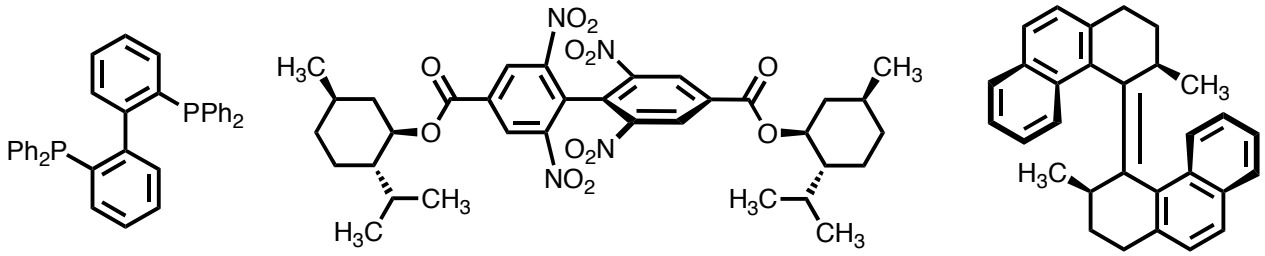
CHIRAL CONFORMATIONAL MANIFOLDS: HARNESSING HIDDEN ASSYMMETRY

Reported by: Michael J. Evans 1 October 2009

INTRODUCTION

The interplay between chirality and conformation is subtle. Although the vast majority of molecular conformations are chiral, organic chemists have only recently begun to appreciate conformational factors in the development of new asymmetric catalysts and useful molecular machinery. For the purpose of discussing applications of chiral conformations, it is convenient to identify three types of molecules that differ in their conformational symmetry properties (Figure 1): 1) those that racemize through an achiral intermediate, such as BIPHEP, 2) those that racemize via a fully chiral pathway ("rubber glove" molecules, *vide infra*), and 3) those with persistent but interconvertible diastereomeric conformations (e.g. molecular motors). These three classes represent a relatively untapped source of asymmetry and have been used to shed light on the relationship between chirality and conformation.

Figure 1. Three Classes of Molecules with Useful Chiral Conformations



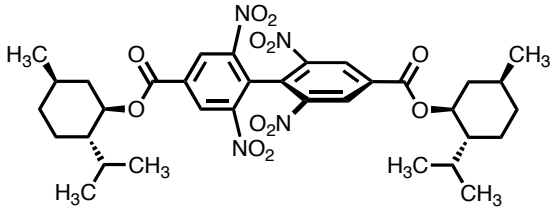
Class 1 **Class 2** **Class 3**

This relationship has not always been on as firm ground as it is today. In the early 1950s, chemists engaged in debate about the origin of optical inactivity of meso compounds, asking whether optical inactivity should be ascribed to "internal compensation" of rotation by mirror-image structures within individual molecules, or to "external compensation" by one molecule for the optical rotation of another (its conformational enantiomer)[1]. Proponents of "internal compensation" did not appreciate that only a miniscule percentage of the molecules in meso compounds are in symmetric conformations. In fact, Mislow suggested in 1954[2] that an achiral conformation is not a strict requirement for optical inactivity, as long as all the chiral conformations of a molecule are in the presence of equal amounts of their enantiomers. The synthesis and characterization of an optically inactive molecule with only chiral

conformations dealt a deathblow to advocates of "internal compensation," because it demonstrated that optical activity was a property of bulk compounds and their entire accessible conformational manifolds, *not* individual molecules.

Mislow[3] reported the first example of such a molecule in 1955, **1** (Figure 2). He dubbed the molecule a "rubber glove" because any conformation can be converted into its enantiomer via a fully chiral pathway, much like a rubber glove can be turned inside out to convert it to its opposite hand without the intervention of an achiral structure. Since Mislow's seminal result, he and others have published studies of several other "rubber glove" molecules, some of which are listed in Chart 1[4,5,6]. Catenane **4** represents a particularly interesting case because it cannot be topologically deformed into an achiral structure (unlike **1**-**3**). This catenane represents the first example of a topological rubber glove, for which an achiral racemization pathway cannot even be conceived without the breaking of bonds. An open problem in topological chemistry is measurement of the racemization barrier of a topological rubber glove—in the case of Chambron's catenane, racemization via rotation of the naphthyl moiety has proven too rapid to measure[7].

