

2-12-2006

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James M. Takacs

*University of Nebraska-Lincoln*, [jtakacs1@unl.edu](mailto:jtakacs1@unl.edu)

Kittichai Chaiseeda

*University of Nebraska - Lincoln*

Shin A. Moteki

*University of Nebraska - Lincoln*

D. Sahadeva Reddy

*University of Nebraska - Lincoln*

Di Wu

*University of Nebraska - Lincoln*

*See next page for additional authors*

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Takacs, James M.; Chaiseeda, Kittichai; Moteki, Shin A.; Reddy, D. Sahadeva; Wu, Di; and Chandra, Kusumlata, "Rhodium-catalyzed asymmetric hydrogenation using self-assembled chiral bidentate ligands" (2006). *James Takacs Publications*. 1.  
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**Authors**

James M. Takacs, Kittichai Chaiseeda, Shin A. Moteki, D. Sahadeva Reddy, Di Wu, and Kusumlata Chandra

## Rhodium-catalyzed asymmetric hydrogenation using self-assembled chiral bidentate ligands\*

James M. Takacs<sup>‡</sup>, Kittichai Chaiseeda, Shin A. Moteki,  
D. Sahadeva Reddy, Di Wu, and Kusumlata Chandra

*Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588, USA*

**Abstract:** The chirality-directed self-assembly of bifunctional subunits around a structural metal—typically, zinc(II)—is used to form a heteroleptic complex in which a second set of ligating groups are suitably disposed to bind a second metal, forming a heterobimetallic catalyst system. We find that subtle changes in the structural backbone (i.e., ligand scaffold) of such chiral bidentate self-assembled ligands (SALs) can be used to manipulate the ligand topography and chiral environment around catalytic metal; thus, the scaffold can be optimized to maximize asymmetric induction. Using this combinatorial strategy for ligand synthesis, a preliminary study was carried out in which a library of 110 SALs was evaluated in the rhodium-catalyzed asymmetric hydrogenation of a simple *N*-acyl enamide. The level of enantioselectivity obtained varies from near racemic to greater than 80 % ee as a function of the ligand scaffold, with the possibility of further improvement yet to be explored.

**Keywords:** asymmetric catalysis; asymmetric hydrogenation; rhodium-catalyzed; chiral ligands; self-assembly.

### INTRODUCTION

The field of asymmetric catalysis has been an arena of extraordinary activity in recent years [1], and while tremendous advances have been realized in this rapidly moving field of research, significant problems remain. The key to meeting these challenges hinges on discovering and optimizing new ligands and catalyst systems, and understanding the reasons for their effectiveness. Combinatorial and modular approaches to ligand/catalyst design seem to be particularly attractive strategies [2]. We are investigating the use of metal-directed multicomponent self-assembly in a new combinatorial approach to the design and optimization of new ligands and catalyst systems [3]. Recently, several reports have appeared wherein self-assembly is used to generate novel bidentate ligands and catalyst systems [4]. Herein, we focus on new chiral bidentate ligands for use in rhodium-catalyzed asymmetric hydrogenation. The general strategy is illustrated schematically in Fig. 1. We envision dividing the chiral bidentate ligand in half and coupling those subunits via metal-directed self-assembly.

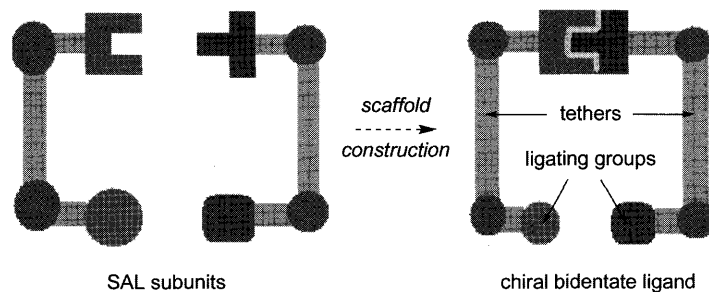
Ultimately, it is the goal of all ligand designs, to create an appropriate “chiral pocket” around the catalytic metal center while establishing the appropriate electronic characteristics for efficient catalysis. Modular approaches to new chiral bidentate ligands often start with one or a small set of scaffolds (or equivalently, backbone or template subunits) and sequentially append the ligating groups as substituents. The idea is to systematically vary the nature of the ligating groups (i.e., vary the elemental

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\**Pure Appl. Chem.* **78**, 197–523. An issue of reviews and research papers based on lectures presented at the 13<sup>th</sup> IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17–21 July 2005.

