

# Recent Developments in the Application of Oxazoline-Containing Ligands in Asymmetric Catalysis

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## 1. Introduction

Because of their ready accessibility, modular nature, and applicability in a wide range of metal-catalyzed transformations, compounds containing a chiral oxazoline ring have become one of the most

successful, versatile, and commonly used classes of ligands for asymmetric catalysis.<sup>1–3</sup> The large majority of these ligands are derived from readily available chiral amino alcohols in a few high-yielding synthetic steps. As a consequence, the enantiocontrolling stereocenter resides on the carbon atom neighboring the coordinating nitrogen of the oxazoline ring and, therefore, in close proximity to the metal active site, thus having a direct influence on the stereochemical outcome of the reaction.

Since the first report in 1986 of the use of chiral oxazoline-based ligands in asymmetric catalysis,<sup>4</sup> a diverse range of ligands with one, two, or more oxazoline rings incorporating various heteroatoms, additional chiral elements, and specific structural features have been used with great success in a wide range of asymmetric reactions. The aim of this review is to report the use of such ligands in homogeneous metal-catalyzed asymmetric synthesis, concentrating in particular on those oxazoline-containing ligands reported since 1998, when an extensive review on the application of bis(oxazoline) ligands in asymmetric catalysis was published,<sup>1</sup> and covering to the best of our knowledge all new oxazoline-based ligands reported in the literature until the end of 2003. In recent years, the use of phosphinooxazoline<sup>2</sup> and ferrocenyloxazoline<sup>3</sup> ligands in asymmetric catalysis has also been reviewed, and therefore the areas discussed within these papers will be only outlined briefly. This review concentrates principally on homogeneous oxazoline-containing ligands; however, some examples of heterogeneous complexes, which can be recovered and reused, have been included. A comprehensive review on the use of heterogeneous bis(oxazoline) ligands in enantioselective catalysis has been recently published.<sup>5</sup>

## 2. Bidentate Mono(oxazoline) Ligands

### 2.1. Mono(oxazoline) *P,N*-Ligands

#### 2.1.1. Phosphinooxazoline Ligands with Only a Stereocenter

The phosphinooxazoline (PHOX) ligands **1**, first developed independently in 1993 by Pfaltz, Helmchen, and Williams as highly effective non-*C*<sub>2</sub>-symmetric ligands for asymmetric allylic alkylation,<sup>6</sup> have been applied with great success in a diverse range of asymmetric reactions. These include both

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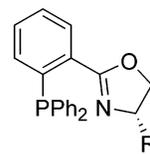


Helen McManus was born in Co. Kildare, Ireland, and graduated with an Honors B.Sc. degree in chemistry from University College Dublin in 1999. Working in the group of Professor Pat Guiry, she has recently completed her Ph.D. studies on the preparation of bidentate and tridentate oxazoline-containing ligands and their application in metal-catalyzed asymmetric synthesis. During her Ph.D. work, she also spent time in 2002 in Uppsala University in the research group of Professor Pher Andersson (asymmetric transfer hydrogenation) and in 2003 in Università di Bologna under the supervision of Professor Pier Giorgio Cozzi (asymmetric Nozaki–Hiyama allylation).



Pat Guiry, born in Co. Tipperary, graduated from University College Dublin with an Honors B.Sc. degree in chemistry and a Ph.D. under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his Ph.D. studies he also worked in Marseille under the supervision of Dr. Jean-Pierre Finet (Cu-catalyzed N-arylation) and at Texas A&M with Sir Derek Barton (mechanistic studies of arylation). He moved in 1990 to the group of Dr. John Brown FRS at the Dyson Perrins Laboratory, Oxford University, for postdoctoral studies in the area of asymmetric catalysis. He returned to University College Dublin as a College Lecturer in 1993, where he started his independent research. His research interests are the design and preparation of chiral ligands and their application in asymmetric catalysis, total synthesis, and the chemistry/biology of amphetamines. To date, he has graduated 16 Ph.D. students and currently has 10 Ph.D. students and 5 postdoctoral researchers in his research group. He has been a Visiting Professor in the group of Professor Andreas Pfaltz at the Max Planck Institut für Kohlenforschung at Mülheim in 1996 and in the group of Professor Mark Lautens in the University of Toronto in 2004. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. He was promoted to senior lecturer in 2002 and to professor of Synthetic Organic Chemistry in 2003. He was appointed lead coordinator of the Centre for Synthesis and Chemical Biology in 2002 and chief executive of the Conway Institute of Biomolecular and Biomedical Research at University College Dublin in June 2004. A keen tennis player, he represented Ireland in the Italia Cup (ITF World Team Competition) in Berlin and in the Home Nations Series in Glasgow, both in 2003.

inter- and intramolecular Heck reactions, conjugate additions to enones, enantioselective hydrogenation



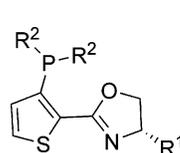
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- a R = Bn    d R = *t*-Bu  
 b R = *i*-Pr    e R = Me  
 c R = Ph

of imines and olefins, transfer hydrogenation of ketones and imines, hydrosilylations of ketones, alkene/CO-copolymerizations, aza-Claisen rearrangements, and Diels–Alder<sup>7</sup> and aza-Diels–Alder reactions,<sup>8</sup> the majority of which have been discussed in a recent review by Helmchen and Pfaltz.<sup>2</sup>