Figure 2. Chemically Achiral Molecules with Only Chiral Conformations



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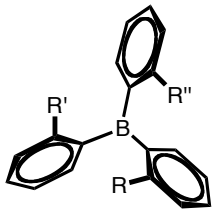

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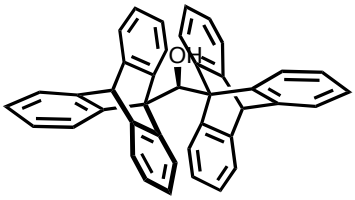

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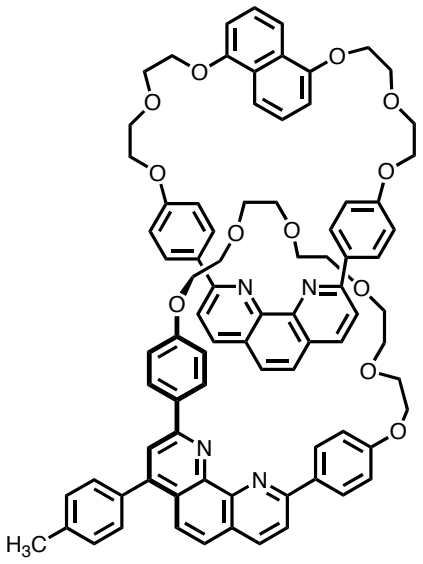

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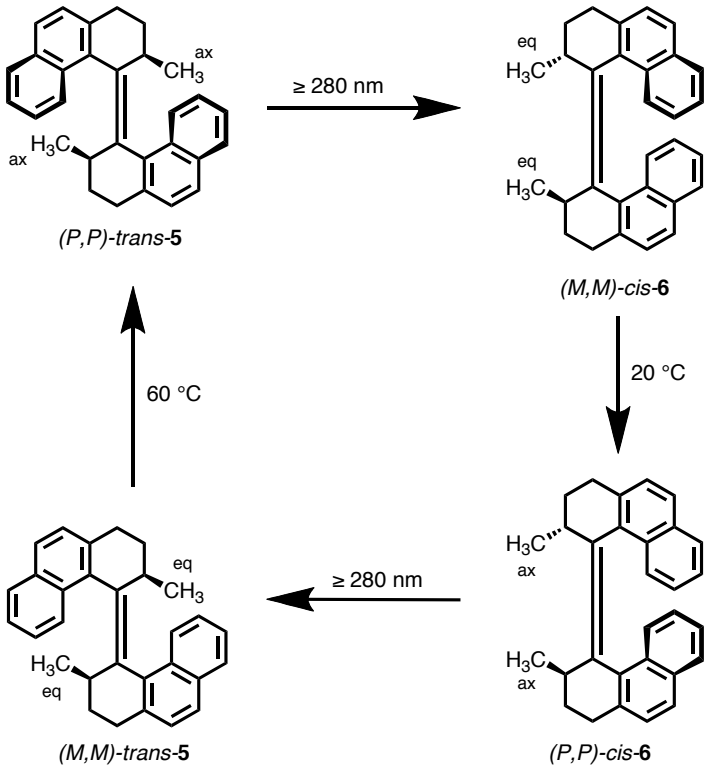
ASYMMETRY IN MOLECULAR MOTORS

Although rubber gloves represent a fascinating class of molecules from the perspective of molecular topology, their practical utility is limited because they behave essentially as achiral molecules in the absence of chiral media—racemization is so rapid that resolution of rubber-glove enantiomers is impossible. More interesting are Class 3 species (see Figure 1) whose chiral conformational manifolds could potentially be exploited to do useful work on the nanomolecular scale (molecular motors). A great deal of recent research has focused on designing and improving this class of molecules.

