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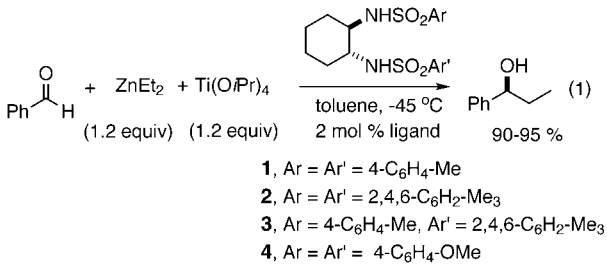

Probing the Conformation of Flexible Catalysts in Solution**

Jaume Balsells, Juan M. Betancort, and Patrick J. Walsh*

Understanding the origins of enantioselectivity in catalytic asymmetric reactions is of special interest because of the magnitude of the impact of enantioselective synthesis on the pharmaceutical industry.[1] However, before delineating the subtle interactions between catalyst and substrate that are responsible for the degree of enantiofacial differentiation, more fundamental questions concerning the operation of the catalyst must be addressed.[2] Knowledge of the parameters which govern the reactivity of the catalyst including the order in the catalyst and reagents, the location of the catalytically active binding site, and the shape of the chiral pocket are essential to relate enantioselectivity data to catalyst – substrate interactions. In catalysts with rigid, well-defined structures possessing limited conformational freedom, such studies are less complicated. However, in many highly enantioselective processes, the chiral environment of the catalyst is dynamic and the enantioselectivities are dependent on the complex interplay of conformational mobility and catalyst – substrate interactions.[2] Herein we examine one such system, the asymmetric addition of alkyl groups to aldehydes with bis(sulfonamide) ligands [Eq. (1)]. We present evidence that indicates that the bis(sulfonamido) ligand adopts a C_2-symmetric conformation in the active form of the catalyst.

The asymmetric addition reaction [Eq. (1)] was developed by Ohno, Kobayashi, and co-workers.[3, 4] Its broad utility and excellent enantioselectivities with a wide range of aldehydes and organozinc reagents were demonstrated by Knochel and co-workers.[5–10] The mechanism of this efficient process was proposed to involve the in situ formation of bis(sulfonamido)titanium complexes.[3, 4, 11, 12] We subsequently reported the synthesis and structures of these species and determined that they perform analogously to the catalyst generated in situ [Eq. (1)].[12] In the solid-state structures of bis(sulfonamido)-titanium complexes complexes (Figure 1), we found that one oxygen atom from each sulfonyl group was coordinated to the titanium center. Coordination of the sulfonyl oxygen atoms to the titanium center could serve to define a more rigid asymmetric environment and may be important in the transfer of asymmetry in the transition state of the asymmetric addition reaction. To explore this possibility, it is necessary to determine the conformation of the bis(sulfonamido) ligand in the active catalyst. Two independent approaches based on structure – enantioselectivity studies were devised to accomplish this goal.

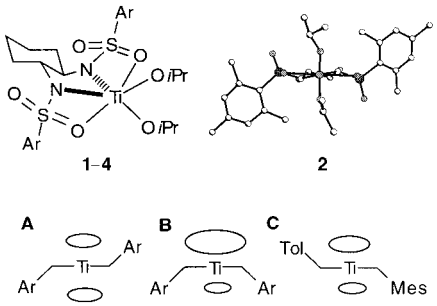

Figure 1. Drawing of the titanium complexes with ligands **1** – **4** (left); the molecular structure with ligand **2** (right) and representations of the titanium complexes with ligands **1** – **4** in the C_2-symmetric *anti* conformation (**A**) and the *syn* conformation (**B**); the pseudo C_2-symmetric conformaton with ligand **3** (**C**).

Two limiting conformations of the bis(sulfonamido) ligand bound to titanium can be envisioned. The first is the C_2-symmetric conformation seen in the crystal structures, where the aryl groups are positioned *anti* to each other (Figure 1, **A**). In the second limiting conformation, the aryl groups are *syn* to each other (Figure 1, **B**, to simplify the discussion, the conformations are abbreviated with line structures). The C_2-symmetric conformation (**A**) has two equivalent binding sites on the titanium center, which are represented by the ovals in Figure 1. In the catalyst formed from ditolyl ligand **1** [Eq. (1)], we would expect these binding sites to be more accessible

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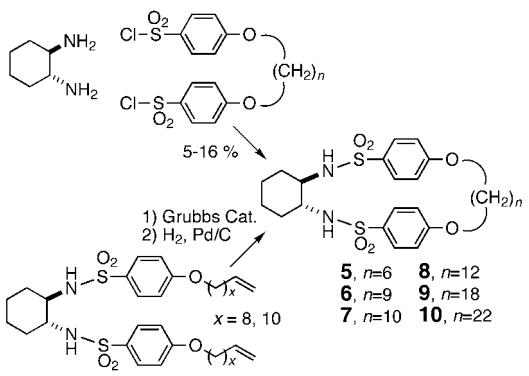
than those of the dimesityl ligand **2** since the mesityl groups are larger. In the *syn* conformation of the ligand (Figure 1, **B**), the two binding sites are inequivalent with the binding site opposite the aryl rings being more available.