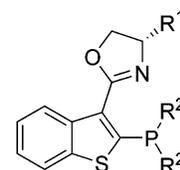
The ease of accessibility of these ligands from readily available chiral starting materials and their modular structure have led to the development of a wide array of phosphinooxazoline ligands similar to **1** by extensive variation of the ligand backbone oxazoline ring and phosphine moiety. Although the simple phosphinooxazolines **1** remain the most versatile ligands for controlling the stereochemical outcome of a variety of metal-catalyzed processes, it has been possible to improve enantioselectivities in some cases by specific modification of the ligand structure.<sup>2</sup> In this section, the application of new phosphinooxazoline ligands in asymmetric catalysis will be discussed.

Chiral phosphinooxazoline ligands with a heterocyclic backbone have been used with great success in a number of asymmetric reactions. A heterocyclic framework is of advantage as it can directly influence the electronic and steric properties of the ligands. Tietze has applied the novel chiral thiophene **2b** and **6**, benzothiophene **3a**, **3b**, and **4**, and benzofuran **5**



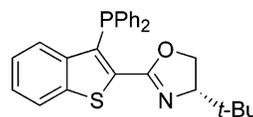
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- a R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = Ph  
 b R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Ph  
 c R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = *o*-Tol  
 d R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Cy

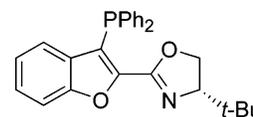


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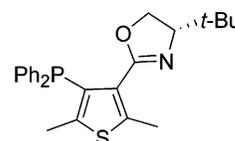
- a R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = Ph  
 b R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Ph  
 c R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = *o*-Tol  
 d R<sup>1</sup> = Ph, R<sup>2</sup> = Ph



4



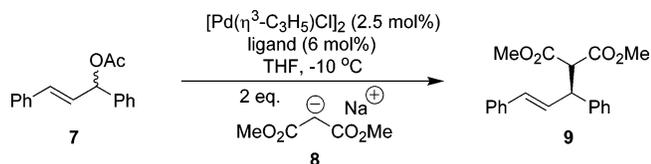
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oxazoline ligands in the Pd-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with

## Scheme 1



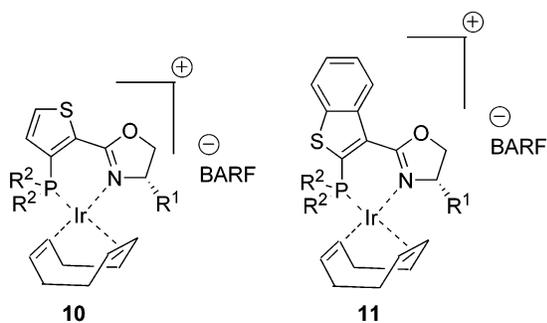
**Table 1. Asymmetric Palladium-Catalyzed Alkylation of 7 Using Ligands 2–6 (Scheme 1)**

entry	ligand	time (h)	yield (%)	ee (%)
1	<b>2b</b>	14	83	75 ( <i>S</i> )
2 <sup>a</sup>	<b>3a</b>	2	92	97 ( <i>S</i> )
3	<b>3b</b>	6	91	94 ( <i>S</i> )
4	<b>4</b>	14	86	88 ( <i>S</i> )
5	<b>5</b>	14	89	86 ( <i>S</i> )
6	<b>6</b>	14	89	86 ( <i>S</i> )

<sup>a</sup> Reaction was carried out at 0 °C.

sodium dimethyl malonate **8** (Scheme 1 and Table 1).<sup>9</sup> In all cases the enantioselectivity (75–97% ee), yield (83–92%), and reaction rate were high, with the best result of 97% ee and 92% yield being achieved with the benzothiophene ligand **3a** after 2 h at 0 °C.

Cozzi has reported the preparation of cationic iridium–HetPHOX complexes **10a–d** and **11a–d** from the heterocyclic phosphinoxazoline (HetPHOX)



- 10**
- a R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = Ph
  - b R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Ph
  - c R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = *o*-Tol
  - d R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Cy

- 11**
- a R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = Ph
  - b R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Ph
  - c R<sup>1</sup> = *i*-Pr, R<sup>2</sup> = *o*-Tol
  - d R<sup>1</sup> = Ph, R<sup>2</sup> = Ph

BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

ligands **2a–d** and **3a–d**, respectively, and has used these in the asymmetric hydrogenation of the unfunctionalized olefin (*E*)-1,2-diphenylpropene **12**, allylic alcohol **13**, and imine **14** (Table 2).<sup>10</sup> These iridium complexes were highly active, giving complete conversions after 2–4 h at low catalyst loadings (1–2 mol %) in almost all cases and excellent enantioselectivities (up to 99% ee), thus furnishing results comparable to those obtained with the phosphinoxazoline ligands **1**.<sup>2,11</sup>

