Dirhodium Tetra(*N*-arylsulfonylprolinates) as Chiral Catalysts For Asymmetric Transformations of Vinyl- and Aryldiazoacetates

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Rhodium(II) prolinates are superb catalysts for asymmetric transformations of vinyldiazoacetates and phenyldiazoacetates. The most well-developed transformation is the [3 + 4] annulation between vinyldiazoacetates and dienes which is a very general method for the stereoselective synthesis of highly functionalized seven-membered rings. Recent studies have led to a general method for asymmetric intermolecular C–H activation which displays promising regio- and diastereocontrol in addition to the enantiocontrol.

Introduction

For many years we have been interested in the synthetic potential of the cyclopropanation reactions of vinyldiazoacetates catalyzed by dirhodium tetracarboxylates.[1] The impetus for this work was the discovery that vinyldiazoacetate cyclopropanations are highly diastereoselective.[2] Furthermore, the resulting vinylcyclopropanes are prone to stereoselective ring expansions.[3−5] Some of the most significant applications of this chemistry are summarized in Scheme 1.[6] Most notable is the reaction between vinyldiazoacetates and dienes because the resulting *cis*-divinylcyclopropanes undergo a Cope rearrangement.[7] This results in the formation of seven-membered rings with full control of relative stereochemistry at up to three stereogenic centers. The reaction is applicable to a wide range of dienes, including acyclic and cyclic dienes,[5,8−12] oxygenated dienes,[13][14] furans,[15−17] pyrroles,[18−20] and benzenes.[21] Having developed general methods for the diastereoselective synthesis of a range of different ring systems using vinylcarbenoid reactions, the natural progression for this chemistry was to design methods that would control the absolute stereochemistry of the reactions. Our studies to prepare methods for the asymmetric reactions of vinyldiazoacetates and phenyldiazoacetates are summarized in this review.

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Chiral Catalyst Development

The obvious way to achieve asymmetric vinylcarbenoid cyclopropanations would be to use one of the chiral copper or rhodium amide catalysts that had been used so successfully in asymmetric diazoacetate cyclopropanations.[22−26] However, copper and rhodium amide catalysts are not very effective at catalyzing carbenoid formation from vinyldiazoacetates.[27][28] A very active catalyst such as a dirhodium tetracarboxylate is needed as otherwise the vinyldiazoacetates will rearrange to pyrazoles rather than form vinylcarbenoid intermediates.[29] The literature precedence, however, for asymmetric cyclopropanation using dirhodium tetracarboxylates was not promising.[30][31] The highest reported value for asymmetric induction was for the intramolecular cyclopropanation of the diazoketosulfonate **1**,

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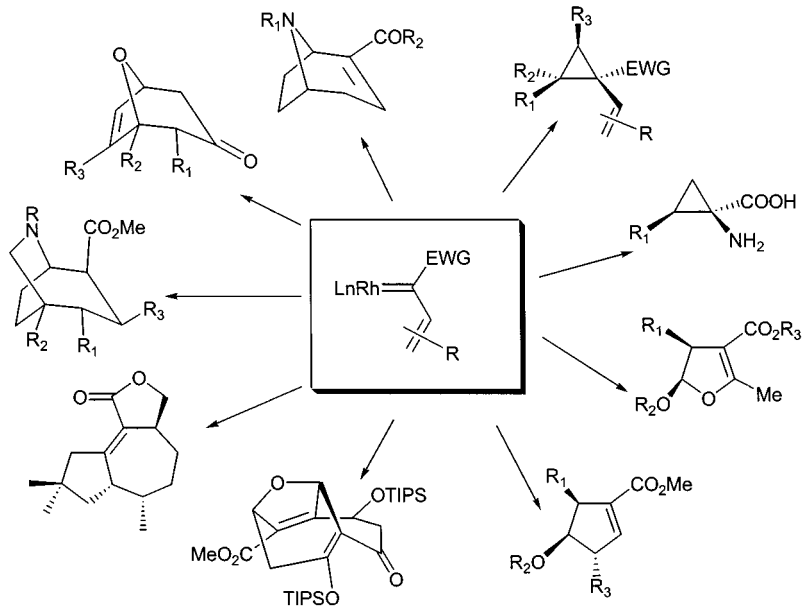
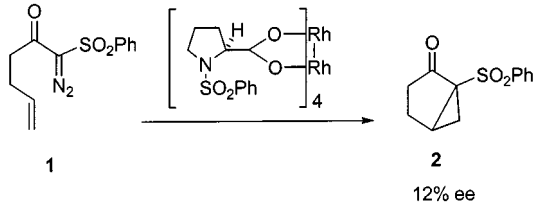


Scheme 1. Synthetic applications of vinylcarbenoids

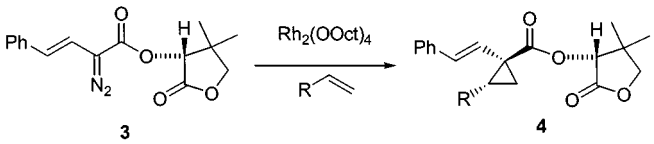
which resulted in the formation of the cyclopentanone **2** in 12% ee (Scheme 2).[31]



Scheme 2. Asymmetric intramolecular cyclopropanation with dirhodium tatraprolinate catalysis

Due to the perceived difficulties with the chiral catalyst approach for asymmetric vinyldiazoacetate cyclopropanations, strategies using chiral auxiliaries were first explored. α-Hydroxy esters, such as (*S*)-methyl lactate or (*R*)-pantolactone, were found to be excellent chiral auxiliaries for vinyldiazoacetate cyclopropanations.[29][32] The reaction of the vinyldiazoacetate **3** with a series of alkenes resulted in cyclopropanes **4** with > 90% de (Scheme 3).[29] This chiral auxiliary approach has been applied to the reaction of vinyldiazoacetates with dienes, vinyl ethers, furans, and pyrroles, leading to the asymmetric synthesis of cycloheptadienes,[29] dihydrofurans,[33] 8-oxabicyclo[3.2.1]octa-3,6-dienes,[34] and tropanes,[35][36] respectively.

