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A Simple Iridium Catalyst with a Single Resolved Stereocenter for Enantioselective Allylic Amination. Catalyst Selection from Mechanistic Analysis

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Abstract: A study of the relationship between the stereochemical elements of a phosphoramidite ligand and the stereoselectivity of iridium-catalyzed amination of allylic carbonates is reported. During catalyst activation, a complex of a phosphoramidite ligand possessing one axial chiral binaphtholate group and two resolved phenethyl substituents converts to a more reactive cyclometalated complex containing one distal chiral substituent at nitrogen, one substituent that becomes part of the metalacycle, and one unperturbed binaphtholate group. Systematic changes were made to the different stereochemical elements. Replacement of the distal chiral phenethyl substituent with a large achiral cycloalkyl group led to a catalyst that reacts with rates and enantioselectivities that are similar to those of the original catalyst with the phenethyl group. Studies of the reactions of diastereomeric ligands containing (*R*) or (*S*) binaphtholate groups on phosphorus, along with one (*R*)-phenethyl and one achiral cyclododecyl group on nitrogen, show that the complexes of the two diastereomeric ligands undergo cyclometalation at much different rates. To access both diastereomeric catalysts and to determine if the reaction can occur selectively with an even simpler ligand containing a phenethyl substituent at nitrogen as the only resolved stereochemical element, the catalyst derived from a phosphoramidite containing a biphenolate group was studied. Catalysts generated from this ligand were shown to react in all cases examined with nearly the same rates, regioselectivities, and enantioselectivities as catalysts derived from the original more elaborate ligand. The absolute stereochemistry of the product implies that the major enantiomer is formed from the (R_a,R_c)-atropisomer of the catalyst containing the biphenolate group.

Introduction

Information on the structures and reactions of intermediates in catalytic reactions can guide the selection of improved catalysts. At the same time, the translation of this structural information into improved catalysts for enantioselective processes can be challenging. A recent study from our laboratories provides one example of how distinct an active catalyst can be from its catalyst precursors.[1] An iridium−phosphoramidite complex, which catalyzes the amination and etherification of allylic carbonates with high regioselectivity and enantioselectivity,[2−7] catalyzes these reactions after cyclometalation drastically alters its structure.[1] To help determine the relationship between the structure and reactivity of the resulting complex, we have conducted studies to determine the influence of the different portions of the cyclometalated structure on reactivity and selectivity. Along with providing information on the interplay between stereochemical elements, these studies have led to a catalyst that reacts with yields, rates, and enantioselectivities that are comparable to those of the original more elaborate catalyst, but with a ligand that contains one phenethyl group as the sole resolved stereochemical component.

The aminations and etherifications of terminal allylic carbonates catalyzed by iridium complexes of certain phosphoramidites form branched chiral amines and ethers in high yields, with high branched-to-linear ratios and with high enantiomeric excesses.[1−14] The regioselectivity of this process complements the typical regioselectivity of palladium-catalyzed allylic amination. Further, the simplicity of the synthesis of phosphoramidite ligands contrasts with the more lengthy synthesis of some ferrocenyl ligands that have provided branched allylic amines with high branched-to-linear ratios and high enantiose-

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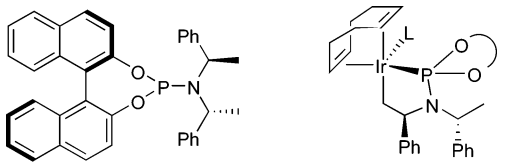

(R_a,R_c,R_c)-**L1** (R_a,R_c,R_c)-**1**

Figure 1. Original phosphoramidite ligand **L1** and activated cyclometalated catalyst **1**.

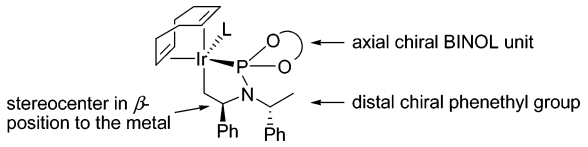

Figure 2. Stereochemical elements of the cyclometalated Ir(I) complex generated with ligand **L1**.

lectivity from amination reactions with palladium catalysts.[15] The selectivity of the iridium-catalyzed reactions is more akin to that of molybdenum-catalyzed allylic substitutions,[16−21] but the scope of the allylation reactions catalyzed by the iridium complexes encompasses heteroatom nucleophiles that are not included, as least currently, in the scope of reactions catalyzed by molybdenum complexes. These reactions also contrast with rhodium-catalyzed allylic aminations and etherifications that have been conducted so far with achiral catalysts.[22−31]

The first highly enantioselective, iridium-catalyzed aminations and etherifications of allylic carbonates were conducted with phosphoramidite ligand **L1** containing a binaphtholate unit and a bis-phenethylamino group.[2,3,6] The active catalyst in these reactions is generated by cyclometalation at one methyl group of the phenethylamino substituent.[1] This cyclometalation breaks the C_2 symmetry of the ligand and generates a product with C_1 symmetry. The structure of the presumed active catalyst stabilized by a fifth dative ligand, complex **1**, is shown in Figure 1.

In principle, this information that the active catalyst contains the cyclometalated structure should allow one to prepare new ligands for this catalytic process by choosing structures in a logical manner. Moreover, the cyclometalated structure provides a platform to study the origin of the effects of changes to the different stereochemical elements of the ligand (see Figure 2) and the interconnections between these elements on enantioselectivity. A hierarchy among the different stereochemical elements and the basis for the difference in activity between catalysts generated from different diastereomeric ligands was not clear from the initial studies with the catalyst generated in situ or even after identifying the cyclometalated structure of the activated catalyst.

We reported in communication form that a ligand (**L2**) with a resolved binaphthyl group, one phenethyl group, and one achiral *N*-benzyl group distal to the metal generates a complex that catalyzes the allylation of cinnamyl carbonate with enantioselectivities higher than 90%.[4,32] Reactions of this catalyst were much slower than those of the original catalyst, but these results demonstrated that the more distal stereocenter in the cyclometalated complex could be omitted while maintaining high selectivity.[33−35] We have now conducted detailed studies on the effect of the distal substituent, the origins of the difference in reactivity of diastereomeric catalysts, and studies that evaluate the effect of eliminating each of the resolved stereochemical elements. These studies have (1) led to a family of new C_1-symmetric phosphoramidite ligands that reveal the relative importance of different structural features of the ligands on reaction rate and enantioselectivity, (2) shown an unexpected origin of the difference in reactivity of diastereomeric catalysts, and (3) led us to design a catalyst that reacts with nearly equal enantioselectivity as the original catalyst, but which contains a single phenethylamino substituent as the sole resolved stereochemical element. Because phenethylamine is an inexpensive optically active building block, these studies uncover a practical catalyst for allylic substitution in concert with revealing concepts that should further advance efforts to design catalysts for enantioselective transformations.

