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Conformationally Driven Asymmetric Induction of a Catalytic Dendrimer

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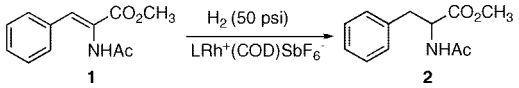
The exquisite selectivity realized by enzymes relies on the dynamic conformational properties produced by molecular folding to communicate structural information over large distances to the active site. In contrast, synthetic catalysts generally depend on static, proximal structural information for selectivity.[1] The quest for truly biomimetic molecules that exploit a chiral, folded secondary structure in asymmetric catalysis[2] remains as an unrealized objective in the search for function in abiological systems.[3] Achieving this objective would minimally require the amplification and relay of local stereochemistry to the reactive/catalytic site via an intervening secondary structure. Although the branched, macromolecular structure of a dendrimer offers unique potential to replicate the microenviroment of an enzyme active site,[4] reports of rate enhancements or even modest increases in selectivity by dendrimers with catalytic cores are rare.[5] These enhancements have been attributed to polarity changes or substrate preconcentration within the microenvironment of the dendrimer.[6] The design of dendritic catalysts that function by noncovalently propagating chiral information to a catalytic site represents a particularly challenging objective, which has not yet been achieved.[7] Here, we show how remote chirality within a dendritic catalyst can be relayed over 14 bonds to control the enantioselectivity of a prototypical reaction.

To explore the potential for a conformationally dynamic molecule to transmit remote chirality to a catalytic process, we presented a pair of first-generation dendrons at the 3 and 3′ positions of a 2,2′-bis(diphenylphosphinoxy)biphenyl scaffold (Figure 1). These dendrons exist in highly mobile helical conformations that are capable of expressing local chirality at the termini as an *M* or *P* helical bias.[8] Likewise, the conformational lability of the biphenyl core,[9] and that of the corresponding nine-membered rhodium chelate,[10] permits a rapid interchange between the two forms of axial chirality. Accordingly, dendritic precatalysts **C2**−**C4** interconvert among a minimum of six diastereomeric conformations. The efficacy of these molecules as asymmetric catalysts requires a delicate balance between flexibility, needed to communicate remote chirality to the catalytic site via this conformational interchange, and structural integrity during the entire catalytic process.

[Dend]Rh$^+$ precatalyst **C2** was composed of dendrons displaying (*S*)-(1-methoxypropan-2-yl)-2-acylaminobenzoate termini. Application of this precatalyst to the hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate, **1**, in toluene produced (*R*)-**2** in 18% ee (Table 1).[11] Although the selectivity of **C2** was significantly lower than that of the corresponding atropisomeric precatalyst derived from (*S*)-1,1′-binaphthyl-2,2′-diol (**C1**),[12] it revealed the potential for the structure to relay the local terminal chirality to the catalytic site.



1 **2** (1)

Reasoning that the low *M*−*P* helical interconversion barrier of the ester-terminated dendron in **C2** might be a source of low selectivity, we turned our attention to catalysts derived from oxazoline-terminated dendrons.[13] The oxazoline nitrogens in these systems form stronger hydrogen bonds with the pyridine-2,6-dicarboxamide N−H's than the corresponding ester carbonyl groups. The rigidified helical structure experiences a higher helical interconversion barrier (for dendrons in **C3**, $\Delta G^{\ddagger} = 12.3$ kcal/mol) and a greater *P* helical bias, compared with the ester-terminated dendrons in **C2** ($\Delta G^{\ddagger} \leq 8.0$ kcal/mol, not measurable by NMR). In accord with this notion, hydrogenation of **1** using precatalyst **C3** in toluene produced the *S* enantiomer of **2** in 57% ee. To further enhance the helical bias in the dendrons, we explored the isopropyl-substituted analogue **C4**. This catalyst provided product **2** in 87% ee in toluene at rt and 91% ee at −20 °C. Dendritic catalysts **C2**−**C4** exhibited enantioselectivities in toluene higher than those in THF, in contrast to **C1**.