<sup>‡</sup>Corresponding author

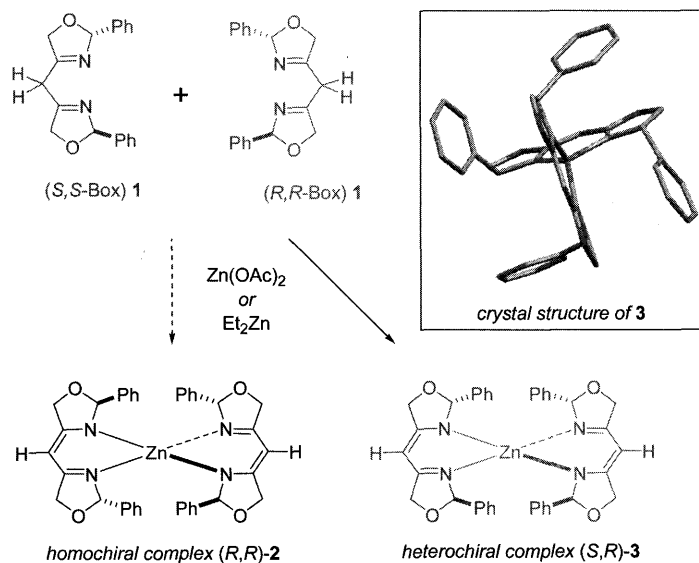
identity, shape, steric demand, and electronic character) to tune or optimize the topography about the metal as well as define the appropriate electronic nature for metal–ligand interaction. A key to our approach is that the ligand scaffold is established along with the selection of ligating groups in the last step of ligand synthesis. This approach is fundamentally different from others and, at least in theory, defines a powerful approach to preparing a diverse set of ligands and ligand scaffolds.



**Fig. 1** Assembling the chiral bidentate ligand from roughly equal halves generates the ligand scaffold in the last step of the synthesis.

### Chirality-directed self-assembly

The “scaffold construction” reaction depicted in Fig. 1 can be accomplished via the reversible metal-directed multicomponent self-assembly of chiral bisoxazoline (box) ligands, a very simple complexation reaction that we have recently shown proceeds with a high level of chiral self-discrimination. It defines a simple strategy for preparing neutral, heteroleptic zinc(II) complexes [5]. When a racemic mixture of box ligands (e.g., 1 equiv each of (4*S*,4'*S*)-**1** and (4*R*,4'*R*)-**1**) is combined with Zn(OAc)<sub>2</sub>, three complexes could form, the homochiral complexes (*S,S*)-**2** and (*R,R*)-**2** (i.e., chiral self-recognition) and/or the heterochiral complex (*S,R*)-**3** (i.e., chiral self-discrimination). The tetrahedral coordination geometry of zinc(II) strongly favors self-discrimination in this case; only the neutral, heterochiral complex (*S,R*)-**3** is observed. Its crystal structure is illustrated in Fig. 2.