Results and Discussion

1. Initial Ligand Design. Our first studies were conducted to determine if the distal phenethyl group in the cyclometalated complex of Figure 2 could be replaced by an achiral substituent that would impart steric and electronic properties that are analogous to those of a phenethyl group. To do so, we prepared a series of phosphoramidites **L3**−**L16** in Table 1 that contain (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) and an amino group containing one arylethyl substituent and one achiral cyclic or acyclic aliphatic or benzylic substituent. After cyclometalation at the arylethyl group, the achiral substituent would lie distal to the metal. We focused on the synthesis of ligands with achiral substituents that lacked a methyl group because the absence of a methyl group in the achiral substituent would prevent competitive cyclometalation at the arylethyl substituent and the achiral substituent. Further, we chose structures that could be prepared from amines that are either available commercially or could be prepared by simple reductive amination of the appropriate cyclic or acyclic ketones with an optically active arylethylamine. As described in the final section of this paper, these studies led to further development of catalysts that lacked an optically active biaryl group as the second stereochemical element.

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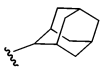
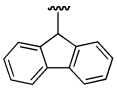
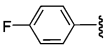
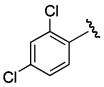
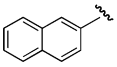
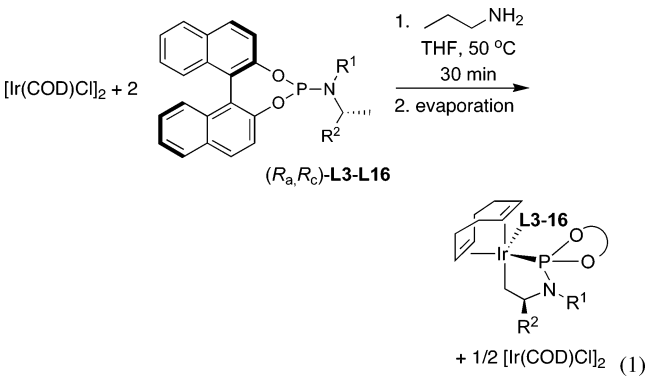
Table 1. Effect of Substituents in C_1-Symmetric Phosphoramidite Ligands (R_a,R_c)-**L3**−**16** on the Allylic Amination of Eq 3 with Catalysts Generated by the Procedure in Eq 1[a]

entry	R^1	R^2	ligand	ee[b] (%)	b/l[c]	reaction time (h)[d]
1		Ph	**L3**	78	95:5	4
2		Ph	**L4**	91	95:5	3
3		Ph	**L5**	94	96:4	4
4		Ph	**L6**	96	95:5	1.5
5		Ph	**L7**	91	94:6	24
6		Ph	**L8**	47	93:7	14
7		Ph	**L9**	87	95:5	18
8		Ph	**L10**	89	96:4	3
9			**L11**	97	95:5	1.5
10			**L12**	97	97:3	2
11			**L13**	98	94:6	5
12			**L14**	90	nd[e]	5 d (< 50% conversion)
13			**L15**	93	95:5	5
14			**L16**	96	97:3	3

[a] Reactions were conducted at room temperature on a 1.0 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate:amine:catalyst of 100:120:2. [b] Enantioselectivities were determined by chiral HPLC; the *R* enantiomer was the major enantiomer in all reactions. [c] Branched-to-linear ratios were determined by crude ^{1}H NMR. [d] Reactions were monitored by gas chromatography. [e] Not determined because of the low yield of substitution product.

2. Ligand and Catalyst Preparation and Structure. All of the phosphoramidite ligands were prepared following protocols reported by Alexakis[36] and closely related to those reported by Feringa[37] and their co-workers for the preparation of C_2-symmetric phosphoramidites. This method simply involves reaction of PCl_3 with a secondary amine and NEt_3, followed by addition of (*R*)-BINOL. All ligands in this study were isolated in pure form and were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, as well as microanalysis.



(1)

Equation 1 shows the protocol followed to generate the activated catalyst from the various phosphoramidite ligands, and Table 1 includes the substituents on the phosphoramidites **L3**−**L16** that were studied as part of this work. The cyclometalated complexes were generated by addition of 1 equiv of the ligand to 0.5 equiv of $[Ir(COD)Cl]_2$ to form [Ir(COD)Cl(**LX**)] (X = **3**−**16**), followed by heating this iridium chloride complex with 30 equiv of propylamine at 50 °C for 20 min and evaporation of the volatile materials to generate an air-stable and moisture-stable solid. We have shown with ligand **L6** that this procedure forms 1 equiv of the trigonal bipyramidal complex [(COD)Ir(κ^2-**L6**)(κ^1-**L6**)] (**2**), which is analogous to **1**, in 91% yield (determined by ^{31}P NMR spectroscopy with an internal standard in a capillary tube). Because complex **2** contains one cyclometalated and one monodentate phosphoramidite ligand, this procedure regenerates 1 equiv of $[Ir(COD)Cl]_2$ during the cyclometalation. Thus, the final solid that is added as catalyst is a 1:1 mixture of **2** and 1/2 $[Ir(COD)Cl]_2$. We have shown that the presence of $[Ir(COD)Cl]_2$ accelerates the catalytic process by accepting the κ^1-phosphoramidite and promoting the equilibrium for dissociation of this ligand from **1**.[38]

^{31}P NMR spectra of the crude solutions generated upon heating $[Ir(COD)Cl]_2$ with phosphoramidites **L3**−**L16** and propylamine at 50 °C indicated that the complexes generated from ligands that lack methyl groups on the amino substituents undergo cyclometalation to form complexes that are analogous to **1** and **2**. The formation of these cyclometalated complexes was revealed by the appearance of two doublets in the ^{31}P NMR spectrum at chemical shifts similar to those of **1** after heating with propylamine. Only the square planar Ir(I) complex from $[Ir(COD)Cl]_2$ and isopropyl-substituted ligand **L10** generated mixtures of species upon heating with propylamine. Different species could be generated from **L10** by cyclometalation at the phenethyl group or at one of the diastereotopic methyl groups of the isopropyl substituent. Several products formed from heating with propylamine, and we were unable to isolate a pure species. Nevertheless, the formation of mixtures of products was consistent with our hypothesis that competitive cyclometalation could occur at the achiral substituent if it contained methyl groups β to nitrogen.