One could envision a mechanism for communication of the terminal stereochemistry to the catalytic center whereby the helical secondary structure of the dendron directly influences the environ-

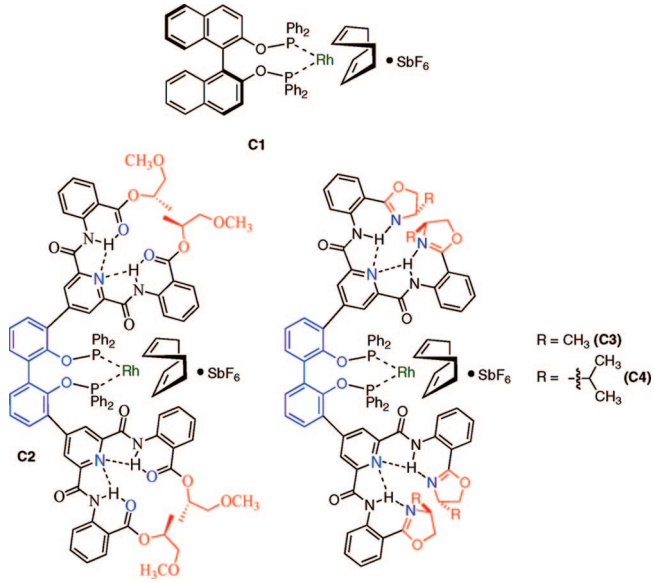


Figure 1. Structure of LRh$^+$(COD) SbF_6^- precatalysts.

Table 1. Hydrogenation of (*Z*)-Methyl 2-acetamido-3-phenylacrylate[a]

catalyst	solvent	*T* (°C)	ee (%)[b]	catalyst	solvent	*T* (°C)	ee (%)[b]
C1	toluene	rt	57 (*S*)	**C4**	toluene	rt	87 (*S*)
	THF	rt	68 (*S*)		toluene	−20	**91 (S)**
C2	toluene	rt	18 (*R*)		THF	rt	84 (*S*)
	THF	rt	14 (*R*)				
				***R*-C5**	toluene	rt	97 (*R*)
C3	toluene	rt	57 (*S*)				
	THF	rt	46 (*S*)	***S*-C5**	toluene	rt	99 (*S*)

[a] Reaction conditions: 0.3 mol % of LRh$^+$(COD)SbF_6^-, 50 psi. [b] Enantiomeric excesses determined by GC (Chirasil-L Val).

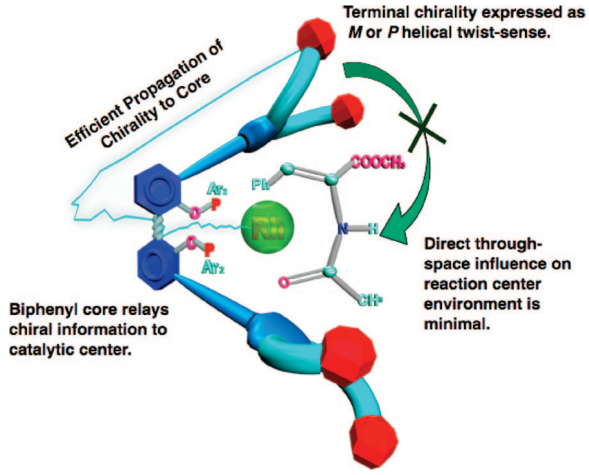


Figure 2. Chiral information propagates from the dendron terminal groups to the catalytic center via the biphenyl core, which serves to relay chirality to the catalytic site via its axial chirality.