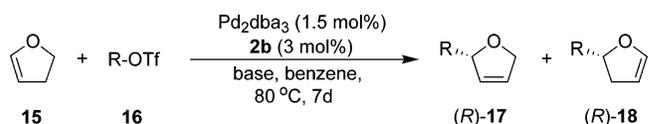
Guiry has applied the benzothiophene-derived ligands **3a**, **3b**, and **3d** and the thiophene-derived ligands **2a** and **2b** in the palladium-catalyzed intermolecular asymmetric Heck phenylation and cyclohexenylation of 2,3-dihydrofuran **15** (Scheme 2).<sup>12</sup> The *tert*-butyl-substituted thiophene–oxazoline derivative **2b** was found to be the ligand of choice, giving high yields, regioselectivities, and enantioselectivities for both reactions, irrespective of the

**Table 2. Asymmetric Hydrogenation Using Complexes 10a–d and 11a–d<sup>a</sup>**

Entry	Substrate	Product	Complex	Conversion (%)	Ee (%)
1			<b>10a</b>	>99	77
2			<b>10b</b>	>99	95
3			<b>10d</b>	>99	99
4	<b>12</b>		<b>11a</b>	>99	70
5			<b>10a</b>	>99	94
6	<b>13</b>		<b>11b</b>	>99	94
7 <sup>b</sup>			<b>10a</b>	>99	83
8 <sup>b</sup>	<b>14</b>		<b>11a</b>	>99	86

<sup>a</sup> [Ir(lig)cod]BARF (1–2 mol %), 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 2 h. <sup>b</sup> 0.1 mol % complex.

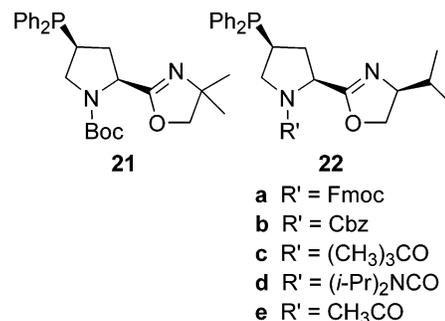
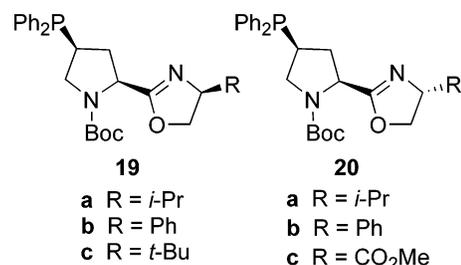
## Scheme 2



R	Base	Yield (%)	Ee (%)
		<b>17 (18)</b>	<b>(R)-17 ((R)-18)</b>
<b>a</b> phenyl	<i>i</i> -Pr <sub>2</sub> NH	97 (2)	95 (nd)
<b>b</b> cyclohexenyl	Et <sub>3</sub> N	96 (4)	97 (nd)

base used [triethylamine, proton sponge (1,8-bis(dimethylamino)naphthalene) or diisopropylamine].

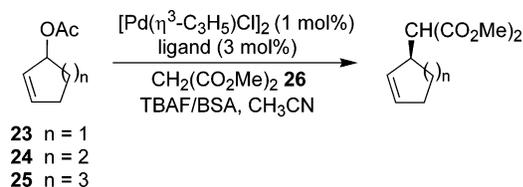
Gilbertson has reported the synthesis of proline-derived phosphinoxazoline ligands **19–22**, which



possess three stereocenters, and has tested these ligands in Pd-catalyzed allylic alkylation<sup>13,14</sup> and in the intermolecular Heck reaction.<sup>13,15</sup>

Pd-catalyzed alkylation of the cyclic substrate 2-cyclopentenyl acetate **23** with dimethyl malonate **26** using these ligands (Scheme 3 and Table 3)

## Scheme 3


**Table 3. Palladium-Catalyzed Allylic Alkylation of 23–25 and 7 Using Ligands 19–22 (Scheme 3)**

entry	ligand	substrate	temp (°C)	time (h)	yield (%)	ee (conf) (%)
1	<b>19a</b>	23	0	1	94	90 ( <i>S</i> )
2	<b>19b</b>	23	0	1	99	76 ( <i>S</i> )
3	<b>19c</b>	23	0	1	92	68 ( <i>S</i> )
4	<b>20a</b>	23	0	1	93	68 ( <i>S</i> )
5	<b>20b</b>	23	0	1	91	76 ( <i>S</i> )
6	<b>20c</b>	23	0	1	95	58 ( <i>S</i> )
7	<b>21</b>	23	0	1	90	80 ( <i>S</i> )
8 <sup>a</sup>	<b>22a</b>	23	0	5	98	69 ( <i>S</i> )
9 <sup>a</sup>	<b>22b</b>	23	0	1	97	75 ( <i>S</i> )
10 <sup>a</sup>	<b>22c</b>	23	0	0.5	96	35 ( <i>R</i> )
11 <sup>a</sup>	<b>22d</b>	23	0	2	98	30 ( <i>R</i> )
12 <sup>a</sup>	<b>22e</b>	23	0	0.5	96	42 ( <i>S</i> )
13 <sup>a</sup>	<b>19a</b>	24	25	5	93	80 ( <i>S</i> )
14 <sup>a</sup>	<b>19a</b>	25	0	3	96	80 ( <i>S</i> )
15 <sup>a</sup>	<b>22c</b>	25	25	1	96	51 ( <i>R</i> )
16 <sup>a</sup>	<b>22d</b>	25	25	4	96	60 ( <i>R</i> )
17 <sup>a</sup>	<b>19a</b>	7	0	6	100	30 ( <i>S</i> )

<sup>a</sup> Reactions were run with 2 mol % Pd to 3 mol % ligand.