To obtain a more crystalline product, we prepared a complex with PPh_3 as the κ^1 ligand by cyclometalation of the Ir(I) complex of phosphoramidite **L5** and replacement of the monodentate phosphoramidite with PPh_3 (eq 2). This complex was

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(37) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.
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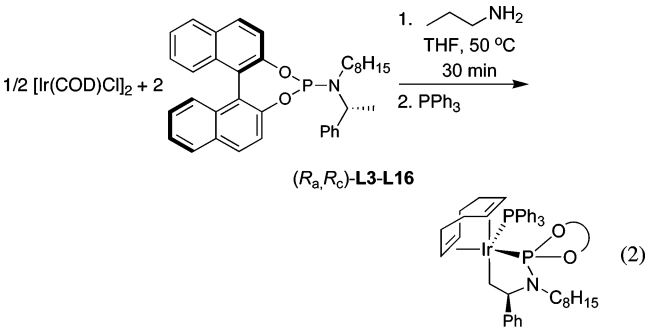


(2)

formed in the crude reaction as a 1:0.4 mixture of isomers that appears to result from varied stereochemistry at the metal. The complex crystallized as a single isomer, and this form of **3** was characterized by conventional spectroscopic methods and X-ray diffraction. An ORTEP diagram of **3** is shown in Figure 3. This complex is nearly superimposable on the structure of the PPh_3 adduct of the catalyst generated from **L1**,[1] except that the cycloalkyl group resides at the position of the phenethyl group.

3. Reactions Catalyzed by Cyclometalated Complexes of L3−L6. The ability of ligands **L3**−**L16** to generate catalysts for enantioselective amination of terminal allylic carbonates was probed by conducting the reaction of methyl cinnamyl carbonate with *p*-methoxy benzylamine at room temperature (eq 3) catalyzed by the complex generated according to eq 1. The branched-to-linear ratios, enantioselectivity of the branched product, and the approximate times required to reach >95% conversion are shown in Table 1 for the reactions catalyzed by cyclometalated complexes of the various ligands.

From these data, one can extract several trends. First, a comparison of the results in entries 1−7 shows that increased size of the achiral distal substituent attached to the nitrogen leads to improved enantioselectivities. As the size of the cycloalkyl group was increased from six to seven to eight and then to a 12-membered carbocycle, the enantioselectivity increased. The reaction also required the shortest times when catalyzed by the complex derived from the ligand with the largest 12-membered carbocycle. A comparison of these results to those of catalysts derived from ligands with benzylic or fluorenyl substituents showed that the rates were much faster when this substituent was more three-dimensional than planar.

Second, one can conclude that variation of the aryl group on the arylethyl substituent does not dramatically affect the enantioselectivity or regioselectivity but does allow for fine-tuning of enantioselectivity and presumably matching of substrate with catalyst. The highest enantioselectivity was observed with the catalyst derived from the ligand with a 2,4-dichlorophenyl group. The fastest rates were observed with the catalyst derived from the ligand with a 2-methoxy group. This fast rate parallels the results reported by Alexakis with a bis-arylethyl substituent on the phosphoramidite[39] and a recent result of Helmchen.[34] The highest branched-to-linear selectivity was measured with the catalyst derived from ligands containing a 2-naphthyl or a 4-fluorophenyl group, although these small differences in an already high selectivity are difficult to clearly assess by ^{1}H NMR spectroscopy.

(39) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426.

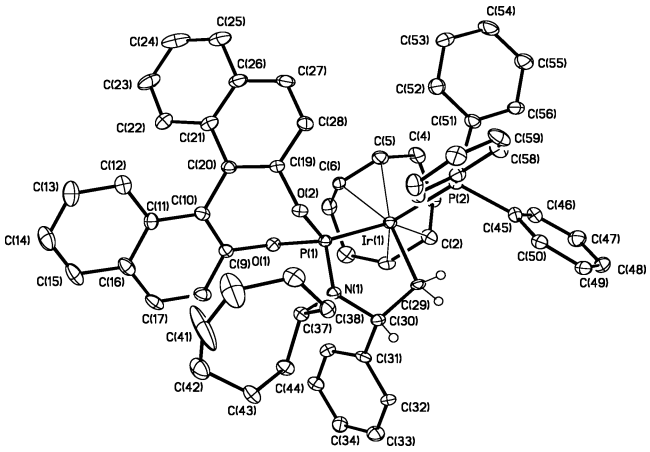
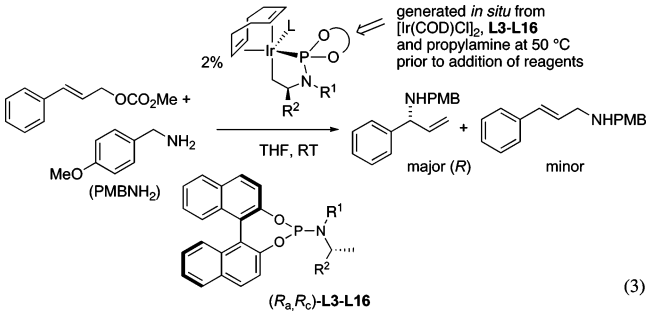


Figure 3. ORTEP diagram of the trigonal bipyramidal Ir(I)-complex **3** with PPh_3 as the monodentate phosphorus ligand.