**Fig. 2** Chirality-directed self-assembly enables the design strategy to be reduced to practice.

The chirality-directed self-assembly of the racemate can be extended to mixtures of pseudo-racemates such as (*S,S*)-**4** and (*R,R*)-**5** (Fig. 3). Treatment with  $\text{Zn}(\text{OAc})_2$  (or  $\text{Et}_2\text{Zn}$ , vide infra) affords the corresponding neutral zinc(II) complex, which we designate as **SAL-6**. Subunits (*S,S*)-**4** and (*R,R*)-**5** are bifunctional, and **SAL-6** bears pendant phosphite moieties. Having formed **SAL-6**, the crucial question is whether the pendant phosphites can coordinate a second metal. To test this, **SAL-6** was treated with an equivalent of  $[(\text{cod})_2\text{Rh}]\text{BF}_4$ . The  $^{31}\text{P}$  NMR signal at 130.2 ppm, characteristic of a free phosphite, is lost upon addition of  $[(\text{cod})_2\text{Rh}]\text{BF}_4$ , and a new doublet appears at 112.7 ppm ( $J_{\text{Rh,P}} = 248.6$  Hz). The results are consistent with the formation of the chiral heterobimetallic rhodium complex  $[(\text{SAL-6})\text{Rh}(\text{cod})]\text{BF}_4$  as illustrated.

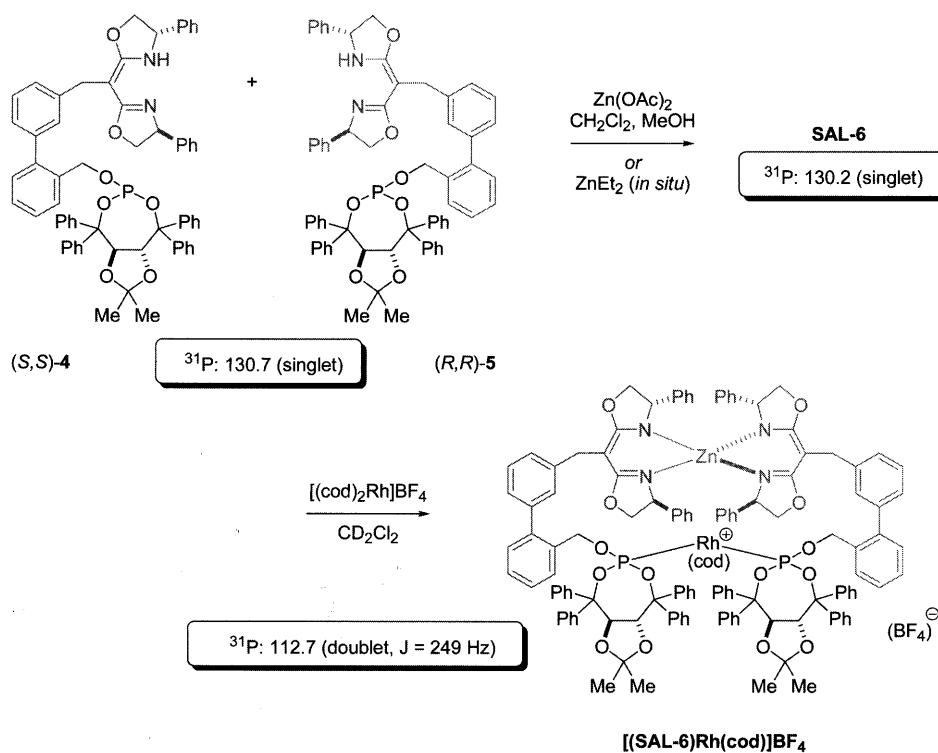


Fig. 3  $^{31}\text{P}$  NMR evidence supports the formation of a heterobimetallic complex from **SAL-6**.