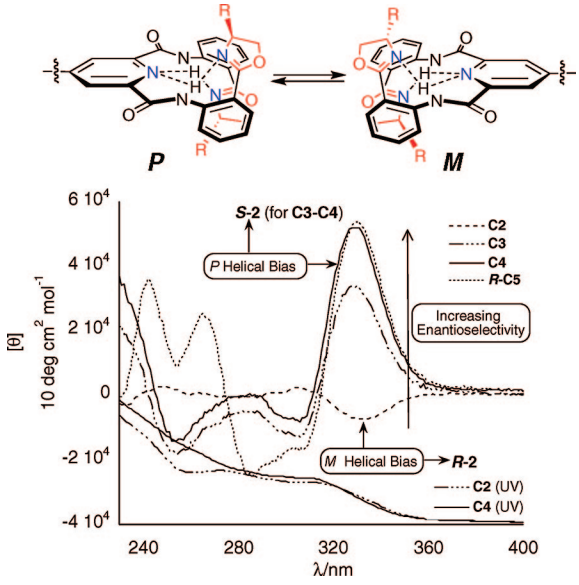


Figure 3. Top: Dynamic interconversion of *M* and *P* helical conformations in oxazoline-terminated dendrons. Bottom: Circular dichroism and UV spectra of $LRh^{+}(COD)SbF_6^{-}$ precatalysts in acetonitrile at rt.

ment around the rhodium center (Figure 2). Alternatively, the dendron helicity might be relayed via the axial stereochemistry of the biphenyl core, which then directs the stereoselectivity. It is noteworthy that the sense of chirality of the product **2** depends on the helical configuration of the dendron. For example, circular dichroism (CD) spectra of **C2** displayed a negative excitonic couplet centered at ca. 316 nm, which indicated a preference for an *M* helical conformation of the dendrons (Figure 3).[8d] Conversely, the positive couplet centered at ca. 309 nm for **C3**/**C4** reveals a *P* helical bias.[13b] Accordingly, the *M* bias in **C2** produces (*R*)-**2**, whereas the *P* bias in **C3** and **C4** produces (*S*)-**2**. The amplitude of the excitonic couplet similarly correlates with enantioselectivity in the order **C2** < **C3** < **C4**.

To understand how this helical bias is relayed to the catalytic center, an atropisomeric analogue of **C4** was constructed from (*R*)-1,1′-binaphthyl-2,2′-diol [(*R*)-**C5**] (Figure 4). By analogy to **C1**, the *R* configuration of the binapthyl core in (*R*)-**C5** would favor the formation (*R*)-**2**, whereas the *P* helical bias of the dendron would afford (*S*)-**2**, resulting in a potential mismatch. The fact that (*R*)-

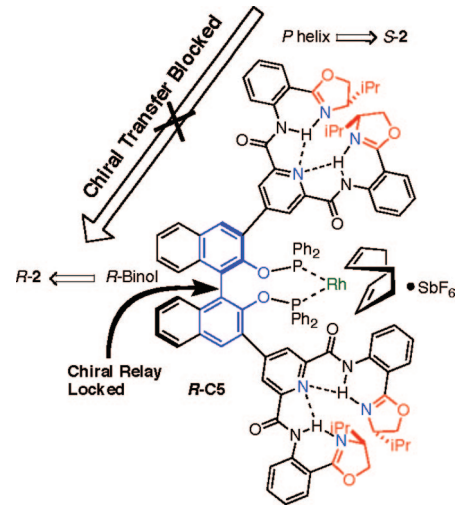


Figure 4. Atropisomeric nature of binaphthyl core locks axial chirality of central core in (*R*)-**C5**, which precludes relay of dendron helicity to catalytic center.

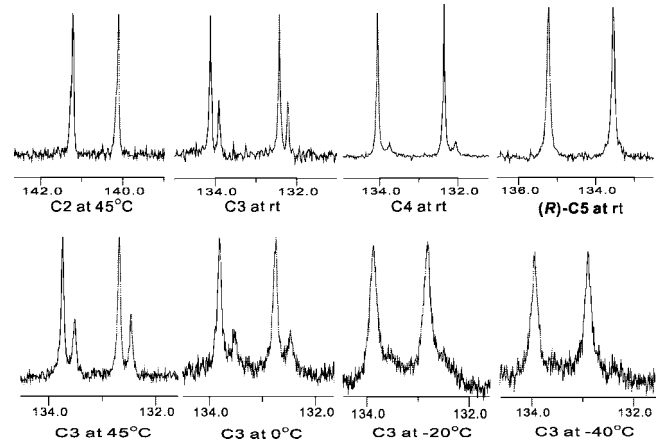


Figure 5. Top: ^{31}P NMR spectra of **C2**−**C5**. Bottom: Temperature-dependent spectra of **C3**.