(3)

Third, one sees from these data that the reactions with the catalyst containing an isopropyl substituent on nitrogen react with reasonably high enantioselectivity and fast rates. Although this catalyst is not the most reactive or selective, and conclusions from studies of this ligand can be made only tentatively, the results with this ligand do warrant a brief comment. We showed previously that the reaction of cinnamyl carbonate with benzylamine catalyzed by the complex generated from the phosphoramidite derived from diisopropylamine occurs with a considerable 61% enantioselectivity.[1] The major enantiomer from this reaction was the same as that from reactions catalyzed by the complex of the phosphoramidite with a bis-phenethylamino group. We assume that the active catalyst components that result from cyclometalation of the isopropyl group of the ligand **L10** would also form the same enantiomer as the catalysts generated from the bis-phenethyl ligand **L1** and the previously studied[2] diisopropylamino ligand (binaphtholate)P(NPr$^i_2$). If so, then the composite selectivity of the species generated from cyclometalation at the phenethyl and isopropyl groups of **L10** would lie between the 61% and 95% ee of the two catalysts generated from these two ligands. The product from the reaction catalyzed by complexes generated from **L10** was formed in 89% ee. The greater similarity of this value to the enantiomeric excess from the reactions catalyzed by the complexes generated from **L1** suggests that the species resulting from cyclometalation at the phenethyl group is formed in larger quantities or is more reactive than the species resulting from cyclometalation at the isopropyl group.

Allylic aminations catalyzed by the mixture of $[Ir(COD)Cl]_2$ and cyclometalated complex **2** generated from **L6**, which

Table 2. Amination of Allylic Carbonates Catalyzed by Complexes Generated from Ligand **L6**[a]

entry	carbonate	amine	yield[b] (%)	ee (%)	b/l[c]
1	Ph, OCO_2Me	NH_2	93	95 (*R*)	99:1
2	Ph, OCO_2Me	S, NH_2	78	97	97:3
3	Ph, OCO_2Me	O, NH_2	86	98	96:4
4	Ph, OCO_2Me	$HNEt_2$	83	98	98:2
5	Ph, OCO_2Me	O, NH	93	96	95:5
6	Ph, OCO_2Me	NH_2	92	97	95:5
7	Ph, OCO_2Me	MeS, NH_2	94	97	98:2
8	OCO_2Me	NH_2	80	97	98:2
9	OCO_2Me	NH_2	76	96	96:4

[a] Reactions were conducted at room temperature on a 1.0 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate/amine/catalyst of 100:120:2. [b] Isolated yields from two independent runs. [c] Branched-to-linear ratio-determined from crude ^{1}H NMR spectra.

contains a cyclododecyl group as the distal substituent at the nitrogen in the metalacycle, occur in yields and enantioselectivities that are as high as those with the catalyst derived from the original ligand **L1**. Results from a series of reactions of aromatic and aliphatic amines with both aliphatic and cinnamyl carbonates catalyzed by the complex generated from **L6** are summarized in Table 2. The reactions of methyl cinnamyl carbonate with benzylamine and two heteroarylmethylamines occurred in good to excellent yields with high branched-to-linear ratios and high enantiomeric excesses with 1 mol % of $[Ir(COD)Cl]_2$ and 2 mol % of **L6**. Further, reactions of acyclic secondary amines with this allylic carbonate occurred in excellent yield with high selectivities, and reactions of aromatic amines occurred with similarly high chemoselectivity and enantioselectivity. Finally, the reactions of a linear aliphatic carbonates occurred in equally high yield and selectivity with the simpler ligand **L6** as with the original more elaborate ligand **L1**.

4. Origins of the Difference in Activity of Diastereomeric Catalysts. a. Relative Rates of Reaction of Catalysts Derived from Diastereomeric Ligands. With a catalyst that is highly active and selective and that contains only two stereochemical elements, the phenethyl group and the axial chirality of the binaphtholate unit, we sought to determine the relative contributions of these two elements to the enantioselectivity. To begin these studies, we determined the relative rates and enantioselectivity of reactions with each of the two diastereomeric ligands and with a mixture of the two diastereomers. These studies of the reactivity of the diastereomers revealed an unexpected origin of the difference in reactivity.

Figure 4 shows the appearance of product from the reaction of aniline with methyl cinnamyl carbonate (eq 4) catalyzed by the complexes (R_a,R_c)-**2** and (S_a,R_c)-**2** (generated from the (R_a,R_c) and (S_a,R_c) diastereomers of ligand **L6**) and the catalyst generated from (*rac*$_a$, R_c)-**2** in THF-d_8 at 25 °C. The appearance of product was determined by monitoring the reactions by ^{1}H NMR spectroscopy. The catalyst was generated by reaction of propylamine with a mixture of $[Ir(COD)Cl]_2$ and the different

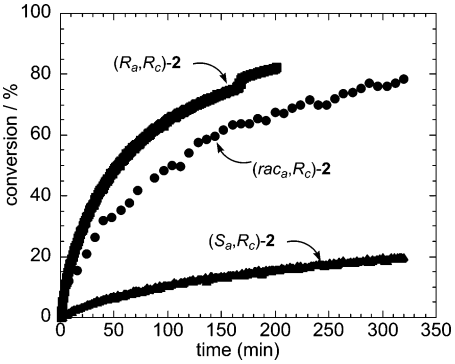
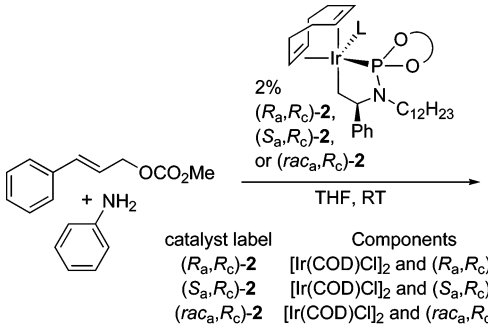
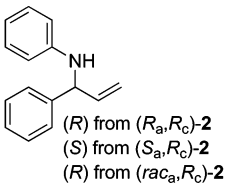


Figure 4. Comparison of relative rates for the reactions of aniline with methyl cinnamyl carbonate catalyzed by (1) (R_a,R_c)-**2** formed from (R_a,R_c)-**L6**; (2) (S_a,R_c)-**2** formed from (S_a,R_c)-**L6**; and (3) (*rac*$_a$,R_c)-**2**, which refers to the stereoisomeric forms of **2** generated from a 1:1 mixture of (R_a,R_c)-**L6** and (S_a,R_c)-**L6**.

stereoisomers of **L6** at 50 °C for 20 min, followed by removal of all volatile materials.