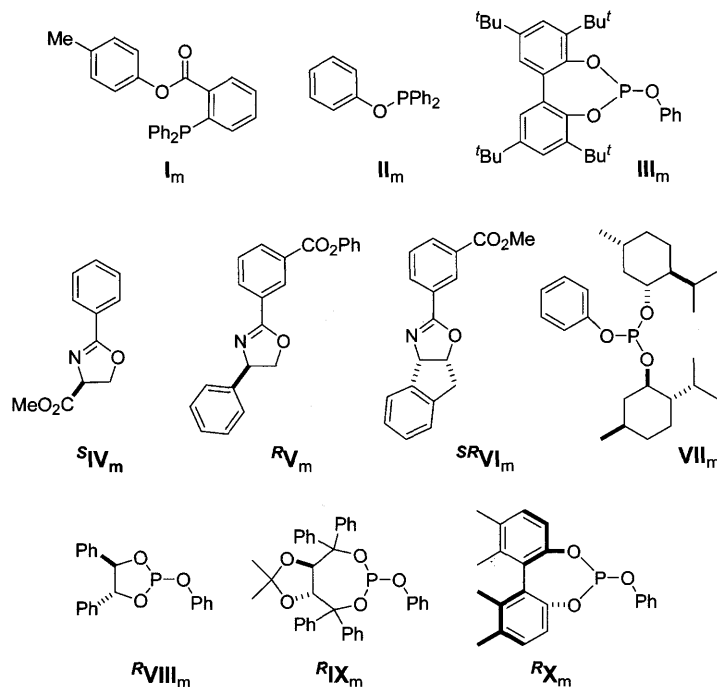
## RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION

The need to carry out enantioselective hydrogenation is frequently encountered in chemical discovery and process research, and therefore is relevant to a wide range of synthetic intermediates and of substantial industrial importance. As nicely summarized in a recent review by Blaser [6], there are significant drawbacks with the currently available catalyst systems, and the reaction also constitutes a common testing ground for new ligand systems for asymmetric catalysis [7]. Having used palladium-catalyzed allylic amination to demonstrate proof of principle for our chiral SAL concept [3], asymmetric hydrogenation offers us the opportunity to evaluate the SAL approach with a different metal and in very different reaction.

### Selecting the ligating groups using monodentate ligand mixtures

Reetz [8] and Feringa [9] independently reported a new concept in asymmetric catalysis, the idea of screening combinatorial mixtures of simple monodentate ligands. In rhodium-catalyzed hydrogenation reactions, each found that the enantiomeric excess obtained from certain mixtures of ligands was higher than that obtained with either ligand alone. This approach is now being quite widely pursued [10].

In the SAL approach, we have considerable flexibility as to the choice of ligating groups. In short, we want to select the combination(s) of ligating groups that will most likely afford efficient catalysts (efficiency as defined by yield and reaction rate as well as selectivity), and then rely on the ability to vary the SAL scaffold to optimize their orientation and hence the enantioselectivity. To aid in selecting the most promising ligating group(s) for preparing the SAL library, we screened various combinations of the monomeric model ligands ( $I_m-X_m$ ) shown in Fig. 4 in the rhodium-catalyzed hydrogenation of the amino acid precursor, enamide **7**; the monomeric ligands shown correspond to ligating groups that could readily be incorporated in the SAL precursors described above.



**Fig. 4** A collection of monomeric ligands ( $I_m-X_m$ ) screened in the rhodium-catalyzed hydrogenation of enamide **7**.

The tabulated screening data (Table 1) provide a great deal of information. Note the goal of our study is not to necessarily identify the optimal monodentate ligand for the reaction; others have successfully pursued that approach as described above. Rather, our purpose is to identify promising ligating groups that can readily be incorporated into our SAL precursors to prepare SAL libraries with which the potential for ligand tuning via scaffold optimization can be evaluated. The various combinations of ligands  $I_m-X_m$  give rise to wide variations in yield and enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of enamide **7**. While space does not permit a detailed discussion of the data here, the axially chiral BIPHEP phosphite derivative [11]  $SX_m$  stands out as the most interesting ligand screened. Almost every combination with it gives an appreciable level of enantioselectivity; its hetero-

combination with the TADDOL-derivative  $R^IX_m$  is particularly intriguing and will be pursued in due course. Considering the data in Table 1, the BIPHEP phosphite ligating group appears to be the obvious lead structure for an initial SAL library [12].