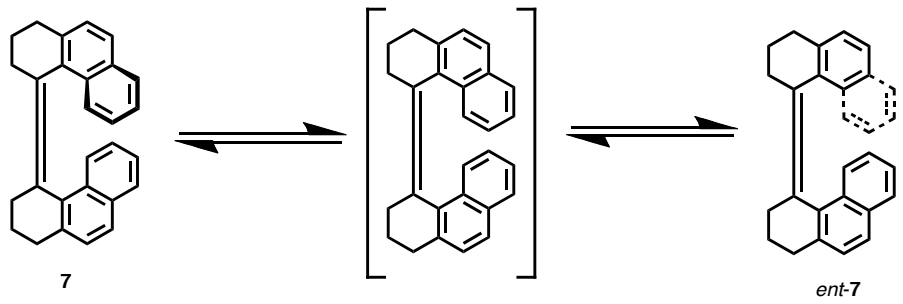
ATP synthase[8] is nature's prototypical example of a molecular motor. A chiral, helical proton gradient drives the unidirectional rotation of a rotor subunit, which induces conformational changes in the enzyme that trap ADP and phosphate and release ATP. Inspired by nature's example, chemists have devised small-molecule motors that rely on a much smaller chiral element to enforce unidirectional rotation. In 1999, the Feringa group demonstrated this concept for the first time[9] (Scheme 1).

Scheme 1. The First Light-driven Unidirectional Molecular Motor



The design of this system relied on two primary control elements: the rapid, reversible photoisomerization of double bonds and the preference of the methyl groups to adopt axial orientations for steric reasons. Photoisomerization forces the methyl groups equatorial as one set of rings rotates with respect to the other, and a thermodynamically favored conformational change places the methyl groups in axial positions and inverts the helicity of the structure. From the view of the bottom ring, the top ring undergoes a full 360° clockwise rotation after two cycles of photoisomerization and conformational relaxation. Importantly, all four "stages" of the motor are chiral and diastereomeric. If an achiral structure were present along the rotational pathway, rotation of the top ring with respect to the bottom ring would generate enantiomeric structures in equal amounts, leading to uncontrollable bidirectional rotation (Scheme 2). The methyl groups serve the dual purpose of rendering the rotational pathway free of an achiral intermediate and fixing the direction of rotation.

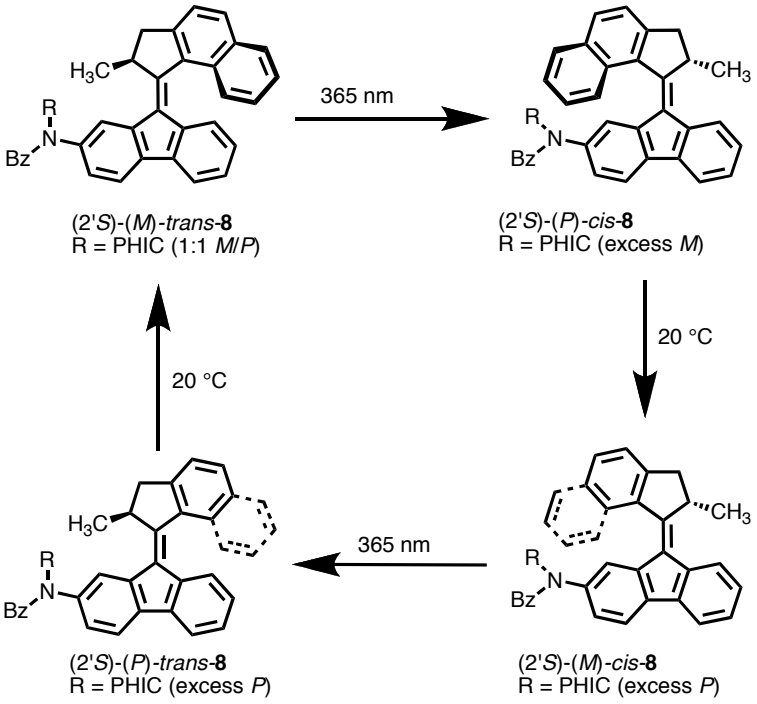
Scheme 2. Bidirectional Rotation Facilitated by an Achiral Intermediate