(4)

The reaction is clearly faster when catalyzed by the complex derived from the (R_a,R_c)-diastereomer of ligand **L6** than it is from that derived from the (S_a,R_c)-diastereomer. These data are consistent with our previous observation that the reactions catalyzed by complexes derived from (R_a,R_c,R_c)-**L1** occurred much faster than those derived from the diasteromeric (S_a,R_c,R_c)-**L1**. The allylic amine products formed from the allylic substitution catalyzed by complexes generated from (R_a,R_c)-**L6** and (S_a,R_c)-**L6** are antipodes of each other. We had previously shown that the major enantiomers of the allylic amines formed from catalysts generated from (R_a,R_c,R_c)-**L1** and from (S_a,R_c,R_c)-**L1** are also antipodes of each other.[2]

We also evaluated the rate of the same reaction catalyzed by complexes of the mixture of diastereomeric (*rac*$_a$,R_c)-**L6** ligands. Reactions catalyzed by the complexes derived from the mixture of diastereromeric (*rac*$_a$,R_c)-**L6** ligands occurred at rates that are closer to those of reactions catalyzed by the complex generated from pure (R_a,R_c)-**L6** than from pure (S_a,R_c)-**L6**. However, this allylic amination is somewhat slower when catalyzed by complexes derived from (*rac*$_a$,R_c)-**L6** than from pure (R_a,R_c)-**L6**. The enantioselectivity of the reaction initiated with the mixture of diastereomeric (*rac*$_a$,R_c)-**L6** ligands was

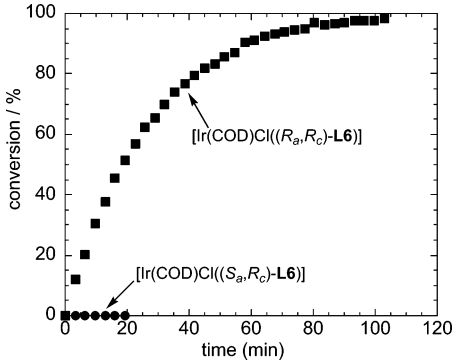
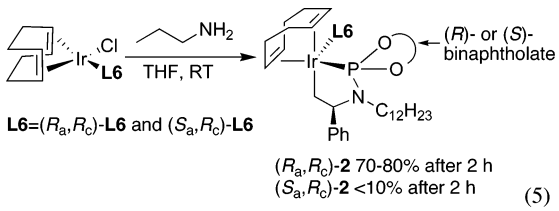


Figure 5. Relative rates of cyclometalation of [Ir(COD)Cl((*R*$_a$,*R*$_c$)-**L6**)] and [Ir(COD)Cl((*S*$_a$,*R*$_c$)-**L6**)] in the presence of propylamine at room temperature monitored by ^{31}P NMR spectroscopy.

90%. This value is close to, but slightly lower than, the 96% ee obtained from the reaction initiated with the pure (*R*$_a$,*R*$_c$)-**L6** ligand.

b. Relative Rates of Cyclometalation of the Two Diastereomeric Ligands. Studies of the rate and yield of cyclometalation of the square planar Ir(I)-complexes [Ir(COD)(Cl)(**L6**)] derived from (*R*$_a$,*R*$_c$)-**L6**, (*S*$_a$,*R*$_c$)-**L6**, and (*rac*$_a$,*R*$_c$)-**L6** were conducted. These studies revealed the origin of (1) the difference in rates between the reactions catalyzed by complexes containing diastereomeric ligands and (2) the difference in rates between reactions catalyzed by complexes generated from the diastereomerically pure (*R*$_a$,*R*$_c$)-**L6** and from the mixture of diastereomers. The cyclometalation of the two diastereomers of [Ir(COD)(Cl)(**L6**)] in the presence of 30 equiv of propylamine (eq 5) was monitored by ^{31}P NMR spectroscopy. As illustrated in Figure 5, {Ir(COD)Cl[(*R*$_a$,*R*$_c$)-**L6**]} converted at room temperature in less than 2 h to the cyclometalated, trigonal biypyramidal Ir(I) compound **2**. In contrast, addition of an excess of propylamine to {Ir(COD)Cl[(*S*$_a$,*R*$_c$)-**L6**)]} led to little conversion of the starting Ir(I) chloride. Heating of {Ir(COD)Cl[(*S*$_a$,*R*$_c$)-**L6**)]} at 50 °C for 1 h led to an increased conversion of this starting complex, but several products were formed instead of the single product from heating of {Ir(COD)Cl[(*R*$_a$,*R*$_c$)-**L6**]}.



(5)

This information led us to test the relative rates for cyclometalation of [Ir(COD)(**L1**)Cl] containing the (*R*$_a$,*R*$_c$,*R*$_c$) and (*S*$_a$,*R*$_c$,*R*$_c$) forms of the original ligand **L1**. [Ir(COD)Cl]$_2$ and (*R*$_a$,*R*$_c$,*R*$_c$)-**L1** (2:1 ratio of ligand to iridium) and 30 equiv of propylamine reacted over the course of 1.25 h at room temperature to form the cyclometalated complex **1** (Figure 1) reported previously.[1] After this short time at room temperature, only 25% of the square planar complex [Ir(COD)((*R*$_a$,*R*$_c$,*R*$_c$)-**L1**)Cl] remained. In contrast, [Ir(COD)Cl]$_2$ and the diastereomeric ligand (*S*$_a$,*R*$_c$,*R*$_c$)-**L1** did not form the corresponding cyclometalated complex at room temperature; only the square planar complex {Ir(COD)Cl[(*S*$_a$,*R*$_a$,*R*$_c$)-**L1**]} and free ligand was observed after standing with 30 equiv of propylamine at room temperature for 1.25 h.

These data show that the difference in reactivity of complexes generated from the diastereomeric catalysts is due, at least in part, to differences in the propensity of the two diastereomeric square planar complexes {Ir(COD)Cl[(*R*$_a$,*R*$_c$)-**L6**)]} and {Ir(COD)Cl[(*S*$_a$,*R*$_c$)-**L6**)]} to undergo cyclometalation. The small difference in enantioselectivity between the reaction of *p*-methoxybenzylamine and methyl cinnamyl carbonate catalyzed by the complex generated from the pure (*R*$_a$,*R*$_c$)-**L6** ligand and the mixture of diastereomers (*rac*$_a$,*R*$_c$)-**L6** (90%) implies that only a few percent of the minor enantiomer of the product forms from the reaction catalyzed by the intermediates containing the (*S*$_a$,*R*$_c$) diastereomer of **L6**.