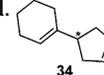
revealed that the stereocenter on the oxazoline ring was not the dominant stereocontrolling factor because ligands **20a,b** gave the same sense of enantioselection as their respective diastereomers **19a,b** in which the oxazoline stereocenter has the opposite configuration (Table 3, entries 1–2 vs entries 4–5). In addition, ligand **21** with an achiral oxazoline ring also afforded high enantiodiscrimination (80% ee) (Table 3, entry 7). The nature of the protecting group at the proline nitrogen had a pronounced and unusual influence on the stereochemical outcome of the reaction. Of the different groups used, ligand **19a** with a Boc protecting group gave the best enantioselectivities for the addition of dimethyl malonate **26** to cyclic allylic acetates of different ring sizes **23–25** (Table 3, entries 1 and 8–16). An unusual reversal of enantioselection giving the *R* enantiomer for substrates **23** and **25** was obtained with the bulkier pivalate (ligand **22c**) and diisopropylurea (ligand **22d**) groups (Table 3, entries 10, 11, 15, and 16). In direct contrast to other phosphinooxazoline ligands detailed in this review, acyclic substrates such as 1,3-diphenyl-2-propenyl acetate **7** react with much lower enantiodiscrimination than the cyclic substrates **23–25** (Table 3, entry 17).<sup>13,14</sup>

Ligands **19–22** were also tested in the Pd-catalyzed intermolecular asymmetric Heck reaction. The isopropyl-substituted derivative **19a** was optimal, affording high conversions and good enantioselectivities for the cyclohexenylation and phenylation of 2,3-dihydrofuran **15** under optimized conditions (Table 4, entries 1 and 6). Reaction of **15** with two acyclic triflates **27** and **28** proceeded with good reaction rates but only moderate asymmetric induction (Table 4, entries 8 and 9), whereas the phenylation of cyclo-

**Table 4. Asymmetric Intermolecular Heck Reactions Using Ligands 19a<sup>a</sup> and 30–32<sup>b</sup>**

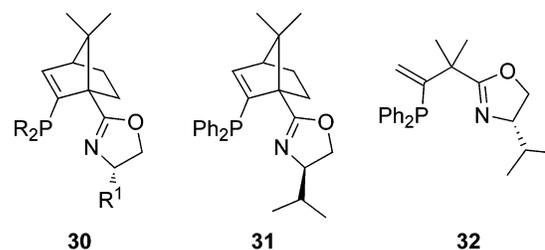
Entry	Ligand	Substrate	Triflate	Product	Time (h)	Conv. (%)	Ee (%) (Conf.)
1 <sup>c</sup>	<b>19a</b>	<b>15</b>	<b>16b</b>	<b>30</b>	24	98	80 ( <i>S</i> )
2	<b>30b</b>	<b>15</b>	<b>16b</b>	<b>31</b>	48	91	76 ( <i>R</i> )
3	<b>31</b>	<b>15</b>	<b>16b</b>	<b>30</b>	72	45	76 ( <i>S</i> )
4	<b>30a</b>	<b>15</b>	<b>16a</b>	<b>31</b>	22	100	94 ( <i>R</i> )
5	<b>32</b>	<b>15</b>	<b>16a</b>	<b>32</b>	20	98	6 ( <i>R</i> )
6	<b>19a</b>	<b>15</b>	<b>16a</b>	<b>30</b>	72	85	82 ( <i>S</i> )
7	<b>30a</b>	<b>15</b>	<b>16a</b>	<b>31</b>	22	100	96 ( <i>R</i> )
8	<b>19a</b>	<b>15</b>	<b>27</b>	<b>34</b>	24	80	46 ( <i>S</i> )
9	<b>19a</b>	<b>15</b>	<b>28</b>	<b>34</b>	24	83	23 ( <i>S</i> )
10 <sup>d</sup>	<b>30a</b>	<b>15</b>	<b>28</b>	<b>34</b>	36	85	93 ( <i>R</i> )
11 <sup>e</sup>	<b>30a</b>	<b>29</b>	<b>16b</b>	<b>30</b>	48	78	94 ( <i>R</i> )
12	<b>19a</b>	<b>29</b>	<b>16a</b>	<b>30</b>	48	14	73 ( <i>S</i> )
13 <sup>d</sup>	<b>30a</b>	<b>29</b>	<b>16a</b>	<b>31</b>	24	83	78 ( <i>R</i> )
14	<b>30a</b>	<b>33</b>	<b>16a</b>	<b>31</b>	24	50	96 ( <i>R</i> )