A model that rationalizes the asymmetric induction of the chiral auxiliaries is shown in Figure 1. The critical factor that causes the high asymmetric induction is considered to be an interaction between the carbonyl of the auxiliary and the carbenoid. The extent of this interaction is limited such that carbenoid reactivity is maintained, but the effect of the interaction will be to block one face of the carbenoid. In order to limit unfavorable steric interference between the catalyst "wall" and the auxiliary, interaction of the carbonyl



R	de, %	yield, %
Ph	97	84
4-ClPh	>95	92
4-MeOPh	>95	75
EtO	92	71
AcO	90	42

Scheme 3. Chiral auxiliary approach for asymmetric vinylcarbenoid cyclopropanations

of the auxiliary with the *re* face of the carbenoid is preferred over the *si* face. Consequently, the *si* face of the carbenoid is open to attack by the alkene leading to the formation of the (1*R*,2*R*) diastereomer of the cyclopropane.[29]

Even though α-hydroxy esters worked well as chiral auxiliaries for vinyldiazoacetate cyclopropanations, a more practical method would be asymmetric catalysis if an effective chiral catalyst could be identified. Chiral catalysts based on the rhodium carboxylates would be ideal because these catalysts are kinetically very active. At the onset of our work, however, no rhodium(II) carboxylate catalyst had resulted in > 10% ee in intermolecular cyclopropanations.[30] It was generally considered that the chiral influence of the carboxylate ligands was too far removed from the binding site of the carbenoid for effective asymmetric induction to occur.[22][37] All of these studies had been carried out on alkyl diazoacetates as the carbenoid precursor. We felt, however, that these generalizations about the lack of success of dirhodium tetracarboxylate catalysts may not

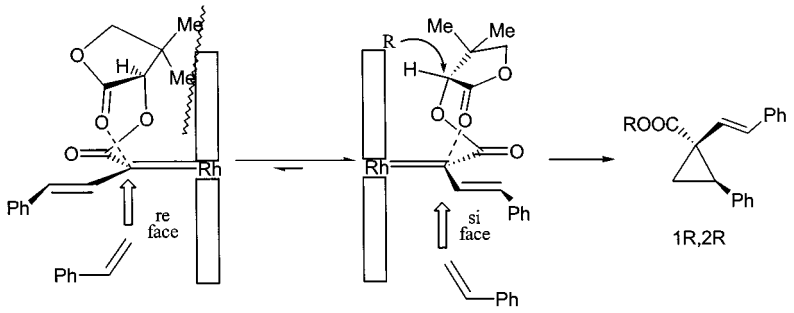
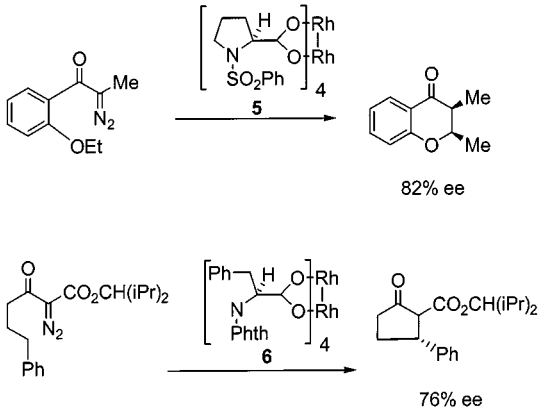


Figure 1. Model for asymmetric induction using (*R*)-pantolactone as a chiral auxiliary

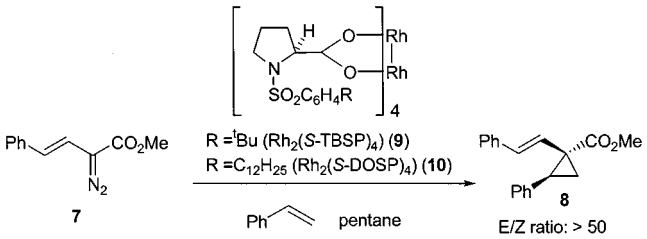
necessarily extend to the vinyldiazoacetate system because the steric demands and diastereoselectivity of the vinyldiazoacetate system is very different from the diazoacetate system.[1]

On surveying the chiral dirhodium carboxylates that had been used in carbenoid reactions, two catalyst systems stood out. Both the dirhodium tetraprolinate **5** developed by McKervey[38−41] and the phthalimidocarboxylate **6** developed by Hashimoto and Ikegami[42−44] had achieved reasonably high asymmetric induction in intramolecular C−H insertion (Scheme 4), although no literature precedence existed for their use in asymmetric intermolecular cyclopropanations.



Scheme 4. Asymmetric intramolecular C−H insertion with dirhodium tatracarboxylate catalysis

The evaluation of a series of prolinate catalysts was carried out using the standard reaction between vinyldiazoacetate **7** and styrene to form the (*E*)-cyclopropane **8** (Scheme 5).[45][46] It quickly became apparent that the vinyldiazoacetate/prolinate combination was exceptional for asymmetric cyclopropanation. As is typical of vinyldiazoacetate cyclopropanations, the (*E*/*Z*) ratio for this reaction is greater than 50:1. Much higher enantioselectivity was observed when pentane was used as solvent. Consequently, the optimum catalysts for this chemistry are Rh_2(*S*-TBSP)$_4$ (**9**), and Rh_2(*S*-DOSP)$_4$ (**10**), which are soluble in hydrocarbon solvents. Rh_2(*S*-DOSP)$_4$ is even soluble in hydrocarbons at −78°C and under these conditions, it is still an active catalyst leading to the formation of **8** in 98% ee. *N*-acylprolinates have also been examined as chiral ligands for the asymmetric cyclopropanation using the vinyldiazoacetate **7**,[47] but in general, they offered no advantages over the *N*-arylsulfonylprolinates in this cyclopropanation system. *N*-Acylprolinate catalysts have resulted in impressive enantioselectivity in a [3 + 2] annulation between diazodimedone and vinyl ethers.[48]

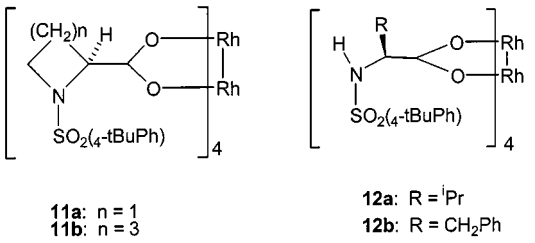


catalyst	temp, °C	ee, %
Rh_2(*S*-TBSP)$_4$	25	**90**
Rh_2(*S*-DOSP)$_4$	25	**92**
Rh_2(*S*-DOSP)$_4$	-78	**98**

Scheme 5. Chiral catalysis approach for asymmetric vinylcarbenoid cyclopropanations

A study on a series of *N*-arylsulfonyl amino acids indicated that a cyclic amine is required for high asymmetric induction.[45] Reasonably high asymmetric induction (81% ee in pentane at 25°C) can be obtained with both the azetidinecarboxylate **11a** and the picolinate **11b**. In reactions catalyzed by complexes derived from acyclic amino acids such as phenylalanine (**12a**) or leucine (**12b**) the enantioselectivity in the formation of **8** is very low (6% and 30% ee, respectively in CH_2Cl_2 at 25°C). Recently, a combinatorial approach was developed by Burgess to ascertain if improved chiral catalysts could be obtained for the asymmetric cyclopropanation of 1,1-diphenylethylene by vinyldiazoacetate **6**.[27] Even though some promising leads were identified, no catalyst was able to match Rh_2(*S*-TBSP)$_4$ (**9**) or Rh_2(*S*-DOSP)$_4$ (**10**) in terms of yield and enantioselectivity.