These data also suggest that a single metalacycle core would be formed by cyclometalation of {Ir(COD)Cl[(*rac*$_a$,*R*$_c$)-(**L6**)]}. The faster rate of cyclometalation of the (*R*$_a$,*R*$_c$) ligand makes it seem likely that the (*R*$_a$,*R*$_c$) ligand of the (*rac*$_a$,*R*$_c$)-**L6** mixture would preferentially undergo cyclometalation. Indeed, heating the mixture of (*rac*$_a$,*R*$_c$)-**L6** and [Ir(COD)Cl]$_2$ in a 4:1 ratio of phosphoramidite to iridium dimer with 30 equiv of propylamine at 50 °C for 30 min led to a 1.9:1 ratio of two diastereomers [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*R*$_a$,*R*$_c$)-**L6**)] and [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*S*$_a$,*R*$_c$)-**L6**)**]** in which the core of the metalacycle generated from the (*R*$_a$,*R*$_c$)-**L6** ligand and the κ^1 ligands is (*R*$_a$,*R*$_c$)-**L6** and (*S*$_a$,*R*$_c$)-**L6**, respectively.

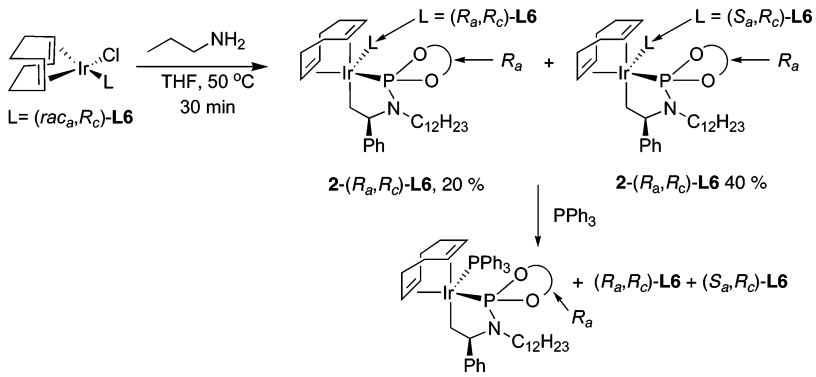
This mixture of diastereomers was observed in the ^{31}P NMR spectrum as two pairs of doublets, and the identity of these diastereomers was confirmed by independent synthesis. [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*R*$_a$,*R*$_c$)-**L6**)] was prepared from the reaction of (*R*$_a$,*R*$_c$)-**L6** with [Ir(COD)Cl]$_2$ (vide supra). [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*S*$_a$,*R*$_c$)-**L6**)**]** was generated independently as a mixture with [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*R*$_a$,*R*$_c$)-**L6**)] by addition of 1 equiv of (*S*$_a$,*R*$_c$)-**L6** to pure [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*R*$_a$,*R*$_c$)-**L6**)]. The assignments of the cyclometalated products were confirmed by reaction of PPh_3 with the mixture of cyclometalated complexes generated from (*rac*$_a$,*R*$_c$)-**L6** (Scheme 1). This addition led to the formation of PPh_3-ligated (*R*$_a$,*R*$_c$)-**2**, as determined by ^{31}P NMR spectroscopy.

The mixture of diastereomers was formed in about 40% yield. This yield is about one-half of the yield of [(COD)Ir{κ^2-(*R*$_a$,*R*$_c$)-**L6**}(κ^1-(*R*$_a$,*R*$_c$)-**L6**)] after heating [Ir(COD)Cl]$_2$ with (*R*$_a$,*R*$_c$)-**L6** and 30 equiv of propylamine for 30 min. This lower yield for formation of the cyclometalated species from (*rac*$_a$,*R*$_c$)-**L6** is consistent with the slightly slower rate of reaction when the catalyst is generated from (*rac*$_a$,*R*$_c$)-**L6** instead of (*R*$_a$,*R*$_c$)-**L6**.[40]

5. A Highly Active and Selective Catalyst from a Single Optically Active Component. These studies of diastereomeric ligands led to information on the mode of catalyst activation, but they did not reveal information about the relative reactivity of the two diastereomers within the catalytic cycle or information on whether the phenethyl group or the binaphthyl group was the dominant component that controlled enantioselectivity. To allow both diastereomers to be generated in the catalytic cycle

(40) Because the catalysts with (*R*$_a$,*R*$_c$)-**L6** and (*S*$_a$,*R*$_c$)-**L6** as the κ^1 ligand are diastereomeric, the rates of reactions catalyzed by the two species will be different. Although we have not isolated pure complex, the complex with (*S*$_a$,*R*$_c$)-**L6** as the κ^1 ligand, a 2:1 ratio of complexes in favor of the species with (*R*$_a$,*R*$_c$)-**L6** is formed, and this greater stability of the compound with (*R*$_a$,*R*$_c$)-**L6** as the κ^1 ligand implies that this diastereomer will react slightly more slowly. This effect would make the catalyst from (*rac*$_a$,*R*$_c$)-**L6** more reactive instead of less reactive, as we observe experimentally. Thus, we attribute the slightly slower reaction of the catalyst generated from (*rac*$_a$,*R*$_c$)-**L6** to the lower yield for formation of the cyclometalated complex from (*rac*$_a$,*R*$_c$)-**L6**.

Scheme 1



with a complex that is related in structure to that derived from ligand **L6**, we studied reactions with catalysts generated from **L17** in Figure 6, which is the biphenolate analogue of binaphtholate ligand **L6**. Because ligand **L17** can undergo atropisomerism, the catalysts with these ligands would be able to access both diastereomers during the catalytic cycle. In addition to providing information on the reactivity of diastereomeric complexes within the catalytic cycle, an enantioselective process with this ligand would be practical because a single, inexpensive phenethylamine would be the only optically active reagent used to prepare the entire catalyst.