In an early example of molecular motors doing extended work, Feringa used a similar system to control the helicity of an appended poly-*N*-hexyl-isocyanate (PHIC)

polymer[10] (Scheme 3). CD spectroscopy showed that (2'*S*)-(*M*)-*trans*-**8** contained a 1:1 mixture of PHIC polymers with (*M*) and (*P*) helicity. Upon irradiation, (2'*S*)-(*M*)-*trans*-**8** was converted into (2'*S*)-(*P*)-*cis*-**8**, and the proximal aryl rings enforced *M* helicity in the nearby PHIC polymer. After thirty minutes, this unstable diastereomer underwent helix inversion to give (2'*S*)-(*P*)-*cis*-**8**, which contained an excess of (*P*)-PHIC. A second cycle of photoisomerization and thermal helix inversion returned **8** to its original state. Again, in this case, no achiral structure is present along the rotational pathway, and equilibration of enantiomers (which would have likely complicated the motor's control of PHIC helicity) does not occur.

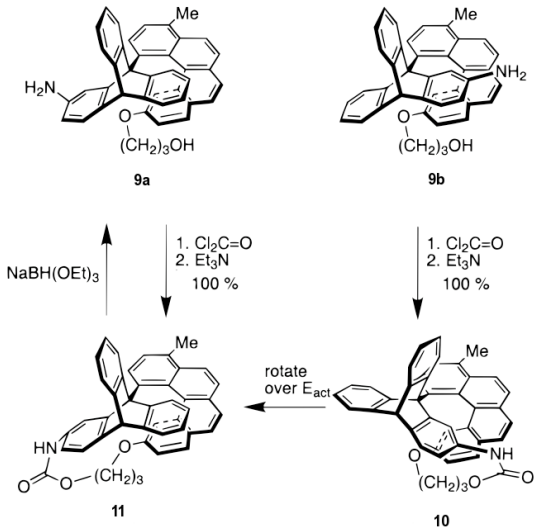
Scheme 3. Motor Control of Polymer Helicity



Kelly developed a chemically driven, unidirectional, single-cycle molecular motor whose direction of rotation is enforced solely by axial chirality[11] (Scheme 4). The motor is "powered" by the chemical energy of phosgene, which mediates urethane formation between the triptycene rotor and the tetraaryl stator. The carbamate **11** represents a thermodynamic minimum, so unidirectional motion is irreversible. However, the conversion of **9a** to **9b** is slow and reversible, so the motor is essentially a single-cycle engine. Efforts to develop a continuous motor with three "firing" substituents on the triptycyl moiety have not yet borne fruit, although some methodology has been developed towards this end[12].

Although it is possible to envision a pathway from **10** to **11** involving an achiral structure, such a pathway is unlikely. An achiral conformer of **10** would demand planarity of the helicene, triptycene, tether, and carbamate, which may not be feasible due to steric constraints. In addition, considerations of microscopic reversibility show that rotation away from such a structure in either direction would necessarily involve equienergetic, enantiomeric rotamers. Spontaneous evolution of diastereomers **10** and **11** from enantiomeric rotamers is not possible in the absence of another chiral molecule, because it represents the creation of an energy difference (between diastereomers) in the absence of a source of energy (a separate chiral, non-racemic species).