C5 produced (*R*)-**2** in 97% ee demonstrates both the dominance of the binaphthyl core and the critical role that the dynamic axial chirality of the biphenyl core plays in communicating the dendron helicity to the rhodium center in **C4**. The ability of biphenyl-based ligands to mediate asymmetric induction upon coordination of a proximal chiral ligand to render the axial antipodes diastereomeric supports this relay mechanism.[14] Although the *P* helical bias of (*R*)-**C5** and (*S*)-**C5** is identical to that of **C4** by CD, locking the axial chirality of the binaphthyl core in (*R*)-**C5** effectively blocks the chiral influence of the dendron on the catalytic center. The "matched" diastereomer, (*S*)-**C5**, constructed from (*S*)-1,1′-binaphthyl-2,2′-diol, affords (*S*)-**2** in 99% ee, which is also consistent with the minor impact of the dendrons on selectivity when the core is conformationally locked. The remarkable improvement in selectivity of **C4** and **C5** compared with that of **C1** likely reflects a synergistic steric effect associated with ortho-substitution of biphenyl or binapthyl cores.[15]

The complexity of the CD spectra precluded direct determination of the sense of axial chirality of biphenyl core in **C2**−**C4**. However, the ^{31}P NMR spectra provided additional support for the role of the biphenyl core as a chiral relay. Each of the complexes exhibited a doublet in their ^{31}P NMR spectra due to the occurrence of phosphorus/rhodium ^{1}J(P,Rh) coupling (Figure 5). These spectra also displayed a second smaller doublet, which decreased in

proportion going from **C3** to **C4**, and was not present in atropisomeric (*R*)-**C5**. The doublet for **C2** appeared as a broadened doublet at ambient temperature that partially resolved into two sets of doublets at 45 °C. The enantioselectivity of **2** inversely correlates with the proportion of the minor doublet. Consequently, these additional peaks likely reflect the coexistence of a minor diastereomeric complex arising from the axial stereoisomers of the biphenyl core. The ratio of the diastereomers improves upon cooling to −40 °C, providing further support for the dynamic nature of these conformational isomers. It is also noteworthy that rhodium coordination significantly improves the ratio of axial stereoisomers.[16] Equal proportions of the diastereomeric conformations are indicated by the ^{31}P NMR spectra of the uncomplexed forms of **C2**−**C4**, each of which displays two peaks of equal intensity (Supporting Information). This contrasts with the spectra of uncomplexed ligand of (*R*)-**C5**, which exhibits a single ^{31}P resonance, as would be expected for a C_2-symmetric atropisomeric system.

In conclusion, we have demonstrated the first example of a dendritic catalyst that directs the stereoselectivity of a catalytic process by dynamically transferring the conformational chirality of a dendritic structure to the catalytic center. Experimental evidence supports a chiral relay mechanism that propagates the local terminal chirality of the dendron to the axial chirality of the biphenyl core via the helical secondary structure of the dendron. The exact details of the kinetic origin of asymmetric induction remains under investigation;[17] however, the empirical relation between conformational preferences of ground-state precatalysts and the sense of asymmetric induction in Rh-catalyzed hydrogenation is well-established.[18] The results reported here illustrate the potential for synthetic supramolecular systems to derive selective function from dynamic structural properties.

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Supporting Information Available: Experimental procedures, compound characterization, and ^{31}P NMR spectra for **C1**−**C5**, and ^{1}H and ^{13}C NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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