Like the phosphoramidites with binaphtholate groups, phosphoramidite **L17** with a biphenolate group was prepared by treatment of *N*-cyclododecylphenethylamine and triethylamine with PCl_3, followed by 2,2′-biphenol. The enantiopure ligand was obtained in 60% yield by this trivial two-step synthesis starting with phenethylamine.

a. Reactions Catalyzed by Complexes of Biphenolate Ligand L17. The reactions of primary and secondary amines with terminal allylic carbonates catalyzed by the complex generated from this truncated ligand occurred with rates, yields, regioselectivities, and enantioselectivities that are nearly identical to those of the ligand **L6**, which contains the resolved binaphtholate substituent. They were even comparable to those obtained with the ligand **L1** that contains a resolved binaphtholate substituent and two phenethyl substituents on the nitrogen. A series of reactions of primary and secondary amines with aliphatic and cinnamyl carbonates catalyzed by the complex generated from biphenolate ligand **L17** are summarized in Table 3. Like the reactions with the complexes generated from the other phosphoramidites, we conducted these reactions after inducing cyclometalation by heating $[Ir(COD)Cl]_2$ with **L17** and propylamine at 50 °C for 30 min.

In general, most reactions occurred to completion at room temperature between 3 and 12 h and with enantioselectivities between 91% and 97%. The branched-to-linear ratios were typically over 20:1. Reactions of methyl cinnamyl carbonate with benzylic heteroarylmethylamines, acyclic dialkylamines, and cyclic aliphatic amines all occurred in good yields and with high regio- and enantioselectivity. Reactions of aromatic amines occurred in similar yields and selectivities. Although we have not explored a wide range of substrate combinations at this time, the reactions of aromatic and benzylic amines with the simple aliphatic methyl carbonate derived from trans-2-hexene-1-ol occur in a fashion similar to those of methyl cinnamyl carbonate. Like reactions of acyclic secondary aliphatic amines with this aliphatic carbonate catalyzed by complexes of other phosphoramidites, the reaction of diethylamine with this allylic carbonate did not occur in high yield or with high regioselectivities when conducted with ligand **L17**.

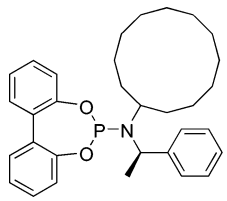


Figure 6. Ligand **L17** with a biphenol backbone, an achiral *N*-alkyl group, and one phenethyl group from resolved phenethylamine.

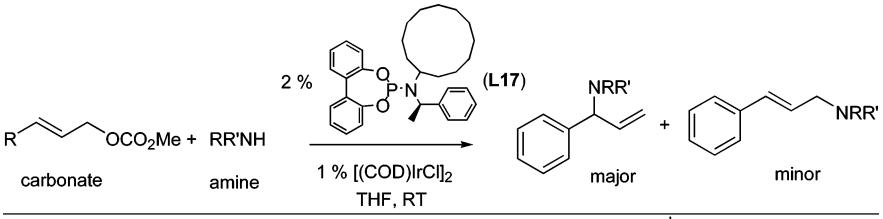
The observation of high branched-to-linear ratios and high enantiomeric excess with such a simple ligand is remarkable. However, the biphenolate unit presumably provides a stereochemical environment at the metal that is similar to that provided by the binaphtholate group in the original ligand, and the large cycloalkyl group presumably plays a role in diverting attack from a trajectory that intersects the space occupied by the distal group. Studies to reveal the interplay between the stereochemistry of the biphenolate group and the stereochemistry of the phenethyl group are described in sections 5b and 6.

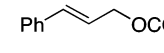
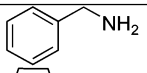
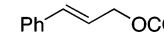
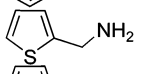
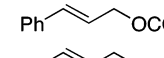
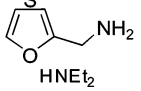
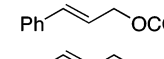
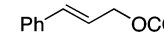
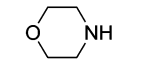
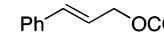
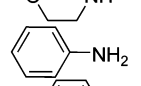
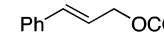
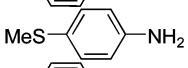
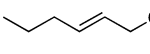
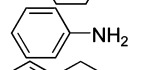
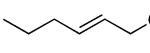
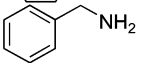
b. Dynamics of the Complexes Generated by Coordination and by Cyclometalation of Biphenolate Ligand L17. Variable-temperature ^{31}P NMR spectra of free **L17**, [Ir(COD)Cl(**L17**)], the cyclometalated complex analogous to **1** that results from heating this square planar complex with propylamine, and phosphine derivatives of the cyclometalated complex were obtained. These data are provided in the Supporting Information as Figures S1−S3. These data allowed us to relate the dynamics of stereoisomerism to the rate of the catalytic reaction.

A single resonance in the ^{31}P NMR spectrum of free phosphoramidite **L17** was observed at room temperature, but two broad resonances, which presumably correspond to the two atropisomers of **L17**, were observed in a 1:0.7 ratio at −80 °C. A single resonance in the ^{31}P NMR spectrum of [Ir(COD)Cl(**L17**)] was also observed at room temperature. This signal broadened at 0 °C, and two resolved singlets were observed at −40 °C in a 1:0.2 ratio. These data suggest that atropisomerism of the free and coordinated ligand is fast on the NMR time scale at room temperature and that the difference in energy between the two atropisomers is small.

The ^{31}P NMR spectrum of the cyclometalated complex resulting from reaction of $[Ir(COD)Cl]_2$ with **L17** and propylamine (Scheme 2) consisted of broad resonances at room

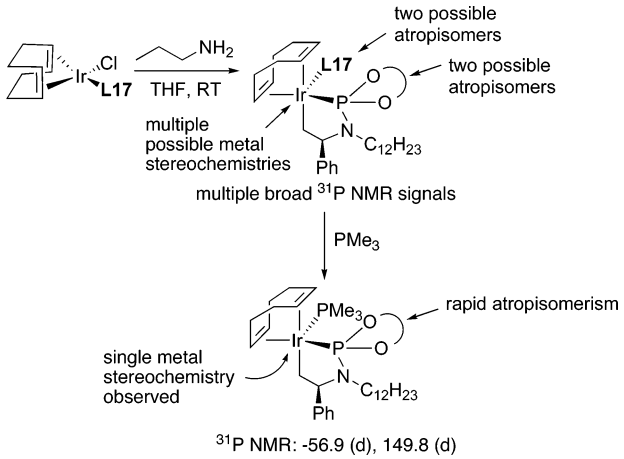
Table 3. Amination of Allylic Carbonates Catalyzed by Complexes Generated from Biphenolate Ligand **L17**[a]



entry	carbonate	amine	yield[b] (%)	ee (%)	b/l
1			86	94 (*R*)	98:2
2			83	94	97:3
3			84	93	99:1
4			72	97	98:2
5			85	95	98:2
6			93	94	99:1
7			81	94	99:1
8			75	95	95:5
9			72	94	99:1

[a] Reactions were conducted at room temperature on a 1.0 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate/amine/catalyst of 100:120:2. [b] Isolated yields from two independent runs.