<sup>a</sup>  $\text{Pd}_2\text{dba}_3$  (1 mol %), ligand **19a** (3 mol %), benzene, (*i*-Pr)<sub>2</sub>NEt, 75 °C. <sup>b</sup>  $\text{Pd}_2\text{dba}_3$  (2.5 mol %), ligand (6 mol %), benzene, (*i*-Pr)<sub>2</sub>NEt, 70 °C. <sup>c</sup> Reaction performed at room temperature. <sup>d</sup> Reaction conducted at 95 °C. <sup>e</sup> 30% of the double bond isomerized product **34** also obtained.



pentene **29** gave good enantioselectivity but with low conversion (Table 4, entry 12).<sup>13,15</sup>

Chiral phosphinooxazoline ligands **30–32** based on (1*S*)-(+)-ketopininc acid have also been used by Gilbertson in the asymmetric palladium-catalyzed intermolecular Heck reaction.<sup>16</sup>

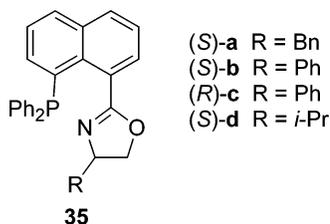


- a**  $\text{R}^1 = t\text{-Bu}$ ,  $\text{R} = \text{Ph}$   
**b**  $\text{R}^1 = i\text{-Pr}$ ,  $\text{R} = \text{Ph}$   
**c**  $\text{R}^1 = \text{Ph}$ ,  $\text{R} = \text{Ph}$   
**d**  $\text{R}^1 = t\text{-Bu}$ ,  $\text{R} = \text{cyclohexyl}$

The diastereomeric ligand pair **30b** and **31** yielded different enantiomeric products for the cyclohexenylation of 2,3-dihydrofuran **15**, indicating that the oxazoline stereocenter and not the chirality of the norbornyl ring determined the sense of the asymmetric induction (Table 4, entry 2 vs 3). However,

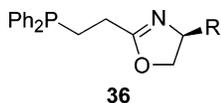
the low enantioselectivity obtained by the corresponding acyclic analogue **32** highlighted the importance of the rigid bicyclic system for high levels of enantioselection (Table 4, entry 5). The *tert*-butyl-substituted oxazoline **30a** was the ligand of choice, giving, in general, moderate to good conversions (50–100%), complete regioselection (in most cases), and high enantioselectivities (78–96% ee) for the reaction of a range of cyclic substrates **15**, **29**, and **33** with different triflates **16a**, **16b**, and **28** (Table 4).

Ma has reported the synthesis of 2-(8'-diphenylphosphino-1'-naphthyl)oxazoline ligands **35** with a

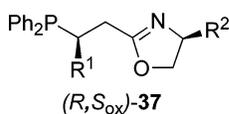


naphthyl group linking the oxazoline ring and the diphenylphosphino group. These ligands were tested in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. The 4-isopropyl-substituted derivative **35d** was the ligand of choice, giving 86% yield and 49% ee (*R*) under optimized reaction conditions.<sup>17</sup>

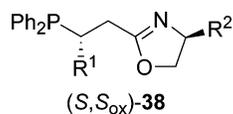
In 1998 Gilbertson reported the synthesis of ligands **36–38**, in which an alkyl chain connects the diphenylphosphino group to an oxazoline ring. These



- a** R = Me  
**b** R = Bn  
**c** R = *i*-Pr  
**d** R = Ph



- a** R<sup>1</sup> = Me, R<sup>2</sup> = *i*-Pr  
**b** R<sup>1</sup> = Ph, R<sup>2</sup> = Bn  
**c** R<sup>1</sup> = Ph, R<sup>2</sup> = *i*-Pr  
**d** R<sup>1</sup> = Ph, R<sup>2</sup> = Ph  
**e** R<sup>1</sup> = Ph, R<sup>2</sup> = *t*-Bu



- a** R<sup>1</sup> = Me, R<sup>2</sup> = *i*-Pr  
**b** R<sup>1</sup> = Ph, R<sup>2</sup> = Bn  
**c** R<sup>1</sup> = Ph, R<sup>2</sup> = *i*-Pr  
**d** R<sup>1</sup> = Ph, R<sup>2</sup> = Ph  
**e** R<sup>1</sup> = Ph, R<sup>2</sup> = *t*-Bu

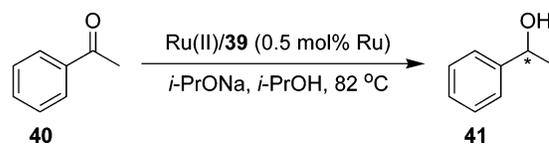
ligands with both one and two stereocenters have been utilized in palladium-catalyzed allylic alkylations.<sup>18</sup> Of the ligands possessing a single stereocenter, ligand **36c** with an isopropyl oxazoline substituent gave the highest enantioselectivity (up to 90% ee) for the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** (Table 5, entry 2). The introduction of a second stereocenter, that on the alkyl chain  $\alpha$  to the diphenylphosphine, enhanced the asymmetric induction in the case of the matched diastereomeric ligands (*R,S*<sub>ox</sub>)-**37** (Table 5, entries 4 and 6). The nature of the counterion also had a significant effect on enantioselection. It was found that the use of tetraalkylammonium fluorides in conjunction with *N,O*-bis(trimethylsilyl)acetamide