**Table 1** Selecting the ligating group for SAL scaffold optimization: the rhodium-catalyzed hydrogenation of enamide **7** using combinations of monomeric ligands.<sup>a</sup>

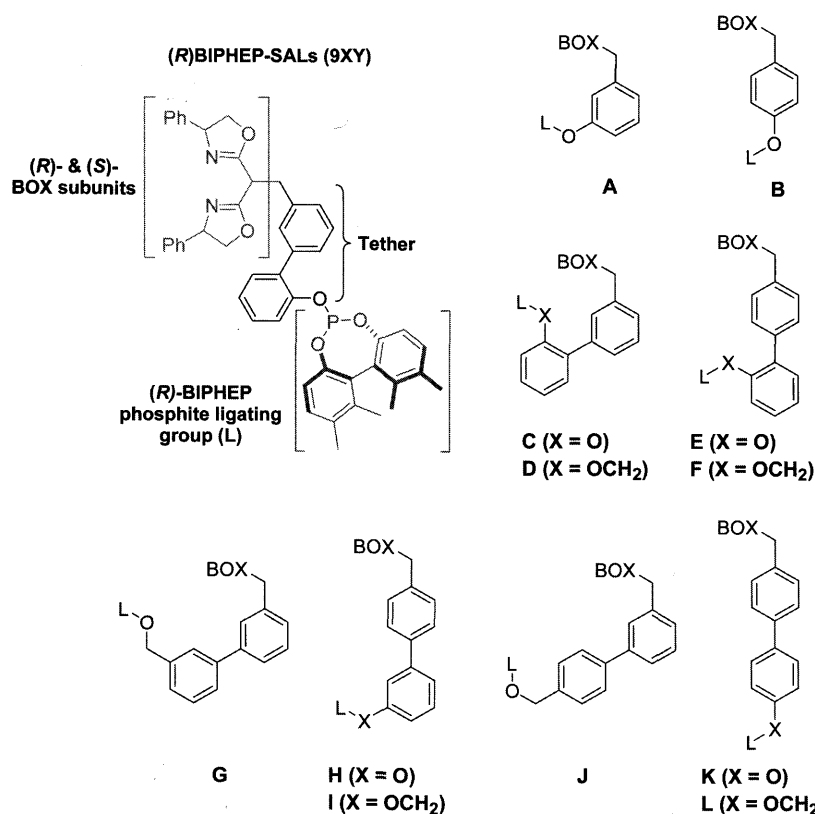
Reaction scheme: Enamide **7** (with NHAc and OMe groups) reacts with 1% Rh(cod)<sub>2</sub>BF<sub>4</sub> and 2.2% total ligand in CH<sub>2</sub>Cl<sub>2</sub> at 25 psi H<sub>2</sub> for 10 h at room temperature to yield amine **8**.

	( <i>S</i> )-IV <sub>m</sub>	( <i>R</i> )-V <sub>m</sub>	VI <sub>m</sub>	VII <sub>m</sub>	VIII <sub>m</sub>	IX <sub>m</sub>	( <i>R</i> )-X <sub>m</sub>
<b>I<sub>m</sub></b>	5 (5 <i>S</i> )	5 (1 <i>S</i> )	13 (5 <i>S</i> )	10 (7 <i>R</i> )	100 (5 <i>R</i> )	10 (2 <i>S</i> )	1 (5 <i>S</i> )
<b>II<sub>m</sub></b>	93 ( <i>rac</i> )	99 (1 <i>S</i> )	26 (3 <i>S</i> )	100 (1 <i>S</i> )	100 (5 <i>S</i> )	90 (1 <i>R</i> )	99 (7 <i>S</i> )
<b>III<sub>m</sub></b>	68 ( <i>rac</i> )	94 ( <i>rac</i> )	55 (8 <i>R</i> )	100 (3 <i>R</i> )	100 (12 <i>S</i> )	100 (1 <i>S</i> )	89 (13 <i>S</i> )
( <i>S</i> )-IV <sub>m</sub>	17 (10 <i>R</i> )	7 (1 <i>S</i> )	3 (8 <i>S</i> )	18 (33 <i>R</i> )	98 (8 <i>R</i> )	15 (3 <i>S</i> )	42 (57 <i>S</i> )
( <i>R</i> )-V <sub>m</sub>		20 (26 <i>R</i> )	42 (43 <i>R</i> )	16 (29 <i>R</i> )	97 ( <i>rac</i> )	14 (3 <i>S</i> )	37 (61 <i>S</i> )
VI <sub>m</sub>			5 (4 <i>S</i> )	14 (6 <i>S</i> )	24 (2 <i>R</i> )	3 (10 <i>R</i> )	19 (43 <i>S</i> )
VII <sub>m</sub>				24 (39 <i>R</i> )	100 (4 <i>R</i> )	19 (4 <i>S</i> )	98 (57 <i>S</i> )
VIII <sub>m</sub>					100 (11 <i>R</i> )	100 (4 <i>R</i> )	100 ( <i>rac</i> )
IX <sub>m</sub>						100 (2 <i>S</i> )	<b>100</b> <b>(76 <i>S</i>)</b>
( <i>R</i> )-X <sub>m</sub>							<b>100</b> <b>(65 <i>S</i>)</b>