Scheme 4. Kelly's Chemically Driven, Unidirectional, Single-cycle Motor

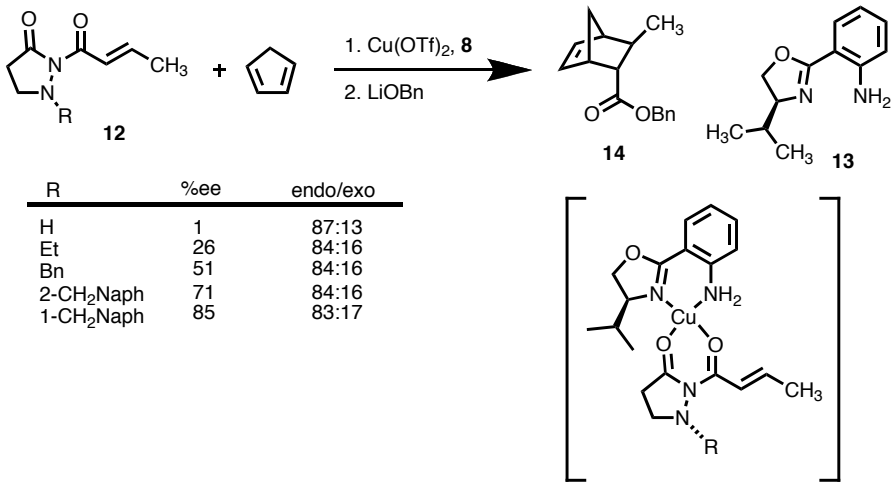


CHIRAL CONFORMATIONS OF ACHIRAL ADDITIVES IN ASYMMETRIC CATALYSIS

Transfer of asymmetry from a chiral ligand to an achiral substrate forms the basis of enantioselective catalysis. In theory, a similar transfer of asymmetry could be achieved from an achiral additive that adopts a chiral conformation upon binding to a chiral catalyst. "Freezing out" chiral conformations of achiral ligands has the potential to generate a massive library of new asymmetric catalysts without the requirement of complicated synthetic sequences or extra resolution steps.

Early work towards this concept was carried out by Sibi[13] during studies of the Diels-Alder reaction of acylpyrazolidinones with cyclopentadiene in the presence of catalytic C_1-symmetric oxazoline **13** and copper(II) triflate. Upon binding, the acylpyrazolidinone substrate **12** adopts a chiral conformation in which the relay group R blocks the *Re* face of the double bond, leading to high enantioselectivity in the presence of bulky relay groups (Figure 3). In subsequent studies of radical conjugate addition to enones[13], the use of Lewis acids with tetrahedral and octahedral geometries, which place the substrate approximately orthogonal to the plane of the chiral ligand, led to reversal of enantioselectivity.

Figure 3. Asymmetry Relay by an Achiral Acylpyrazolidinone



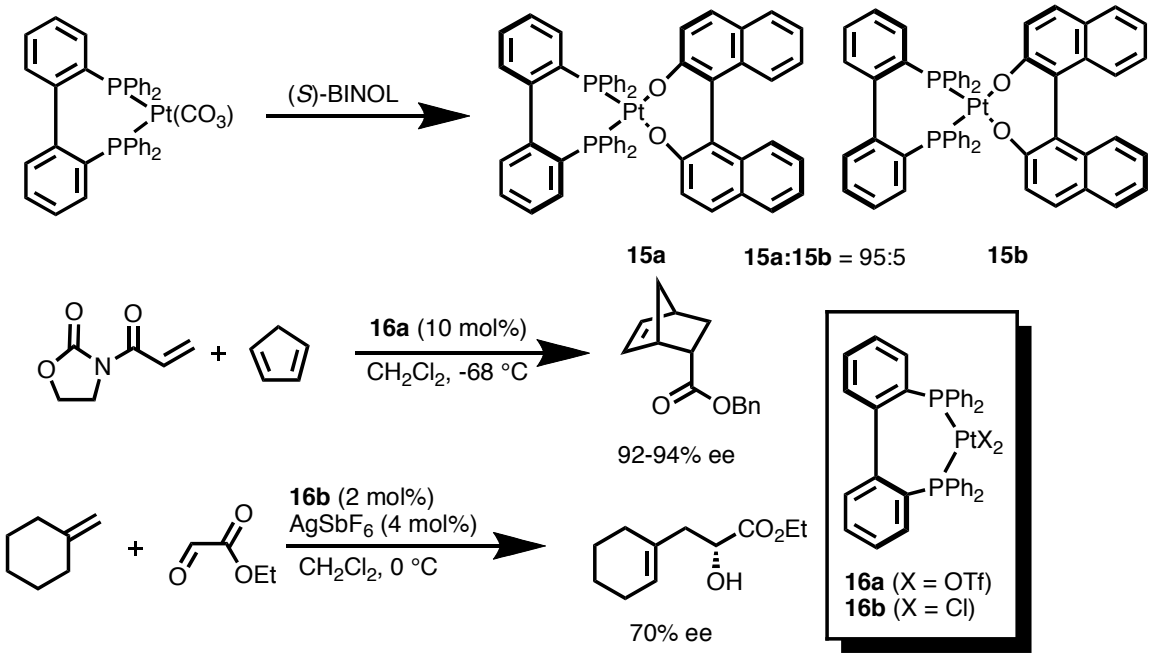
R	%ee	endo/exo
H	1	87:13
Et	26	84:16
Bn	51	84:16
2-CH_2Naph	71	84:16
1-CH_2Naph	85	83:17