High asymmetric induction with the *N*-arylsulfonylprolinate is limited to carbenoid systems that contain en electron-withdrawing group and an electron donating group.[49] The phenyldiazoacetate **13**/ Rh_2(*S*-DOSP)$_4$ system results



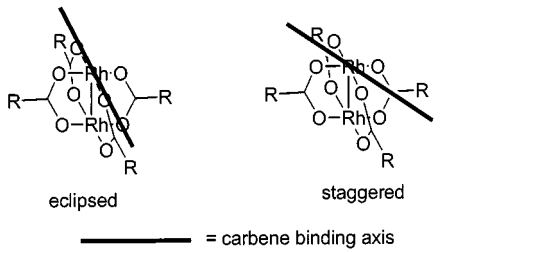
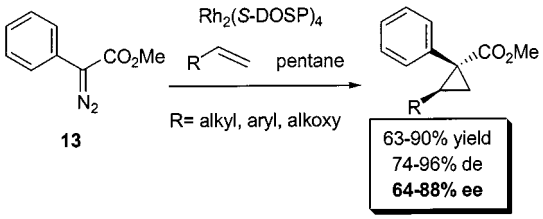


Figure 2. Alignment of carbenoid to rhodium complex

in high asymmetric induction with a series of alkenes (Scheme 6)[50] but the enantioselectivity is very low with ethyl diazoacetate, dimethyl malonate, phenyldiazomethane and vinyldiazomethane.[49] Doyle and McKervey[51] have carried out a study on the asymmetric cyclopropanation by methyl phenyldiazoacetate with a range of chiral catalysts and confirmed that the dirhodium tetraprolinates are the best catalysts for this type of reaction. Zwanenburg[52] has demonstrated that the azetidinecarboxylate **11a**[45] and even an aziridinecaboxylate can be used as a chiral catalyst for phenyldiazoacetate cyclopropanations, but the enantioselectivity obtained with these catalysts (35−57% ee) do not match that obtained with the prolinate catalysts.



Scheme 6. Asymmetric cyclopropanation using methyl phenyldiazoacetate

The development of Rh_2(*S*-TBSP)$_4$ (**9**), and Rh_2(*S*-DOSP)$_4$ (**10**) was achieved through reaction optimization on an empirical basis.[45] A model was then developed to rationalize these results and this is summarized below.[45] We had already developed a model to explain the high diastereoselectivity of vinyldiazoacetate cyclopropanation, in which the alkene is considered to approach the carbenoid in a side-on manner leading to a concerted but non-synchronous cyclopropanation.[1] In order to rationalize the asymmetric catalysis results, additional details about the arrangement of the carbenoid and dirhodium complex needed to be understood. On the basis of molecular modeling, the carbene is considered to preferentially line up staggered to the oxygen ligands of the carboxylates rather than in an eclipsed orientation (Figure 2).[45] This would seem reasonable on steric grounds, but also, a staggered arrangement is required for stabilization of the carbenoid ligand by metal back-bonding because at least in the rhodium(II) dimer, the d_{yz} and d_{xz} orbitals are hybridized to form two new orbitals that lie in this staggered position.

Even with a well-defined approach of the alkene to the vinylcarbenoid complex and with the expectation that the vinylcarbenoid would exist in a staggered arrangement to the dirhodium core, further stereochemical issues must be involved to explain the high enantioselectivity observed in these cyclopropanations. We have presented a detailed account of a predictive model for the asymmetric induction, in which the complex is considered to exist preferentially in a D_2 symmetric conformation.[45] In certain regards, the demanding ligand arrangement is surprising because the prolinate groups would be expected to have considerable conformational mobility. However, due to steric constraints, the *N*-arylsulfonyl group must adopt either an "up (α)" or "down (β)" conformation (Figure 3).[45] The *N*-arylsulfonyl group cannot lie in the periphery of the catalyst as it would bump into the adjacent proline ligand.

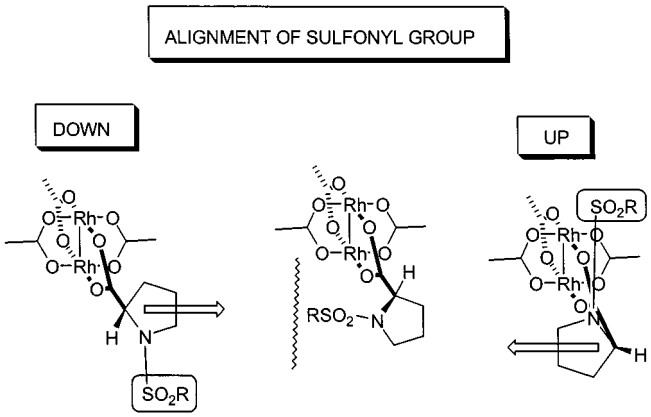


Figure 3. Alignment of arylsulfonyl group

Consideration of the α or β arrangement for the NSO_2Ar group for all four ligands generates four possible orientations, the α,α,α,α form, the α,α,β,β form, the α,β,α,β form and the α,α,α,β form. Of these the D_2 symmetric α,β,α,β form is the most promising (Figure 4).[45] Due to the symmetry of the system both faces of the catalyst would give the same asymmetric induction and only two distinct staggered orientations are possible, and of these, one is very crowded.