<sup>a</sup>The table entries refer to the combination of ligands (1.1 mol % of each) used for that reaction; the chemical yields are shown along with the % ee's obtained and the major enantiomer formed given in parentheses. For example, data in the first row show the results obtained using the combination of 1.1 mol % of ligand **I<sub>m</sub>** with 1.1 mol % of each of the chiral monomeric ligands  $S^IV_m$  through  $R^X_m$ .

### Investigating a combinatorial library of (*R*)BIPHEP-SALS

We prepared and screened a library of 110 SAL combinations (i.e., **SAL-9XY**) in the rhodium-catalyzed hydrogenation of the amino acid precursor, enamide **7**. The SALs screened were drawn from the set of subunits illustrated in Fig. 5 (i.e., SAL subunits A–L). Each subunit contains the BIPHEP phosphite ligating group, and for the most part, the SALs used in the [(**SAL-9XY**)Rh(BF<sub>4</sub>)]-catalyzed asymmetric hydrogenations of enamide **7** were prepared in situ by combining the desired two SAL subunits with Et<sub>2</sub>Zn.



**Fig. 5** The collection of (S)- and (R)-BOX BIPHEP-SAL subunits (A–L) used in combinatorial screening of SAL-9XY (X and Y independently selected from among subunits A through L).

Figure 6 shows the variation in enantioselectivity obtained as a function of the SAL scaffold for the 110 SAL-9XY (X and Y independently selected from among A through L) combinations screened in the present study; the percent ee obtained is plotted from low to high. For reference, using 2 equiv of chiral monophosphite (BIPHEP)POPh ( $X_m$ ) gives 65 % ee in the reaction. Once again, we see wide variation in enantioselectivity, from racemic to above 80 % ee, with roughly two-thirds of the SAL-9XY combinations affording a higher level of asymmetric induction than the model monomer  $X_m$ . Note that the results of the screening reactions reflect only the influence of varying the scaffold structure; every SAL in the screen has the same set of BIPHEP ligating groups. The graph is qualitatively similar to that seen for the palladium-catalyzed asymmetric allylic amination previously reported; however, unlike that study, here the plot levels off. Apparently, many of the variations in scaffold are effectively redundant; that is, they do not significantly alter the topography defined by the BIPHEP phosphite moiety in the chiral rhodium-catalyst. The results suggest that a more diverse set of SAL subunits is needed to further optimize the scaffold structure or that the limit of the capacity to productively orient the BIPHEP phosphite moiety has been reached. Nonetheless, the best SAL combinations identified thus far are already very close to giving useful levels of asymmetric induction.