The requirement of rather specialized acylpyrazolidinone substrates was a significant disadvantage of the above method. A more generalizable approach, which relied on a chiral catalyst prepared from a separate achiral additive, was adopted by Gagné for Diels-Alder and glyoxylate

ene reactions[15]. Treatment of racemic (BIPHEP)$PtCO_3$ with enantiopure (*S*)-BINOL generated a 95:5 mixture of δ and λ diastereomers **15a** and **15b** (Scheme 5). Nonbonding interactions in **15b** destabilized it relative to **15a**, allowing efficient "trapping" of the chiral BIPHEP conformation in **15a**.

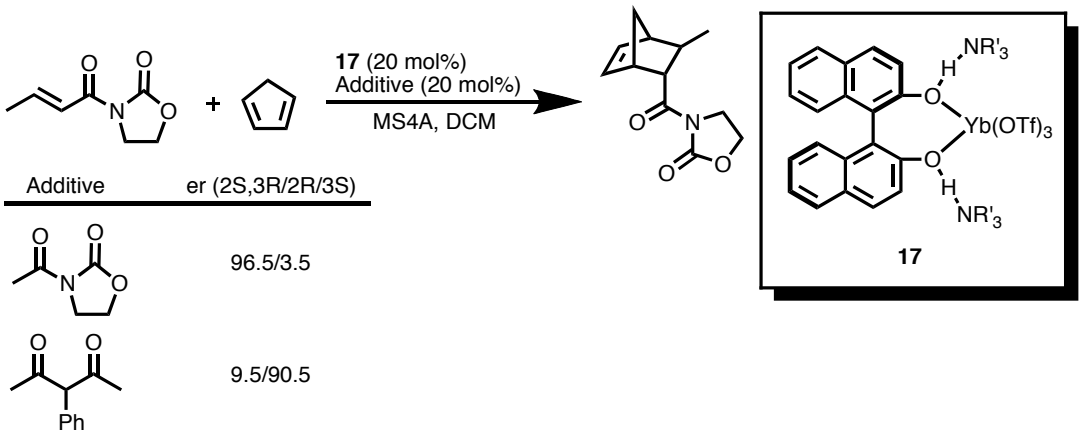
Treatment of enantiopure **15a** with HCl generated **16b**, a catalyst whose only chiral element was the originally achiral BIPHEP moiety. Application of derivatives of this catalyst to the Diels-Alder and glyoxylate ene reactions led to products in high enantiomeric excess (Scheme 5). Previous methods employing BINOL-based catalysts gave only limited selectivity for the glyoxylate ene reaction[16]. Other examples of achiral, atropisomeric ligands that can be resolved by coordination to metal-BINOLate complexes include Vallée's BIPOL ligands[17] (titanium-based) and Doherty's NUPHOS ligands[18] (platinum-based).