All the stereochemical results that have been obtained so far can be rationalized by proposing that the catalysis occurs through this conformation of the complex. This can be represented in Figure 5 with structures **14**−**16** where the thickened vertical lines are indicative of the steric influence of the arylsulfonyl group. Due to the symmetry of the system only one face of the catalyst needs to be considered. Assuming that the alkene approaches side-on over the electron-withdrawing group, then attack would need to occur at the front face of the carbene in **14** because the back is blocked by the

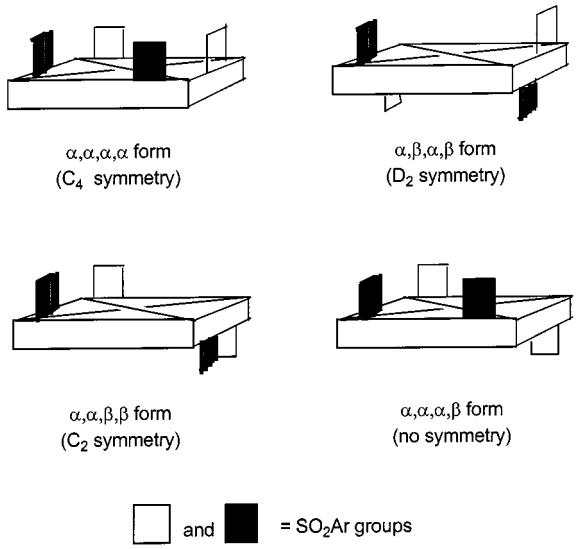


Figure 4. Model of ligand arrangement

arylsulfonyl group. This catalyst is ideally suited to vinyl- and phenyldiazoacetates because in these systems, the approach of the alkene is considered to be much more restrictive than for carbenoids derived from diazoacetates.

bridge at the 2-position of the prolines was achieved using Seebach's method for the asymmetric alkylation of proline (Scheme 7).[53] Reaction of the aminal **19**, derived from the reaction of proline with pivaldehyde, with n-butyl lithium followed by treatment with *meta*-α,α′-dibromoxylene generated the bis-alkylated product **20**. Methanolysis of **20** followed by sulfonylation and ester hydrolysis generated the bridged ligand **21**. A high temperature ligand exchange between rhodium(II) acetate and **21** generated the bridged catalyst **17** in ca. 50% yield.

The synthesis of **18**, which has a *meta*-phenyl bridge at the C-5 *cis* position of the prolines was achieved according to Scheme 8.[54] Reaction of the 1,3-dianion of benzene with pyroglutamate (**22**) generated the bis-imine **23**. Catalytic hydrogenation of the bis-imine **23** followed by *N*-sulfonation and ester hydrolysis generated the bridged ligand **24**. Ligand exchange of **24** with rhodium(II) acetate generated the bridged catalyst **18**.

The comparison of the efficiency of Rh_2(*S*-DOSP)$_4$ (**10**) with the bridged catalysts **17** and Rh_2(*S*-biTISP)$_2$ (**18b**) is shown in Scheme 9.[53][54] Both **17** and Rh_2(*S*-biTISP)$_2$ result in good asymmetric induction in the standard reaction of vinyldiazoacetate **7** with styrene but the (1*R*,2*R*) isomer of cyclopropane **8** is preferentially formed, which is opposite to that obtained with Rh_2(*S*-DOSP)$_4$. The most likely explanation for change in asymmetric induction by Rh_2(*S*-DOSP)$_4$ compared to **17** and Rh_2(*S*-biTISP)$_2$ is that the preferred staggered orientation for carbenoid binding is different for Rh_2(*S*-DOSP)$_4$ and the other two catalysts, and this causes different faces of the carbenoid to be exposed for reaction. A very significant solvent effect is seen with the Rh_2(*S*-DOSP)$_4$ catalyst and this has been suggested to be because the ligands have conformational mobility and align in a preferred orientation for good asymmetric induction in non polar solvents.[51] The rigid bridged prolinate complexes do not display the same solvent effect. The asymmetric induction with **17** is independent of solvent but overall this catalyst is inferior to Rh_2(*S*-DOSP)$_4$. In the case of Rh_2(*S*-biTISP)$_2$, the highest levels of asymmetric induction occur when CH_2Cl_2 is used as solvent. Under these conditions Rh_2(*S*-biTISP)$_2$ is equivalent if not better than Rh_2(*S*-DOSP)$_4$ as a chiral catalyst.

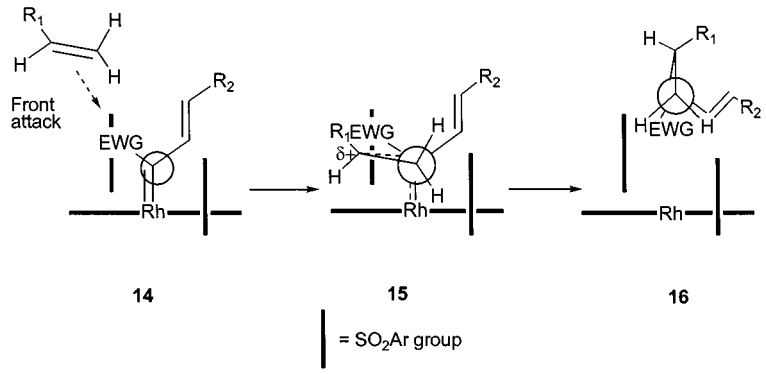
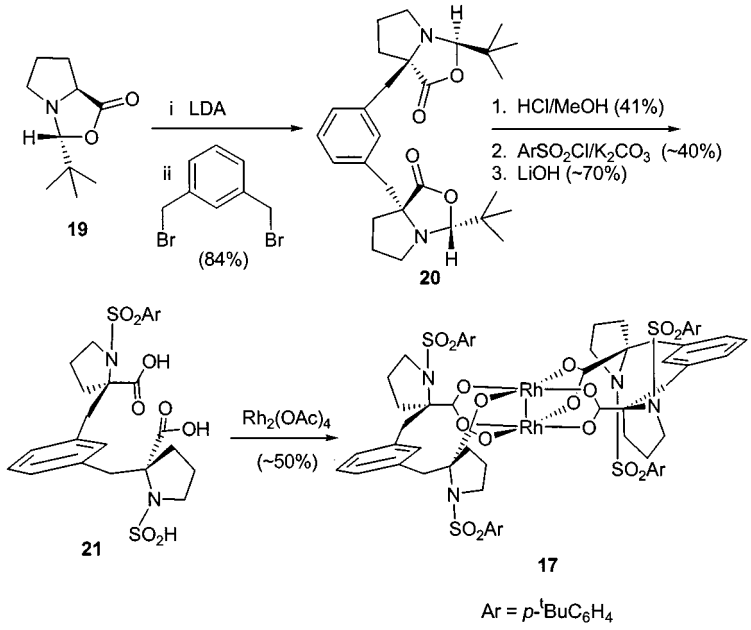