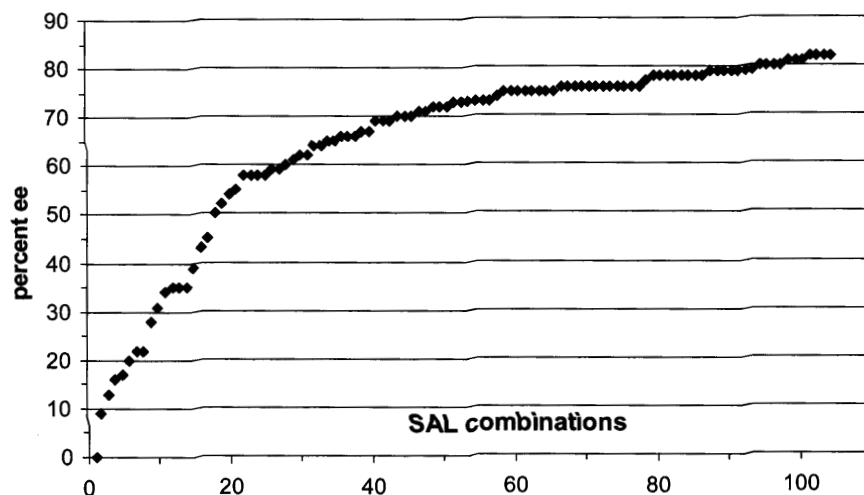
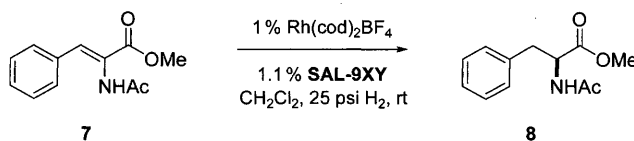


Fig. 6 A graphical summary of the % ee values obtained for the various SAL-9XY combinations of BIPHEP-SAL subunits A–L plotted in ascending order.

The detailed results of the screening reactions are summarized in Table 2. Again, the data demonstrate wide variation in both yield and enantioselectivity for the [(SAL-9XY)Rh(BF<sub>4</sub>)]-catalyzed asymmetric hydrogenation. While the latter ranges from racemic to above 80 % ee, the *S*-enantiomer predominates in all nonracemic products obtained. Eleven combinations (i.e., those highlighted in boldface in Table 2) give 80 % ee or greater. An interesting trend emerges from the data obtained with this combinatorial library of 110 SALs. Nine of the eleven most successful combinations contain subunit **F**; for example, the combination using two **F** subunits, **SAL-9FF**, is among the best, affording 81 % ee (87 % yield). However, small changes in the SAL scaffold can result in large differences in enantioselectivity and yield. For example, contrast the results obtained using **SAL-9FF** (81 % ee, 87 % yield) to those obtained using the closely related structure **SAL-9EE** (9 % ee, 3 % yield). It is also interesting to note that, while each of the SALs in Table 2 is structurally unique, some differ only very subtly in scaffold structure. For example, **SAL-9FI** can be prepared by combining (*S*)-**F** with (*R*)-**I** or by combining (*R*)-**F** with (*S*)-**I**. The resulting diastereomeric SALs generally behave similarly, 82 % ee (92 % yield) and 81 % ee (97 % yield), respectively, for the two combinations described.

**Table 2** [(SAL-9XY)Rh(BF<sub>4</sub>)]-Catalyzed asymmetric hydrogenation of dehydroaminoacid derivative **7** using various combinations of BIPHEP-SAL subunits **A–L**.<sup>a</sup>