**Table 5. Palladium-Catalyzed Asymmetric Alkylation of 1,3-Diphenyl-2-propenyl Acetate **7** with **26** Using Ligands **36–38**<sup>a</sup>**

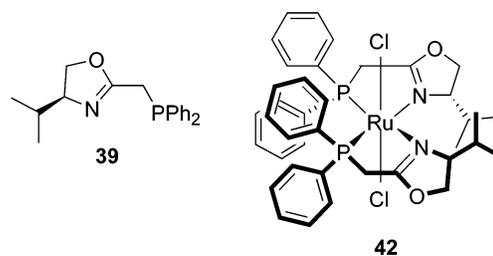
entry	ligand	cation	solvent	yield (%)	ee (%) (conf)
1 <sup>1</sup>	<b>36c</b>	<i>n</i> -Bu <sub>4</sub> N <sup>+</sup>	CH <sub>2</sub> Cl <sub>2</sub>	94	86 ( <i>R</i> )
2 <sup>2</sup>	<b>36c</b>	Hex <sub>4</sub> N <sup>+</sup>	CH <sub>2</sub> Cl <sub>2</sub>	62	90 ( <i>R</i> )
3 <sup>3</sup>	<b>36c</b>	K <sup>+</sup>	CH <sub>2</sub> Cl <sub>2</sub>	87	66 ( <i>R</i> )
4	<b>37a</b>	<i>n</i> -Bu <sub>4</sub> N <sup>+</sup>	CH <sub>3</sub> CN	86	94 ( <i>R</i> )
5	<b>38a</b>	<i>n</i> -Bu <sub>4</sub> N <sup>+</sup>	CH <sub>3</sub> CN	86	72 ( <i>R</i> )
6	<b>37c</b>	<i>n</i> -Bu <sub>4</sub> N <sup>+</sup>	CH <sub>3</sub> CN	80	95 ( <i>R</i> )
7	<b>38c</b>	<i>n</i> -Bu <sub>4</sub> N <sup>+</sup>	CH <sub>3</sub> CN	91	90 ( <i>R</i> )
8	<b>37c</b>	Hex <sub>4</sub> N <sup>+</sup>	CH <sub>3</sub> CN	99	97 ( <i>R</i> )

<sup>a</sup> [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (5 mol %), ligand (10 mol %), CH<sub>2</sub>(CO<sub>2</sub>Me)<sub>2</sub> (**26**), BSA, room temperature. <sup>b</sup> Reaction run at 0 °C.

#### Scheme 4



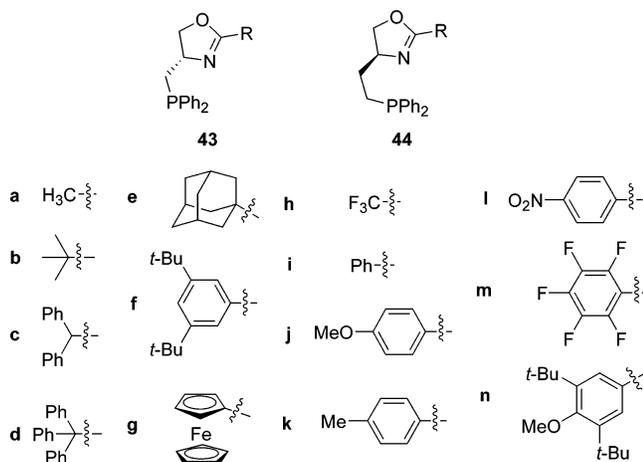
	Time (min)	Yield (%)	ee (%) (Conf.)
<i>in situ</i>	15	97	68 ( <i>R</i> )
<b>42</b>	180	96	72 ( <i>R</i> )



(BSA) to generate the dimethyl malonate nucleophile generally afforded higher enantioselectivities than the usual system of potassium acetate/BSA due to the presence of bulky noncoordinating tetraalkylammonium counterions (Table 5, entries 1–3). As for the majority of phosphinoxazoline ligands, the alkylation of 2-cyclopentenyl acetate **23** with **26** proceeded with a much reduced enantiodiscrimination, giving an optimum result of 42% ee in 50% yield with ligand **37a**.

Braunstein found that at least four isomeric complexes of the type [RuCl<sub>2</sub>(ligand)<sub>2</sub>] formed on reaction of [RuCl<sub>2</sub>(cod)]<sub>n</sub> with ligand **39** in which a single carbon alkyl chain connects the oxazoline ring with the diphenylphosphino group. On generation *in situ*, this isomeric mixture was highly active (97% yield after 15 min) in the asymmetric transfer hydrogenation of acetophenone **40**, affording the 1-phenylethanol product **41** in 68% ee (Scheme 4). The only isolated ruthenium complex, the *trans,cis,cis* complex **42**, was less active (96% yield after 3 h) than the isomeric mixture but gave a slightly higher enantioselectivity of 72% ee.<sup>19</sup>

Using divergent solution-phase syntheses, Burgess generated libraries of JM-Phos ligands of type **43** (first generation)<sup>20</sup> and **44** (second generation).<sup>21</sup> These ligands differ from the previously discussed phosphinoxazoline ligands in that the diphenylphosphino moiety is incorporated into the chiral substituent at the 4-position of the oxazoline ring.