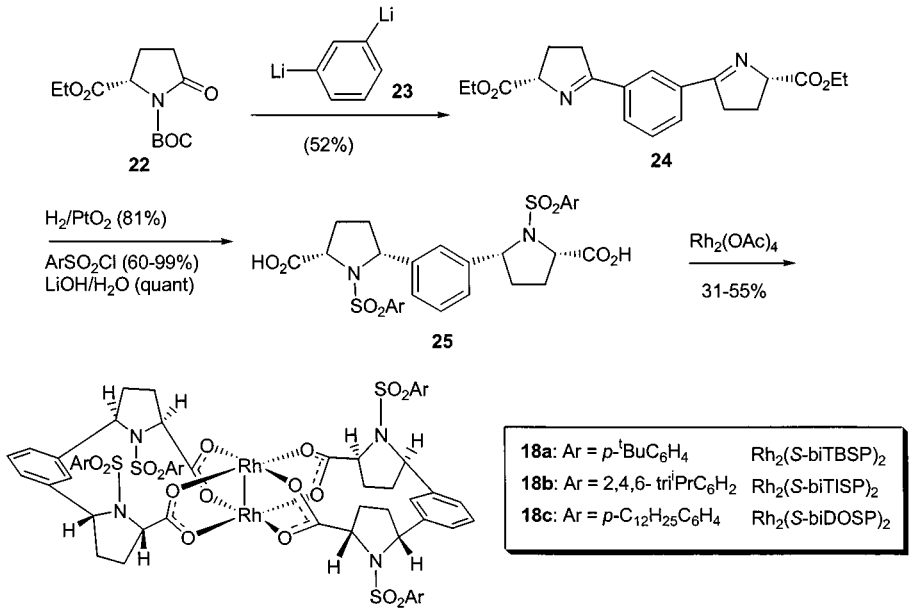
Figure 5. Model for asymmetric induction by dirhodium tetraprolinates

The model presented in Figures 2−5 has been of great value in predicting the asymmetric induction in this chemistry. Furthermore, the concept that the arrangement of identical chiral ligands of low symmetry can result in a complex of higher symmetry has been the driving force behind our design of a second generation of chiral catalysts. Even though the *N*-arylsulfonyl groups would not preferentially exist in the periphery of the catalyst, other orientations than the D_2 symmetric arrangement are feasible.[45] In order to ensure that the complex was locked in a D_2 symmetric arrangement, new ligands were designed in which two of the prolinates were bridged together. For such ligands to bind to the dirhodium core, the sulfonyl groups would be forced to adopt an α,β arrangement leading to a D_2 symmetric complex.

After extensive molecular modeling studies, two systems, **17**[53] and **18**,[54] were identified as having promise as bridging ligands. The synthesis of **17**, which has a *meta*-xylene



Scheme 7. Synthesis of D_2-symmetric catalyst **17**

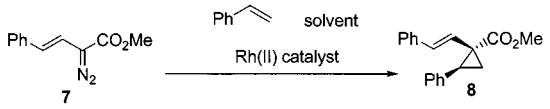


Scheme 8. Synthesis of D_2-symmetric catalyst **18**

Synthetic Applications

1. Asymmetric Synthesis of Cyclopropane Amino Acids

The vinylcyclopropanes can be readily converted into cyclopropane amino acids. Cyclopropane amino acids have been used extensively as confromationally constrained amino acids in peptidomimetics, but their synthesis is often challenging.[55][56] The application of this chemistry for the synthesis of phenylalanine analogs is shown in Scheme 10.[45] Oxidative cleavage of **8** to form the acid **26** followed by reaction under Curtius rearrangement conditions results in the formation of the cyclopropane amino acid **27**. The diastereomeric amino acid **28** is readily obtained by esterification of **27** to form the diester **29** followed by hydrolysis of the least crowded ester to form the acid **30**. Reaction of **30** under Curtius rearrangement conditions forms **28**. As both enantiomers of the catalyst are available, all four stereoisomers of the cyclopropane amino acids could be formed. The initial cyclopropanation is applicable to a wide range of alkenes, and so, in principle, a range of cyclopropane amino acids could be made using this chemistry. Recently, Burgess has used this strategy for the synthesis of 3-phenyl-2,3-methanophenylalanine.[27]

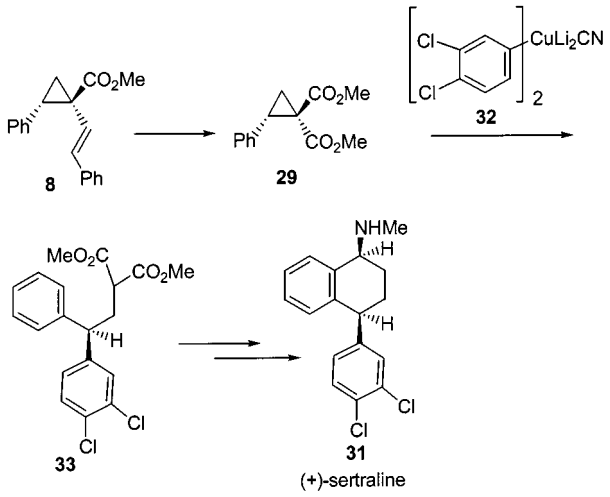


		%ee for the formation of **8** by Rh(II) catalysts		
solvent	temp, °C	Rh_2(*S*-DOSP)$_4$	**17**	Rh_2(*S*-biTISP)$_2$ (**18b**)
n-alkane	25	90 (*R,R*)[1c]	56 (*S,S*)[3]	74 (*S,S*)
CH_2Cl_2	25	74 (*R,R*)[1c]	59 (*S,S*)[3]	90 (*S,S*)
CH_2Cl_2	-50	**88 (*R,R*)**	83 (*S,S*)[3]	**98 (*S,S*)**

Scheme 9. Comparison of **17** and **18** with Rh_2(*S*-DOSP)$_4$

2. Asymmetric Synthesis of (+)-Sertraline

An elegant application of the asymmetric cyclopropanation chemistry in synthesis has been reported by Corey for the asymmetric synthesis of the antidepressant (+)-sertraline [**31**, Scheme 11)].[57] Oxidative cleavage of **8** followed by treatment with diazomethane generated the cyclopropane **29**. Cuprate **32** induced ring opening of **29** generated the diaryl derivative **33**, which was readily converted into (+)-sertraline by a series of standard reactions.



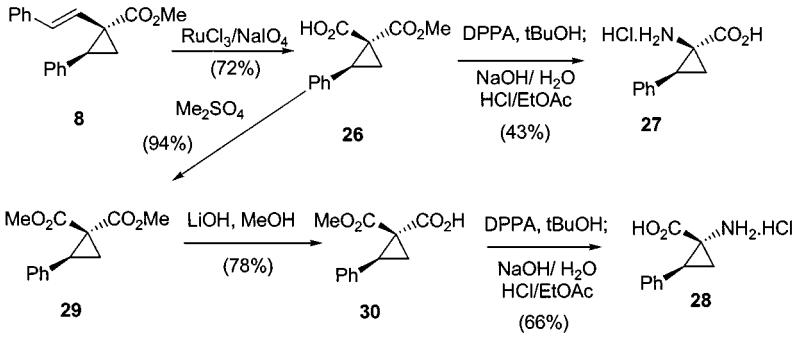
Scheme 11. Asymmetric synthesis of (+)-sertraline

3. Asymmetric Synthesis of Fused Cyclopentenes

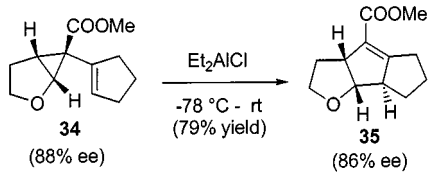
The combination of the asymmetric cyclopropanation with Lewis acid catalyzed rearrangement of the vinylcyclopropane to a cyclopentene proceeds with full control of relative stereochemistry.[4][58] In certain cases good control of absolute stereochemistry is also possible in these rearrangements.[59] An example is the conversion of the fused cyclopropane **34** to the tricyclic system **35** (Scheme 12).