SAL-9XY	R-A	R-B	R-C	R-D	R-E	R-F	R-H	R-I	R-J	R-L
<b>S-A</b>	49 (62)	66 (79)	16 (61)	78 (73)	35 (59)	78 (75)	100 (72)	49 (73)	23 (71)	75 (69)
<b>S-B</b>	50 (69)	69 (76)	7 (58)	61 (75)	26 (64)	79 (78)	<b>97</b> <b>(81)</b>	47 (78)	46 (76)	49 (72)
<b>S-C</b>	5 (57)	18 (70)	3 (58)	52 (78)	2 (58)	66 (79)	35 (43)	33 (76)	24 (75)	17 (73)
<b>S-D</b>	4 (34)	1 (35)	2 (13)	51 (79)	1 (35)	<b>73</b> <b>(80)</b>	17 (35)	71 (79)	54 (79)	35 (75)
<b>S-E</b>	6 (41)	11 (66)	4 (rac)	24 (70)	3 (9)	43 (75)	23 (22)	47 (73)	34 (69)	27 (65)
<b>S-F</b>	13 (64)	55 (72)	7 (59)	<b>81</b> <b>(82)</b>	9 (67)	<b>87</b> <b>(81)</b>	42 (45)	<b>92</b> <b>(82)</b>	<b>90</b> <b>(82)</b>	<b>70</b> <b>(80)</b>
<b>S-G</b>	10 (62)	54 (73)	10 (58)	<b>60</b> <b>(80)</b>	11 (69)	35 (78)	61 (50)	31 (76)	25 (76)	45 (78)
<b>S-H</b>	13 (31)	46 (60)	14 (17)	59 (74)	6 (28)	28 (71)	18 (16)	100 (76)	44 (55)	66 (66)
<b>S-I</b>	21 (53)	96 (76)	38 (76)	96 (77)	58 (73)	<b>97</b> <b>(81)</b>	94 (54)	97 (79)	82 (76)	96 (76)
<b>S-J</b>	28 (65)	95 (75)	44 (66)	92 (78)	30 (67)	<b>93</b> <b>(80)</b>	98 (52)	67 (76)	57 (78)	37 (76)
<b>S-K</b>	10 (52)	28 (70)	1 (22)	38 (78)	1 (39)	<b>89</b> <b>(82)</b>	10 (20)	68 (79)	13 (75)	26 (75)

<sup>a</sup>The table entries refer to the SAL prepared from the combination of (S)- and (R)-BOX BIPHEP-SAL subunits (1.1 mol % of each) used in that reaction; the chemical yields are shown along with the % ee's obtained and the major enantiomer formed given in parentheses. For example, data in the first row show the results obtained using the SALs formed from the combination of 1.1 mol % of the (S)-BOX BIPHEP-SAL subunit **A** with 1.1 mol % of each of the (R)-BOX BIPHEP-SAL subunits **A** through **L**.

## SUMMARY

We describe preliminary studies on the design and evaluation of chiral SALs for rhodium-catalyzed asymmetric hydrogenation. The results obtained thus far make it clear that, while the shape of the BIPHEP-phosphite ligating group within the macrocyclic metal chelate is invariant, small changes in the ligand scaffold reposition or reorient that shape to a more, or less, effective position for asymmetric catalysis. In some ways, this seemingly mimics a feature of biological catalysts; that is, Nature uses a rather limited set of structures (i.e., amino acid side chains and/or enzyme cofactors) positioned in different ways via macromolecular assemblies to define the topography and characteristics required for efficient asymmetric catalysis.

The current best SAL combinations give greater than 80 % ee, very close to useful levels of asymmetric induction. However, a surprising number of the scaffold variations are effectively redundant; that is, they apparently do not significantly alter the topography defined by the BIPHEP phosphite moiety in the chiral rhodium-complex. This suggests that a more diverse set of SAL subunits is needed to further optimize the scaffold structure or that the limit of the capacity to productively orient the BIPHEP phosphite moiety has been reached. There are many additional opportunities for further scaffold and ligating group optimization to pursue, and further studies on the design and evaluations of SAL libraries are in progress.

## ACKNOWLEDGMENTS

Financial support from the University of Nebraska Research Initiative is gratefully acknowledged. We thank Mr. Daniel Becker, Mr. Brian Cory, and Ms. Brittany Prather for carrying out experiments related to the studies reported herein. We thank the NSF (CHE-0091975) and UNL CMRA for purchase of the diffractometer and the NSF (CHE-0091975, MRI-0079750) and NIH (SIG-1-510-RR-06307) for purchases of the NMR spectrometers used in these studies.

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12. The data summarized in Table 1 represent the results of a preliminary screen of ligating groups. Further studies, including the use of other readily available axially chiral ligating groups such as BINOL and related derivatives, are in progress.