Scheme 2



temperature. At −40 °C, these resonances sharpened, and two predominant sets of doublets were observed, along with at least two additional sets of doublets of lesser intensity. The multiple sets of resonances of the cyclometalated complex could correspond to those of diastereomeric complexes resulting from atropisomeric conformations of the biphenolate groups in the κ^1 and κ^2 phosphoramidites or from two different geometries at the metal center (see Scheme 2). This mixture of isomers was too complicated for further characterization.

Thus, we replaced the κ^1-phosphoramidite in the cyclometalated complex with the achiral phosphine PMe_3 (Scheme 2) to simplify the stereochemistry of the cyclometalated complex. The PMe_3 complex was isolated in 60% yield by adding the phosphine after the cyclometalation step. The product from this ligand substitution displayed a single set of sharp doublets at 149.7 and −57.0 ppm in the ^{31}P NMR spectrum at room temperature. At −40 °C, the two doublets broadened and were unresolved. At −70 °C, the signals split into two sets of broad resonances, and at −90 °C, two sets of broad resolved doublet resonances were observed in a 1:0.2 ratio. These spectral changes are again consistent with an atropisomerism that occurs on the NMR time scale at low temperature and that is rapid at room temperature. These data are also consistent with a relatively small difference in population of the two atropisomeric conformations of the cyclometalated ligand.

This body of spectroscopic data implies that the atropisomerism is fast enough that the cyclometalated catalyst formed from biphenolate ligand **L17** samples both atropisomeric conformations within the catalytic cycle.[41] Moreover, the lack of large difference in the ratio of atropisomers of the free ligand, of the square planar complex, and of the cyclometalated complex implies that the ratio of atropisomers within the catalytic cycle is much smaller than the ratio of enantiomers formed by the catalytic process. Therefore, the high enantioselectivity of the catalyst with the biphenolate group on phosphorus does not appear to result from a predominant conformation of the biphenolate group that is created by the benzylic stereocenter in the metalacycle. Instead, the catalyst generated from **L17** reacts under classic Curtin−Hammett conditions: the difference in energy between the conformers is smaller than the difference in energy between the two transition states, and the conformer that reacts with the larger rate constant leads to the major enantiomer.

(41) Because the catalytic process appears to occur after dissociation of the κ^1 ligand to generate a four-coordinate iridium complex, any stereochemistry at the metal in the five-coordinate complex would be lost upon dissociation and should not affect the enantioselectivity of the catalytic process.

6. The Relationship between the Structures of Catalysts Containing the Simple Ligand L17 and Those Containing the More Elaborate Phosphoramidites. The information on the various diastereomeric catalysts allows one to draw several conclusions about the structures of the catalysts derived from the simple ligand **L17** and to deduce which is the more reactive atropisomer within the catalytic cycle. As mentioned previously in this paper, we have published that the catalysts derived from the (R_a,R_c,R_c) and (S_a,R_c,R_c) diastereomers of ligand **L1** generate enantiomeric products. Consistent with this assertion, reactions catalyzed by complexes of ligands (R_a,R_c)-**L6** and (S_a,R_c)-**L6** generate enantiomeric products, although the yield of product from reactions catalyzed by the (S_a,R_c)-**L6** was low. Thus, the absolute configuration, not just the ee, appears to be affected by the axial chirality of the binaphtholate group. Because the rates and selectivities of biphenolate ligand **L17** are similar to those of binaphtholate ligands **L1** and **L6**, and because the major enantiomer of the product from reaction of the catalyst containing (*R*)-**L17** is the same as that from the catalyst derived from either (R_a,R_c,R_c)-**L1** or (R_a,R_c)-**L6**, we surmise that the diastereomeric conformation of the catalyst containing ligand **L17** that gives rise to the major enantiomer also has an R_a configuration of the biphenolate group. Our data do not show whether the R_a diastereomer is the more stable isomer in solution, but the assertion that the product is derived from this atropisomer, in combination with the conclusion that the ratio of populations of the two atropisomers in the observed complexes is smaller than the ratio of enantiomeric products of the catalytic reaction, makes it likely that the diastereomer with an R_a configuration of the biphenolate group is more reactive than that with an S_a configuration within the catalytic cycle.

Summary

We have developed a catalyst that possesses stereochemistry controlled by a single phenethyl group for enantioselective allylic amination of linear allylic carbonates to form branched amines with high regioselectivity and enantioselectivity. This ligand resulted from a design process that used as its foundation a cyclometalated structure of the active catalyst. In addition, studies of diastereomeric catalysts showed that the origin of the difference in reactivity of diastereomeric catalysts is due, in part, to different rates of catalyst activation. Finally, these studies show that the major enantiomer of the product from reactions catalyzed by complexes containing a ligand **L17** possessing a biphenolate group results from reaction of the (R_a,R_c) atropisomer. The final ligand **L17** presented in this work is prepared by a short synthesis using trivial reactions with inexpensive bulk chemicals as reagents, and this catalyst behaves in a fashion similar to the more complex catalyst with three resolved stereochemical elements studied originally.

Several principles emerge from this work. (1) Most generally, we show that the identification of the structure of an active catalyst can be integral to the rational selection or design of ligands, even for enantioselective catalysis. (2) We show that bidentate ligands can be generated from a simple monodentate ligand by cyclometalation and that this sequence can provide a simple synthesis of a catalyst for enantioselective reactions. (3) We show that cyclometalation can be a pathway to catalyst activation, rather than catalyst deactivation. (4) We show a means by which a highly selective catalyst can be generated from a ligand containing a single resolved stereocenter. It is interesting to consider that the manner in which this single phenethyl stereocenter affects the population and reactivities of an atropisomeric biphenolate group is reciprocal to the manner in which axial chirality in commonly used ligands, such as BINAP, influences the gearing of aryl substituents on a phosphine.[42−47]

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Supporting Information Available: Full experimental section, including figures of variable-temperature NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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