4. Asymmetric Synthesis of Cycloheptadienes

The most useful application of the asymmetric cyclopropanation is the reaction with dienes, which leads to the asymmetric synthesis of cycloheptadienes by means of a



Scheme 10. Asymmetric synthesis of 2,3-methanophenylalanines **27** and **28**

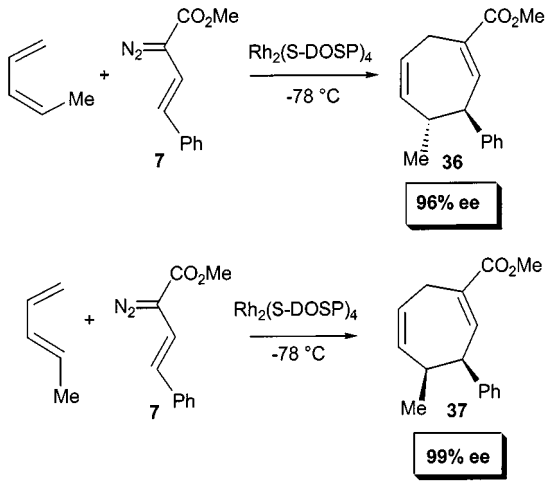


Scheme 12. Asymmetric synthesis of fused cyclopentenes

tandem cyclopropanation Cope rearrangement.[60][61] Illustratory examples are shown for the reaction of the vinyldiazoacetate **7** with *cis*- and *trans*-piperylene (Scheme 13). The cycloheptadienes **36** and **37** are formed with high asymmetric induction and full control of relative stereochemistry, as would be expected for the Cope rearrangement of divinylcyclopropanes. This reaction is of broad scope and a range of dienes and vinyldiazoacetates will undergo this chemistry with high asymmetric induction.

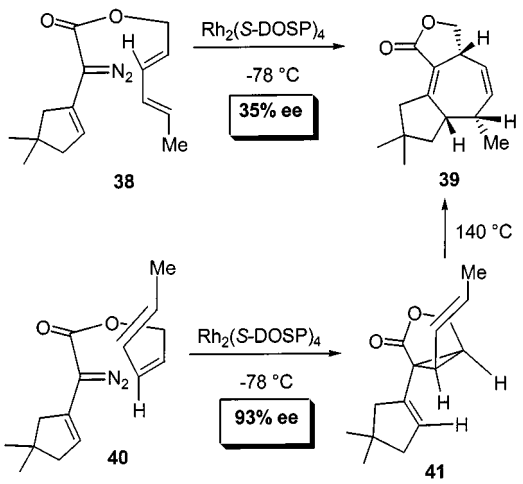
5. Asymmetric Synthesis of *epi*-Tremulane

The utility of the tandem cyclopropanation Cope rearrangement is shown in the intramolecular version that leads to the asymmetric synthesis of *epi*-tremulane (**39**, Scheme 14).[62] Decomposition of **38** that contains an (*E,E*) diene results in the direct formation of **39** in 33% ee. A much better result is obtained starting from the (*E,Z*) diene **40**. This results in the formation of trans divinylcyclopropane **41**. Heating of **41** at 140°C results in the formation of



Scheme 13. Asymmetric synthesis of cycloheptadienes

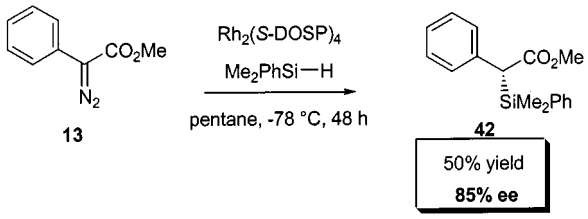
39 in 93% ee. As *trans* dienes fail to react with vinylcarbenoids in intermolecular reactions[1] it is assumed that the chiral influence on the (*E,E*) diene is limited because it is unable to approach close to the catalyst.



Scheme 14. Asymmetric synthesis of *epi*-tremulane

6. Asymmetric Si−H Insertion

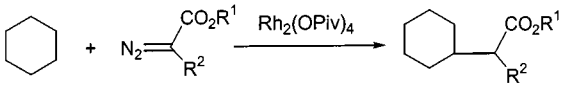
The asymmetric chemistry of vinyldiazoacetates and phenyldiazoacetates is not limited to the asymmetric cyclopropanation. Asymmetric Si−H insertion is also possible as illustrated in Scheme 15. Reaction of methyl phenyldiazoacetate with *tert*-butyldiphenylsilane generates the benzylsilane **42** in 85% ee.[63] Similar reactions with vinyldiazoacetates resulted in the formation of allylsilanes in 74−95% ee.[63] Landais has observed moderate asymmetric induction using (*R*)-pantolactone as a chiral auxiliary or Doyle's Rh_2(*R*-MEPY)$_4$ catalyst.[28] Considerable effort has been expended by Moody and Doyle to discover new chiral dirhodium carboxylate catalysts for the asymmetric Si-H insertion of phenyldiazoacetates, that has included an extensive combinatorial approach.[64][65] So far, none have outperformed Rh_2(*S*-DOSP)$_4$. Recently, a chiral copper catalyst was reported by Jacobsen and Panek that resulted in 84% ee in this reaction.[66]



Scheme 15. Asymmetric Si−H insertion

7. Asymmetric C−H Activation

The ability of carbenoids to undergo C-H insertions is of great synthetic importance because it offers the opportunity for a practical C−H activation process. The intramolecular asymmetric C−H insertion is a well-established process[25] but the synthetic potential of the intermolecular C−H insertion has not been fully developed. Due to the fact that carbenoids derived from phenyl- and vinyldiazoacetates do not display a great tendency to undergo a direct dimerization,[67] it was considered that these intermediates could be useful in intermolecular C−H insertions. A comparison of the reactivity of various carbenoid systems is shown in Scheme 16.[67] Under identical conditions, the carbenoids derived from the phenyldiazoacetate **13** and the vinyldiazoacetate **43** give much higher yields of C−H insertion products than the carbenoid derived from ethyl diazoacetate **44**. In the latter case, dimethyl fumarate and maleate are the predominant products.