Scheme 5. Applications of a Chiral Catalyst Derived from an Originally Achiral Ligand



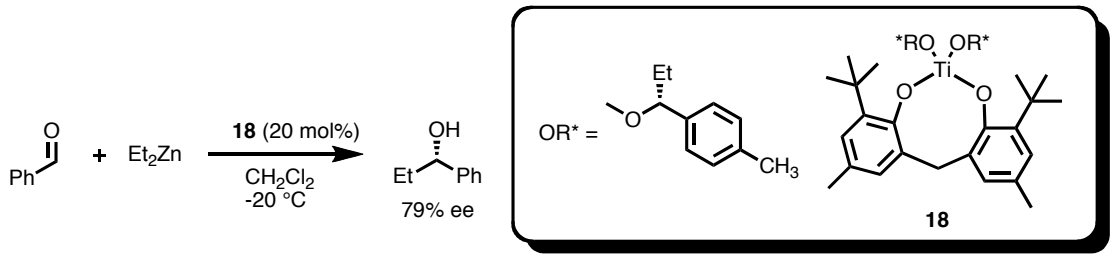
The above examples rely on a chiral catalyst to fix the conformation of an achiral additive when the latter binds to the catalyst. Perhaps the most stunning application of this idea was demonstrated long before the above results. While investigating the ytterbium-catalyzed Diels-Alder reaction of crotonyl oxazolidinones with cyclopentadiene, Kobayashi discovered[19] that two different achiral additives led to different senses of enantiofacial control *from the same enantiomer of chiral catalyst* **17** (Figure 4). He tentatively rationalized this result by considering the coordination environment of ytterbium and noting the transfer of asymmetry from BINOL to the hydrogen-bound amines. The presence of additive affects the site on the catalyst to which the substrate binds, and the two available sites exhibit opposite senses of enantiofacial control.

Figure 4. Enantioselectivity Reversal upon Change of Achiral Additive



Geometric changes brought on by the binding of a substrate to a metal center have also been used to generate highly selective catalysts from achiral additives[20] (Figure 5). Binding of aldehyde to the chiral titanium catalyst **18** (generated from $Ti(OR^*)_4$ and achiral bisphenol) changes the geometry of the catalyst from tetrahedral to trigonal bipyramidal. Changing the substituents on the bisphenol ligand had a strong impact on enantioselectivity, indicating that the achiral ligand played an important role in the transfer of asymmetry.

Figure 5. Geometry-induced Ligand Asymmetry



Feringa[21] and Reetz[22] have recently employed achiral phospine additives in combinatorial approaches for the development of enantio- and diastereoselective hydrogenation catalysts. Both observed an increase in enantioselectivity and conversion upon addition of triphenylphosphine, a propeller-shaped molecule that becomes locked in a chiral conformation upon catalyst binding. Combinatorial approaches to chiral catalyst design involving achiral ligands have the potential to rapidly identify highly selective catalysts.

CONCLUSIONS

Applications of chiral conformations to molecular topology, molecular machines, and asymmetric catalysis promise to remain fascinating research areas in organic chemistry in the future. After Mislow's seminal work delineating the origin of optical activity and demonstrating the subtle interplay between chirality and conformation, a number of molecular topologists have illuminated the

link and expanded the number of academically intriguing "rubber glove" molecules. Feringa's light-driven molecular motors have exploited chirality as an enforcer of rotational direction. In the field of asymmetric catalysis, a number of chemists have demonstrated myriad ways to harness the asymmetry present in chiral conformations of ordinarily achiral molecules, potentially simplifying the process of screening ligands for asymmetric reactions. Challenges remain, however, as the capacity of molecular motors to do useful work is still limited and examples of achiral additives in asymmetric reactions possess limited scope.

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