Communications to the Editor

The Use of Achiral Ligands to Convey Asymmetry: Chiral Environment Amplification

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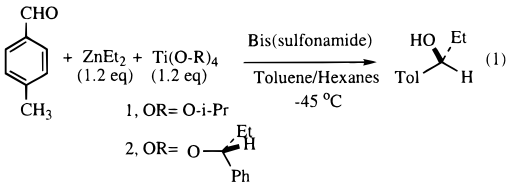
Several highly enantioselective catalysts contain ligands in which the chirality is located far from the metal center (e.g., BINAP,[1] Chiraphos[2] and TADDOLate[3] ligands). The asymmetry is thus extended toward the metal via the phenyl groups,[4] which are conformationally biased by the chiral portion of the ligand. Variation of the achiral groups in such ligands often has a profound impact on the enantioselectivity of the catalyst. In this contribution, we decouple the chiral and achiral portions of the ligand into two separate, yet conformationally dependent, ligands.

This method relies on a chiral ligand and an achiral ligand. The chiral ligand serves as a source of asymmetry but only minimally defines the chiral environment of the catalyst. The chiral ligand interacts with the achiral ligand, causing the latter to preferentially adopt an asymmetric conformation that is largely responsible for defining the chiral environment. Such an interaction serves to transmit *and* amplify the asymmetry of the chiral ligand. A requirement is that the achiral ligand be conformationally flexible so that degenerate conformations of the free ligand become diastereomeric in the coordination sphere of the chiral ligand−metal assembly.

Related strategies have been employed with varying degrees of success. Katsuki used achiral (Salen)Mn(III) complexes and chiral amines[5,6] or amine *N*-oxides[7] in the asymmetric epoxidation. Noyori employed achiral 1,1′-bis(diphenylphosphino)biphenyl with resolved 1,2-diamino-1,2-diphenylethane bound to ruthenium[8] that gave a mixture of diastereomeric catalysts with different reactivities. Our approach differs from these in that we optimized the enantioselectivity of the catalyst by varying the achiral ligands. In doing so, we have observed a change in the enantioselectivity by over 120%.

We have applied this strategy, which we term *chiral environment amplification*, to the asymmetric addition of alkyl groups to aldehydes (eq 1). This process was introduced by Ohno and Kobayashi[9−11] and was applied to a wide range of substrates by Knochel.[12−16] It was proposed[9−11,17] to involve the generation of bis(sulfonamido)Ti(O-*i*-Pr)$_2$ complexes, which were subsequently synthesized and determined to be competent in the asymmetric addition reaction (eq 1).[18]

To better understand the control of asymmetry transfer in this reaction, a series of experiments were performed using achiral (**1**) or chiral (**2**) titanium alkoxide complexes (eq 1, Table 1). When the chiral ligand (*R,R*)-**3** was used with titanium tetraisopropoxide (**1**) according to eq 1, (*S*)-1-(4-tolyl)-propanol was formed in 79% ee (Table 1). The reaction was then performed as above using (*R,R*)-**3**, but with the chiral alkoxide complex (*S*)-**2**. The ee of the (S)-l-(4-tolyl)-propanol was 84%. When the experiment was performed using the enantiomer of the ligand {(*S,S*)-**3**} and titanium alkoxide complex (*S*)-**2**, the (*R*)-enantiomer of the alcohol was formed with 81% ee.[19] Therefore the chiral *trans-bis*(sulfonamide) ligand clearly controls the transfer of asymmetry and the chiral alkoxides have little influence.



This asymmetric addition reaction is an example of ligand-accelerated catalysis, which has important ramification in the following experiments.[20] At −45 °C diethylzinc does not react with aldehydes at an appreciable rate. However the Lewis acidic alkoxide complexes **1** and (*S*)-**2** can promote the alkylation, giving rise to background reactions. Thus, in the absence of bis(sulfonamide) ligands, addition promoted by titanium tetraisopropoxide (**1**) gives racemic alcohol, while chiral titanium complex (*S*)-**2** promoted the addition to give (*S*)-1-(4-tolyl)-1-propanol in 42% ee. The rate of the background reaction relative to the ligand accelerated process can have a significant impact on the ee of the product (Figure 1). After 1 h the background reaction with 4-methylbenzaldehyde promoted by 1.2 equiv of (*S*)-**2** was 12% complete.

Several achiral bis(sulfonamide) ligands were examined in the asymmetric alkylation with (*S*)-**2** (Table 1). With R = 4-*tert*-butylbenzene (**4a**) or R = 4-methoxybenzene (**4b**), *the (R)-configuration of 1-(4-tolyl)-1-propanol was generated in 84 and 78% ee, respectively* [as compared to the background which gave the (*S*)-alcohol in 42% ee (Table 1)]. Thus, by adding these achiral bis(sulfonamide) ligands, the change in ee of the alcohol (Δee) with respect to the background reaction was greater than 120%.