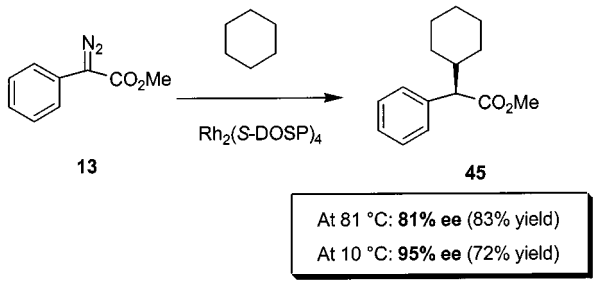


Diazo	R^1	R^2	yield, %
13	Me	Ph	94
43	Et	CH=CHCO$_2$Et	67
44	Et	H	10

Scheme 16. Effect of carbenoid structure on C−H insertion

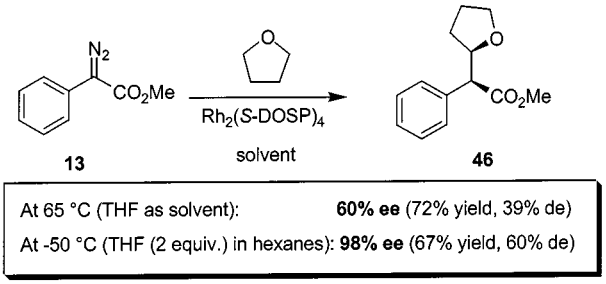
The preliminary studies into asymmetric C-H activation using phenyldiazoacetate **13** were very promising. Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of **13** in refluxing cyclohexane gave the C−H insertion product **45** in 81% ee.[68] On optimizing the reaction by carrying out the reaction at 10°C and degassing the cyclohexane prior to reaction, the C−H insertion product **45** was formed in 95% ee.[69]

The reaction of phenyldiazoacetate **13** with tetrahydrofuran is more complicated because regioisomers and diastereomers could be formed. The regiochemistry of the reaction is excellent and only C−H insertion at the C-2 position was observed.[68] Similar regioselectivity had been seen in the Rh_2(OAc)$_4$ catalyzed decomposition of ethyl diazo-



Scheme 17. Asymmetric C−H insertion into cyclohexane

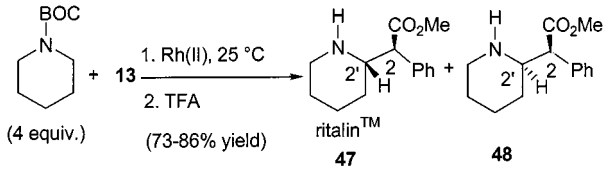
acetate in tetrahydrofuran but the yields were only 20−40%.[70] When the reaction was carried out in refluxing THF a 2:1 diastereomeric mixture of C−H insertion products was obtained in 72% yield with the major diastereomer **46** being formed in 60% ee.[68] Optimization of this process was possible by carrying out the reaction at −50°C with just 2 equivalents of THF and hexane as solvent.[69] Under these conditions, a 4:1 mixture of diastereomers was formed in 67% yield and **46** was obtained in 98% ee. This last result demonstrates that remarkable regiocontrol is possible with this chemistry because a respectable yield of insertion into THF was obtained even though the reaction was carried out in the presence of a vast excess of hexane.



Scheme 18. Asymmetric C−H insertion into tetrahydrofuran

An effective C-H insertion α to nitrogen in *N*-BOC-piperidine would lead to a very direct synthesis of methylphenidate (ritalin™, **47**, Scheme 19). The reaction of methyl phenyldiazoacetate (**13**) with *N*-BOC-piperidine catalyzed by Rh_2(*S*-DOSP)$_4$ (**10**) gave a 1:1 mixture of diastereomers **47** and **48**, and **47** was produced in only 25% ee.[71] Both the diastereoselectivity and enantioselectivity could be improved by carrying out the reaction at lower temperatures but an even better result was obtained on using Rh_2(*S*-biDOSP)$_2$ (**18c**), which resulted in the formation of **47** in 86% ee. Only mono C−H insertions are seen in these reactions even though a four-fold excess of the diazo compound **13** is used. Winkler has recently disclosed that the reaction of **13** with *N*-BOC-piperidine catalyzed by Rh_2(MEPY)$_4$ resulted in the formation of **47** in 45% yield and 69% ee.[72]

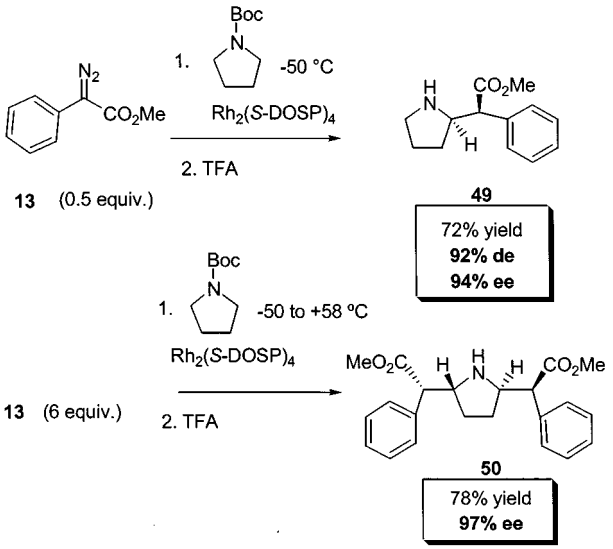
The C−H activation chemistry would be even more powerful, if effective diastereocontrol in addition to regio- and enantiocontrol could be achieved. At this stage the subtle issues that control the diastereoselectivity in this chemistry have not been fully determined, but in certain systems excellent diastereocontrol is possible as illustrated



Rh(II)	47:48	47 ee, %	48 ee,%
Rh_2(*S*-DOSP)$_4$	50:50	25 (2*S*)	79 (2*S*)
Rh_2(*S*-biDOSP)$_2$	71:29	86 (2*R*)	65 (2*R*)

Scheme 19. Asymmetric synthesis of ritalin™

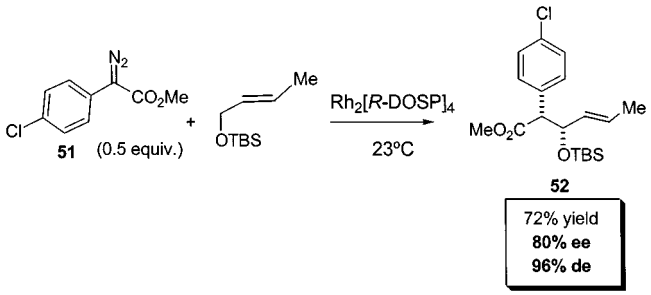
in Scheme 20.[71] Reaction of *N*-BOC-pyrrolidine (4 equiv.) with phenyldiazoactate **13** results in C−H insertion product **49** in 72% yield. The diastereoselectivity in this case is greater than 20:1 and the major diastereomer **49** is formed in 94% ee. In contrast to *N*-BOC-piperidine, when the reaction with *N*-BOC-pyrrolidine is carried out with excess **13**, bis-C−H insertion occurs, leading to a direct synthesis of the elaborate C_2-symmetric amine **50** in 78% yield and 97% ee.