Ligands **43** and **44** were screened for reactivity and enantioselectivity in the palladium-catalyzed alkylation of different substrates using a high-throughput screening methodology. Of the first-generation ligands **43a–m**, the bulky adamantyl-substituted ligand **43e** afforded the highest level of asymmetric induction (94% ee) for the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** (Table 6, entry

**Table 6. Palladium-Catalyzed Asymmetric Allylic Alkylation Using Ligands 43 and 44<sup>a</sup>**

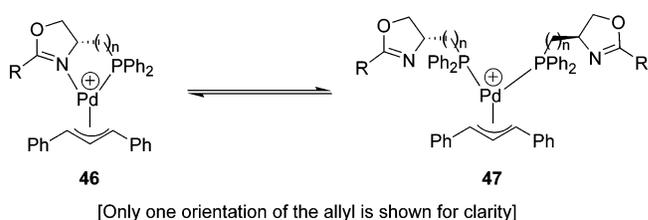
Entry	Substrate	Product	Ligand	Yield (%)	Ee (%) (Conf.)
1			<b>43e</b>		94
2			<b>44b</b>	95	98 ( <i>R</i> )
3			<b>44f</b>	95	98 ( <i>R</i> )
4			<b>44i</b>	80	98 ( <i>R</i> )
5 <sup>b</sup>			<b>43f</b>		74
6 <sup>b,c</sup>			<b>44f</b>	93	80 ( <i>R</i> )
7 <sup>b,c</sup>			<b>44n</b>	77	82 ( <i>R</i> )
8 <sup>b,c</sup>			<b>44f</b>	95	79 ( <i>S</i> )

<sup>a</sup> 2.5 mol % [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, 5 mol % ligand, CH<sub>2</sub>(CO<sub>2</sub>Me)<sub>2</sub> (**26**), BSA, KOAc, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 16 h. <sup>b</sup> 25 °C, 48 h. <sup>c</sup> Pd<sub>2</sub>dba<sub>3</sub> used.

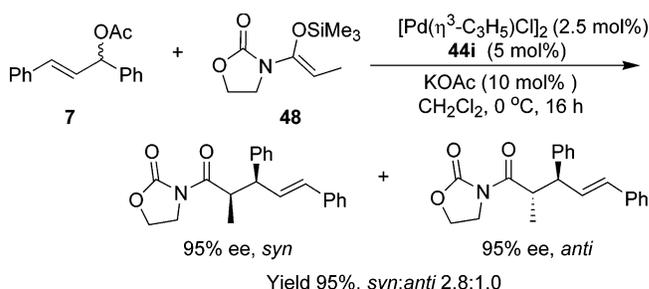
1).<sup>20</sup> This reaction also proceeded with high enantioselectivity when the second-generation JM-Phos ligands were employed (98% ee with **44b**, **44f**, and **44i**) (Table 6, entries 2–4).<sup>21b</sup> Ligands **43** and **44** were also tested with the more challenging allylic alkylation substrates, 4-pivaloxy-2-pentene **45** and 2-cyclohexenyl acetate **24**. In these cases the 3,5-di-*tert*-butylphenyl-substituted ligands **43f** and **44f** yielded good enantioselectivities and high yields (Table 6, entries 5–8).<sup>21b,22</sup>

In the reactions with substrates **7** and **45**, ligand-to-metal ratios greater than 1:1 for both ligand classes were found to cause a dramatic decrease in enantiodiscrimination accompanied in some incidences by a change in the absolute configuration of the product. This was attributed to the existence of an equilibrium between a weak *P,N*-ligand chelate

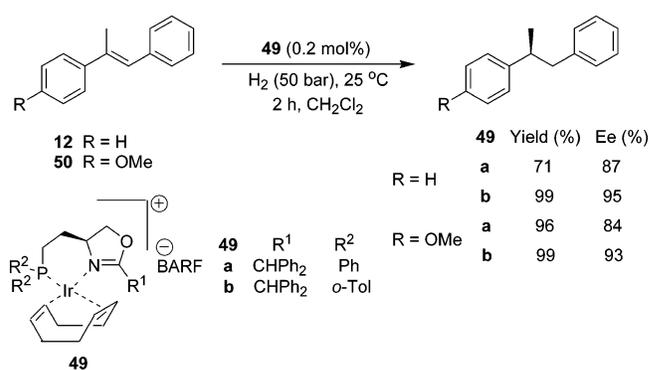
### Scheme 5



### Scheme 6



### Scheme 7



**46** and a diphosphine complex **47** (Scheme 5). The latter, which exists in appreciable amounts at high ligand-to-metal ratios, is thought to react more rapidly than **46** by virtue of two coordinating phosphines and with much lower enantioinduction.<sup>20,21b,22</sup>