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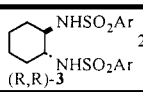
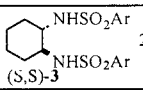
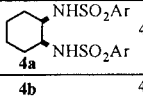
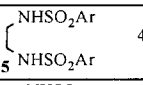
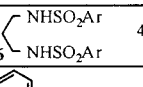
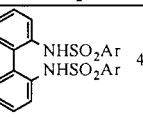
Table 1[a]

$Ti(OR)_4$ R=	Ligand	SO_2Ar Ar=	Conversion (time)	ee (config)
-*i*-Pr	 (R,R)-**3**	2,4-C_6H_3-Me_2	20 (15 min) 63 (60 min)	79 (*S*)
(S)-CHPhEt	(R,R)-**3**	2,4-C_6H_3-Me_2	11 (15 min)	84 (*S*)
(S)-CHPhEt	 (S,S)-**3**	2,4-C_6H_3-Me_2	22 (15 min)	81 (*R*)
(S)-CHPhEt	 **4a**	4-C_6H_4-CMe_3	62 (15 min)	84 (*R*)
(S)-CHPhEt	**4b**	4-C_6H_4-OMe	53 (15 min)	78 (*R*)
(S)-CHPhEt	**4c (4 mol%)**	2,4-C_6H_3-Me_2	15 (60 min)	4 (*S*)
(S)-CHPhEt	**4c (10 mol%)**	2,4-C_6H_3-Me_2	28 (60 min)	32 (*R*)
(S)-CHPhEt	**4d**	1-Naphthyl	11 (60 min)	20 (*S*)
(S)-CHPhEt	**4e**	2,4,6-C_6H_3-Me_3	7 (60 min)	37 (*S*)
(S)-CHPhEt	 **5**	4-C_6H_4-CMe_3	16 (60 min)	22 (*R*)
(S)-CHPhEt	 **6**	4-C_6H_4-CMe_3	16 (60 min)	2 (*R*)
(S)-CHPhEt	 **7**	4-C_6H_4-CMe_3	17 (60 min)	19 (*R*)

[a] 4 mol % ligand was used unless noted. Ee's were determined by GC (30m Supelco β-DEX).

Ligands **4c**−**e**, which contained larger aryl groups, resulted in smaller Δee values (Table 1). Addition of bis(sulfonamide) ligands derived from 1,2-diaminoethane (**5**), 1,3-diaminopropane (**6**), and 2,2′-diaminobiphenyl (**7**) resulted in ee's of 22, 2, and 19% with the (*R*)-enantiomer predominating in each case (Table 1). The product alkoxide is incorporated into the catalyst, resulting in ee's that change over time. For this reason, the ee's in Table 1 are reported at low conversion.

The ee's of products in reactions which exhibit ligand accelerated catalysis[20] reflect not only the enantioselectivity of the catalyst but also the turnover frequency (TOF). The background reaction can be competitive with the ligand-accelerated pathway if the ligand acceleration is low. Under these conditions the background reaction can make a substantial contribution to the ee of the product (Figure 1). However, **4a** and **4b** gave the same ee at 4 and 10 mol % ligand, indicating that the reaction catalyzed by the ligated titanium complex was much faster than the background reaction. In contrast, **4c** gave 4% ee (*S*) at 4 mol% and 32% ee (*R*) at 10 mol%. Thus low ee's may reflect catalysts that exhibit only modest degrees of ligand acceleration or low inherent enantioselectivities.

We believe the *meso*-diaminocyclohexane is particularly good at amplifying the chirality of the alkoxides for several reasons. First, the two static chair conformations of the free ligand are enantiomers which interconvert by cyclohexane ring flip (Scheme 1). Second, coordination of the ligand to the chiral alkoxide−metal assembly results in desymmetrization of the ligand. Furthermore, we have shown that coordination of the sulfonyl-oxygens to titanium is important in the solid-state structures of the bis(sulfonamido)Ti(O-*i*-Pr)$_2$ complexes derived from *trans*-1,2-diaminocyclohexane and may be important in the transition state of the addition.[18] Once the ligand is bound to the Ti(OR*)$_2$ fragment, the sulfonyl oxygens are rendered inequivalent. Upon coordination of the sulfonyl oxygens to titanium, the sulfurs become stereogenic centers, thus extending the chiral environment. These features make ligands derived from *meso*-1,2-diaminocyclohexane particularly adept at amplifying the chiral environment.

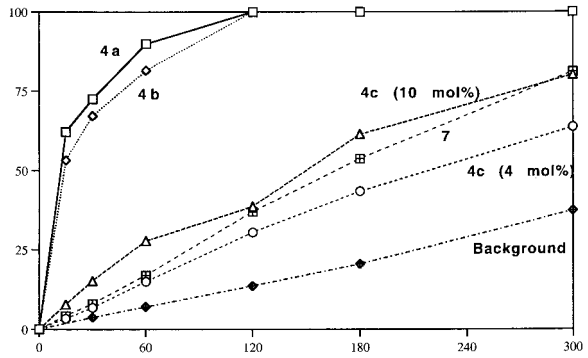
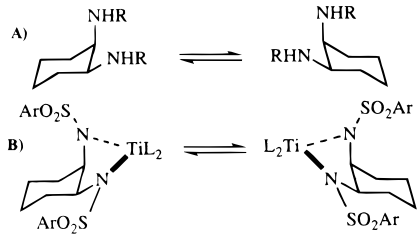


Figure 1. Conversion (%) vs time (min) for **4a**−**d** and **7**.

Scheme 1[a]



[a] (A) The enantiomers of *cis*-1,2-diaminocyclohexane interconvert through ring inversion. (B) Likewise, when L is achiral, the two enantiomers interconvert in a similar fashion. However, if L is chiral, the two structures are diastereomeric and have different energies. (Sulfonyl coordination not shown.)

Chiral environment amplification is a modular approach to asymmetric catalysis. It involves catalyst modification using combinations of chiral ligands and achiral amplifying ligands and is amenable to facile high throughput screening. We are currently applying this technique to other systems.

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Supporting Information Available: Characterization of **2**−**7** and the details of the asymmetric additions are outlined (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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