Scheme 20. Asymmetric C−H insertion into *N*-BOC-pyrrolidine

A further example of highly diastereoselective and enantioselective C−H insertions is the reaction between aryldiazoacetates and allylsilyl ethers.[73] The resulting β-hydroxy ester derivatives are equivalent to aldol products. An illustrative example is shown in Scheme 21. The reaction of aryldiazoacetate **51** with *trans*-2-butenylsilyl ether results in the highly diastereoselective formation of **52**, the equivalent of a *syn*-aldol product, in 72% yield and 80% ee. Particularly attractive is that carbenoid reactions can be carried out with low catalyst loading and so this could be a practical alternative to the aldol reaction for the asymmetric synthesis of certain types of β-hydroxy esters.

The absolute stereochemistry that is obtained in the C−H insertion chemistry is consistent with a three-membered transition state (Figure 6) that is analogous to Doyle's mechanistic model that has been proposed for in-



Scheme 21. Asymmetric synthesis of *syn*-aldol products

tramolecular C−H insertions. A build-up of positive charge occurs at the C−H carbon during the transition stage and thus, insertion at sites where the partial positive charge is stabilized would be favored. The subtle steric requirements of R^1 and R^2 in the transition-state control the diastereoselectivity of the C−H insertion.

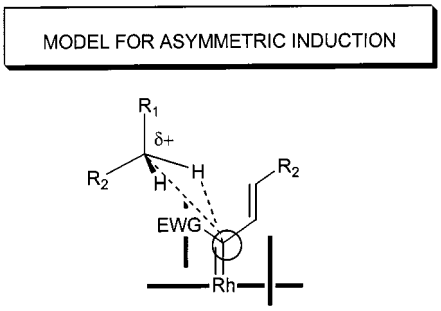


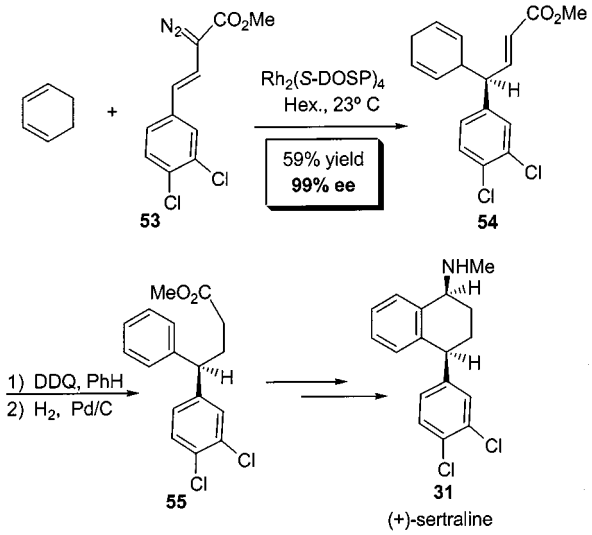
Figure 6. Model for asymmetric induction in C−H insertion

8. Asymmetric Formal C−H Insertion/Cope Rearrangement

The reaction between vinyldiazoacetates and 1,3-cyclohexadiene results in an unusual product.[74] The reaction is equivalent to a tandem C−H insertion/Cope rearrangement, although is has been shown that the C−H insertion product is not an intermediate in this reaction. An illustratory example is the reaction with the vinyldiazoacetate **53**, which results in the formation of the 1,4-cyclohexadiene **54** in 99% ee. The product **54** is readily converted into benzhydryl derivative **55**, which has been previously converted into (+)-sertraline (**31**).[57]

Summary and Outlook

The rhodium(II) prolinates are superb catalysts for asymmetric transformations of vinyldiazoacetates and phenyldiazoacetates. The reaction of vinyldiazoacetates with dienes is a very general method for the stereoselective synthesis of a variety of seven-membered rings, and the asymmetric version is likely to have general use in total synthesis. The asymmetric intermolecular C−H activation is a very promising transformation. Interesting issues of regio- and diastereocontrol exist in addition to the enantiocontrol. The



Scheme 22. Asymmetric synthesis of (+)-sertraline

preliminary results illustrate that both regio- and diastereocontrol are feasible. Studies are in progress to determine the full potential of the asymmetric C−H activation reaction in organic synthesis.

The most interesting concept that has arisen from this work in terms of catalyst design is the possibility of designing catalysts of high symmetry by complexing identical ligands of lower symmetry around a central metal core. This approach greatly simplifies the synthesis of high symmetry chiral catalysts and could have a major impact on the design of new catalysts for asymmetric synthesis.

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Several post-doctoral associates, graduate students and undergraduate students have made major contributions to the chemistry described in this review. Without their dedication and ingenuity, this chemistry would not have reached its current level of broad synthetic utility. David Smith, Melinda McAfee, Dr. Wendy Young, Dr. William Cantrell, Dr. Jeffrey Clark, Dr. Elie Saikali, Dr. Baihua Hu, Dr. Nicholas Huby, Lisa Kuhn, Dr. Craig Thornley, Zhi-Qiang Peng, Dr. Jeffrey Houser, Dr. Brian Doan, Dr. Julius Matasi, Dr. Gulzar Ahmed, Dr. Mark Hodges, Melinda Hodges, Dr. Rebecca Calvo, and Dr. Pingda Ren were primarily responsible for developing the vinyldiazoacetate chemistry. Debra Lake, Dr. Paul Bruzinski, Dr. Norman Kong, Stephen Panaro, and Dr. Tadamichi Nagashima were primarily responsible for developing the dirhodium tetraprolinate catalysts. Tore Hansen initiated the asymmetric C−H activation project and since then, Evan Antoulinakis, Dr. Darrin Hopper, and Douglas Stafford have been actively involved in expanding this research area. These studies were generously supported by the National Science Foundation and by PHS grants DA-06301 and DA-06634.

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