We have examined the enantioselectivity and reactivity of catalysts derived from ligands **1** and **2** [Eq. (1)]. The ditolyl ligand **1** has a high turnover frequency (TOF) and exhibits excellent enantioselectivity. By using the conditions outlined [Eq. (1)], the reaction with **1** was complete in 15 min and produced the alcohol in 97% enantiomeric excess (*ee*). Under identical conditions, the reaction catalyzed with the dimesityl ligand **2** was 84% complete after 8 h and generated the alcohol in 3% ee. The disparity in enantioselectivity and efficiency between these two similar ligands is remarkable.

In an effort to differentiate between conformations **A** and **B**, we prepared an unsymmetrical ligand which contains tolyl and mesityl groups [**3**, Eq. (1)]. If the ligand adopts a pseudo C_2-symmetric conformation (Figure 1 **C**) the two binding sites on this complex will be inequivalent and operate independently. Therefore, in the tolyl–mesityl ligand **3**, the binding site next to the tolyl group is expected to behave like the ditolyl ligand. Likewise, it is anticipated that the binding site near the mesityl group would react like the dimesityl catalyst **2**. Thus, the reaction at the site near the mesityl group should give low enantioselectivity and be slow, while the reaction at the site proximal to the tolyl group should give high enantioselectivity and be fast. If the catalyst adopts a pseudo C_2-symmetric conformation (**C**) the reactivity of the tolyl–mesityl ligand is expected to be dominated by the site near the tolyl group and the enantioselectivity should be similar to ditolyl ligand **1**. If the conformation of the bound ligand is *syn* (**B**) in the active catalyst, it is anticipated that the enantioselectivity of the catalyst derived from **3** would lie between the ditolyl and dimesityl ligands. In the asymmetric addition reaction [Eq. (1)] the tolyl–mesityl ligand **3** gave 1-phenyl-1-propanol in 91% *ee*. The high enantioselectivity of the catalyst formed from **3** suggests that the catalysts derived from **1** and **3** are similar. It is also likely that the two binding sites operate independently and the aromatic groups are oriented in a C_2-symmetric fashion in the transition state.

The second set of experiments involved the synthesis and evaluation of conformationally constrained cyclic bis(sulfonamide) ligands (Scheme 1). By linking the aryl groups together with a short tether, the conformation of the bound ligand is restricted to **B** (see Figure 1). If the ligand in the nontethered catalyst were to assume conformation **B** in the transition state, ligands with short tethers would show similar reactivity and enantioselectivity profiles to ligands with longer chains and to open-chain ligands. If the C_2-symmetric conformation is preferred by the nontethered ligands, ligands with short tethers would exhibit markedly different behavior to those with longer chains.



Scheme 1.

We have synthesized a series of macrocyclic ligands with carbon-based tethers consisting of 6, 9, 10, 12, 18, and 22 methylene units by two synthetic approaches (Scheme 1). The preparation of the ligands **5** ($n=6$), **6** ($n=9$), **7** ($n=10$), and **8** ($n=12$) was accomplished by high-dilution techniques. The longer chain analogues **9** ($n=18$) and **10** ($n=22$) were prepared by ring-closing metathesis with the Grubbs catalyst,[13] which proved to be superior (22–35% yield) to the high-dilution approach.

The reactivity and enantioselectivity of the tethered ligands was compared to the non-tethered ligands (Table 1). The use of the 4-methoxybenzene derivative **4** [Eq. (1)] gave fast reactions and high enantioselectivity (98% *ee*), which indicates that electronic effects caused by electron-donating OR groups are small.

Table 1. Enantioselectivities and percent conversions with ligands **1** and **4**–**10** (2 mol%) with the *R*,*R* configuration in Equation (1)..

Ligand	**1**	**4**	**5** $n=6$	**6** $n=9$	**7** $n=10$	**8** $n=12$	**9** $n=18$	**10** $n=22$
conv. [%] $t=1$ h	100	100	21.6	32.1	39.8	61.3	73.7	97.4
conv. [%] $t=3$ h			57.3	66.6	70.8	80.0	100	100
ee	97	98	−10	25	19	38	76	89
(config)	(*S*)	(*S*)	(*R*)	(*S*)	(*S*)	(*S*)	(*S*)	(*S*)

The results of the asymmetric addition clearly indicate that when the tether is short, the resultant catalysts exhibit low enantioselectivity and significantly lower TOFs than their nontethered counterparts (Table 1). In the most extreme case, where the catalyst is strictly constrained to the *syn* conformation (**5**, $n=6$), the sense of enantioselectivity was *reversed* and the *R* enantiomer of the alcohol narrowly predominated. As the length of the tether is extended, the catalyst reactivity approaches that of the acyclic ligands in both enantioselectivity and TOF. A slightly anomalous, but reproducible behavior in the enantioselectivities of **6** and **7** was noted.

