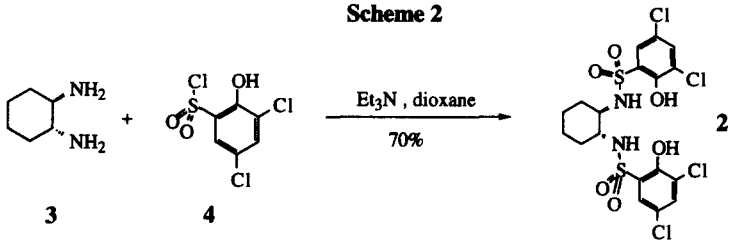


1

Structure based on MM2 calculations, CAChe program

We have chosen a phenolic aromatic sulfonamide as the key cleft-defining group. Because the sulfonamide is acidic (pKa ~ 10), a tetra-anionic version of the ligand can bind with Ti(IV) to form a tetradentate helical structure **1** as shown in Scheme 1. This C_2 symmetric chiral ligand **2** can be easily synthesized by condensation of commercially available (1R, 2R)-(-)-1,2-diaminocyclohexane[4] (**3**) and 3,5-dichloro-2-hydroxybenzenesulfonyl chloride (**4**) (Aldrich) (Scheme 2).

Scheme 2



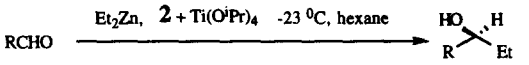
3 4

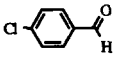
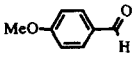
This facile synthesis potentially allows systematic variation of the ligand stereoelectronic properties by changing substituent groups on the aromatic ring. This type of approach has been successfully applied by Jacobsen[5] and Katsuki[6] in the development of asymmetric epoxidation catalysts.

Our first attempts at asymmetric catalysis based on this ligand is the enantioselective alkylation of aldehydes. Several chiral titanate catalysts have been previously discovered which mediate the enantioselective addition of dialkylzinc to aldehydes.[7] Ligand accelerated catalysis occurs in these systems with either chiral disulfonamides[7a-c] or TADDOL[7d-i] as the ligands. Herein, we report an enantioselective alkylation reaction based on the tetradentate ligand **2** (Table1). In this alkylation, good to excellent enantioselectivities (51 to 99% ee) have been realized using 20% of chiral ligand **2**. For benzaldehyde, we can use 5 to 10% ligand and still obtain more than 90% ee (entries 2, 3). For other aldehydes, reducing the ligand amount from 20% to 10% dramatically decreases enantioselectivities. This decrease is probably due to a competition between ligand accelerated catalysis with **2** and nonenantioselective catalysis by $Ti(O^iPr)_4$ or related species. Only using a high percentage of ligand can suppress the nonenantioselective processes. Variation of substituent groups on the aromatic aldehydes used can have a large effect on the enantioselectivity. For example, alkylations of p-methoxylbenzaldehyde and o-methoxybenzaldehyde give only 58% ee (entry 10) and 75 % ee (entry 12), respectively. Alkylation of an alkyl aldehyde proceeds with even lower enantioselectivity (51% ee, entry 16) than alkylation of aromatic and conjugated aldehydes. We were particularly interested in the effect of additional $Ti(O^iPr)_4$ on this addition. Previous studies of a similar catalytic system indicate that excess $Ti(O^iPr)_4$ accelerates the reaction by removing the product alcohol from the catalyst.[7a,i] In our system, the enantioselectivity of the reaction is also influenced by the amount of $Ti(O^iPr)_4$ present.[8] If the molar ratio of $Ti(O^iPr)_4$ to benzaldehyde is reduced from 1.4 to 0.2, the enantioselectivity drops dramatically (from 99 % ee to 4 % ee, entries 1 and 5-7). After mixing equal molar amounts of the ligand **2** and $Ti(O^iPr)_4$, the ^1H NMR spectrum shows a clean pattern with two sets of aromatic protons ($CDCl_3$, δ = 7.56 ppm, d, J = 2.6 Hz; δ = 7.45 ppm, d, J = 2.6 Hz) and the protons from the phenol and sulfonamide have disappeared. This data suggests that the ligand binds Ti(IV) in a tetradentate fashion. Interestingly, we still see the same ^1H NMR spectrum in the aromatic region when the ratio of the ligand **2** to $Ti(O^iPr)_4$ is 1:7 (condition for entry 1). The presence of excess $Ti(O^iPr)_4$ may not change the structure of catalyst precursor, which is produced with equal mole amounts of the ligand and of $Ti(O^iPr)_4$. Without excess $Ti(O^iPr)_4$, the catalytic addition of Et_2Zn to aldehydes is a sluggish process that proceeds with low enantioselectivity (entry 5). Therefore, a possible function of $Ti(O^iPr)_4$ is to participate in transmetallation through interaction with Et_2Zn to form an active titanate alkyl species.

Future studies will emphasize understanding the role that ligand **2** plays in this asymmetric induction and will explore new asymmetric catalytic reactions based on this newly designed tetradentate ligand.

Table 1. Results of the enantioselective addition of Et_2Zn to aldehydes catalyzed by titanate complexes with a chiral tetradentate ligand



entry	Aldehyde (1 equiv)	**2** (equiv)	$Ti(O^iPr)_4$ (equiv)	Et_2Zn (equiv)	Yield	%ee [a]	Config.
1		0.20	1.4	1.8	97	99	(-) S
2		0.10	1.4	1.8	98	99	
3		0.05	1.2	1.2	79	91	
4		0.02	1.4	1.8	56	43	
5		0.20	0.20	1.8	26	4	
6		0.20	0.40	1.8	28	86	
7		0.20	0.80	1.8	99	98	
8		0.20	1.4	1.8	95	99	(-) S
9		0.10	1.4	1.8	83	84	
10		0.20	1.4	1.8	98	58	(-) S
11		0.10	1.4	1.8	61	30	
12		0.20	1.4	1.8	100	75	(-) S
13		0.10	1.4	1.8	67	42	
14		0.20	1.4	1.8	100	75	(-) S
15		0.10	1.4	1.8	100	59	
16		0.20	1.4	1.8	81	51	(+) S
17		0.10	1.4	1.8	50	14	

[a] Determined by HPLC using a CHIRALCEL OD column

Acknowledgements

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Reference and Notes

1. The calculated structure of the titanate complex in Scheme 1 has a tetrahedral geometry, but the actual structure could be more complicated.
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8. Opposite enantioselectivities have been observed in a titanate system with and without excess $Ti(O^iPr)_4$, see 7d; the enantioselectivity is influenced by the amount of $Ti(O^iPr)_4$ in another system, see 7n.

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