The data in Table 1, together with the enantioselectivity of the unsymmetrical ligand **3**, suggest that bis(sulfonamido) ligands that are highly enantioselective are bound to the catalyst in a C_2-symmetric conformation in the transition state of the asymmetric addition reaction. It is then likely that the ligand is maintained in this conformation by the coordination of one of the diastereotopic oxygen atoms of each sulfonyl group to the titanium center. The resulting seven-coordinate titanium is bonded to the bis(sulfonamido) ligand, two alkoxide groups, and the substrate aldehyde. Although titanium species with coordination numbers above six are less common, we have recently isolated and characterized four eight-coordinate complexes of titanium bearing bis(sulfonamido) ligands.[14] It is also conceivable that the catalyst

derived from ligand **2**, with its bulky mesityl groups, cannot achieve a C_2-symmetric conformation in the enantioselectivity-determining step. Thus, a possible explanation for the low enantioselectivity of **2** might be that it adopts a *syn* conformation (Figure 1 **B**).

The use of asymmetric Lewis acid catalysts bearing sulfonamido-based ligands is becoming more prevalent. In several of these systems, it is likely that the coordination of the sulfonyl oxygen atoms to the metal center plays an important role in defining the chiral environment of the catalyst,[15–17] as it does with the titanium bis(sulfonamide) system. The experiments outlined here will be useful in understanding transfer of asymmetry in these, and other, systems (full experimental details can be found in the Supporting Information).

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A Three-Step Synthesis of Halomon

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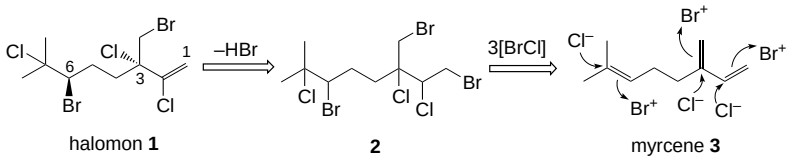
Halomon (**1**), which was isolated from the red algae *Portieria hornemannii*,[1] is a member of a novel class of antitumor agents with selective cytotoxicity against various tumor cell lines (see Scheme 1).[2] Detailed studies on the biological activity of **1** have been hampered due to its limited accessibility. Halomon (**1**) is a small molecule that can be easily synthesized; however, the presence of five halogen atoms on the acyclic carbon chain has created a number of difficulties for regio- and stereocontrolled synthesis.[3, 4] We report herein a very short and straightforward synthesis of **1**.

A close inspection of the structural features of **1** indicates a Markovnikov-type arrangement of Cl^- and Br^+ on the myrcene skeleton.[1] We expected that **1** could be synthesized by three successive Markovnikov-type bromochlorinations of myrcene (**3**) followed by elimination of hydrogen bromide from the intermediate **2** (Scheme 1). Tetraalkylammonium dichlorobromate (R_4NBrCl_2) should be the reagent of choice for this halogenation.[5] Myrcene (**3**) was first treated with excess Bu_4NBrCl_2 to obtain **2**, but this resulted in formation of a complex mixture. A stepwise bromochlorination reaction was then investigated. When **3** was treated with one equivalent of Bu_4NBrCl_2 in CH_2Cl_2 at 0 °C, the trisubstituted double bond of **3** instead of the conjugate diene was bromochlorinated to yield **4** (Table 1) in an excellent example of Markovnikov selectivity (> 43:1) (Scheme 2).[6, 7] This exclusive formation of **4** is remarkable because 2-methyl-2-butene was reported to give a 2.4:1 mixture of regioisomers under similar reaction conditions.[5b] It is likely that in the present case the attack of chloride ion on the less substituted C6 center of a bromonium-like intermediate could be hindered by the long and branched alkenyl substituent at C6. Therefore, the electronically favored attack of chloride ion on the more substituted C7 would become overwhelming. The regioselectivity of reactions of alkenes with Bu_4NBrCl_2 was found to be sensitive to the steric effect of the alkyl substituents.[5b] The high selectivity for **3** was not affected by temperature (−78 °C or 0 °C) nor by alkyl substituents on



Scheme 1. Retrosynthetic scheme for the synthesis of halomon (**1**) from myrcene (**3**).

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