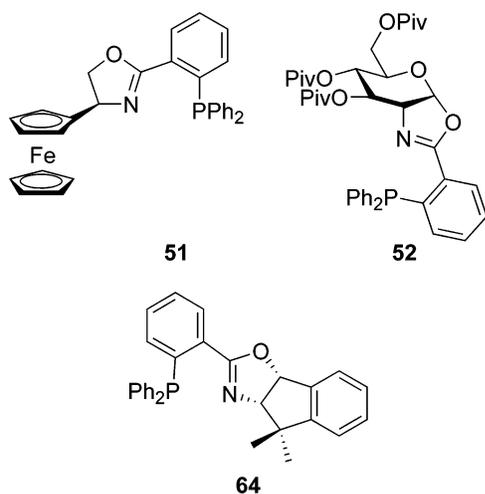
Ligand **44i** was also used in the alkylation of **7** with an unusual nucleophile, the silyl enol ether **48** (Scheme 6). In contrast to the literature, in which only moderate and low yields for this reaction are reported, excellent yields (95%) and enantioselectivities (95% ee) of the two diastereomeric products were obtained. However, the diastereoselectivity of the reaction was only 2.8:1.0.<sup>21b</sup>

Cationic iridium complexes **49** of the JM-Phos ligands **44** have also been employed in the enantioselective hydrogenation of arylalkenes.<sup>23</sup> The best results were achieved with the 1,2-diarylpropene derivatives, (*E*)-1,2-diphenylpropene **12** and the more electron-rich substrate (*E*)-2-(4-methoxyphenyl)-1-phenylpropene **50** (Scheme 7). For both substrates, it was observed that ligands bearing the large, nonspherical diphenylmethyl substituent were optimal. Furthermore, it was found that ligands with di-(*o*-tolyl)phosphino groups gave results superior to those with diphenylphosphino moieties.

Hydrogenation of other substrates such as allylic acetates and alcohols, 2-aryl-2-butene derivatives, and 1,1-disubstituted alkenes gave enantioselectivities that were lower than those obtained using

substrates **12** and **50** and in some cases significantly inferior to the results reported for the phosphinooxazoline ligands **1**. Burgess attributed these low enantioselectivities to the existence of competing double-bond migrations. Evidence for extensive double-bond migration in these reactions was obtained from deuterium-labeling experiments.<sup>23</sup>

By means of a six-step synthesis via a chiral ferrocenyl epoxide intermediate, Patti introduced a ferrocene as the substituent at the 4-position of the oxazoline ring in ligands of type **1**. This ferrocenyl-oxazoline ligand **51** was applied in the Pd-catalyzed

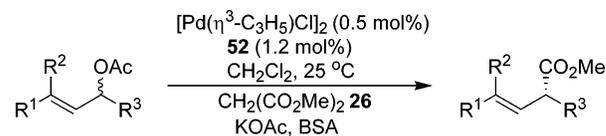


allylic alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** giving 86% yield (after 4.5 h at room temperature with 2 mol % Pd) and 92% ee (*S*).<sup>24</sup> In 2002 Moyano reported an alternative synthesis of the enantiomeric ligand (*S*)-**51** using an enantiopure ferrocenyl-substituted amino alcohol. A palladium–allyl complex of this ligand  $[(\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{-51})\text{PF}_6]$  (5 mol %) afforded an excellent enantioselectivity of 99.6% ee (*R*) for the alkylation of **7** but with low catalytic activity (63% yield after 7 days at room temperature). Alkylation of 4-acetoxy-2-pentene **53** and 2-cyclohexenyl acetate **24** proceeded with much lower levels of enantioselection [44% ee (*R*) and 12% ee (*S*), respectively] at 70 °C in THF.<sup>25</sup>

Kunz has reported the preparation of a glucosamine-derived ligand **52** in which the oxazoline moiety is incorporated in a bicyclic framework.<sup>26</sup> Pd-catalyzed alkylation of symmetrical allyl acetates with this ligand followed a trend similar to that of the phosphinooxazoline ligands **1**, affording excellent asymmetric induction for the diphenyl-substituted analogue **7** but lower enantioselectivities for allyl acetate substrates with primary alkyl substituents **53**–**55** (Scheme 8 and Table 7, entries 1–4). This ligand was also tested in the alkylation of unsymmetrical allyl acetates **56** and **57**. In the reaction of the 3,3-diphenyl-substituted compound **56**, regioisomer **61** was formed exclusively with good stereocontrol. In the case of the trimethyl-substituted allyl acetate **57**, a mixture of both regioisomers (**62** and **63**) was formed, but the enantioselectivity of the chiral product was greater than that obtained when **56** was the substrate (Table 7, entries 5 and 6).

Ligand **64**, with a tricyclic oxazoline group derived from the non-natural amino alcohol *cis*-2-amino-3,3-

### Scheme 8

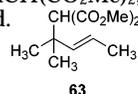


<b>7</b> R <sup>1</sup> , R <sup>3</sup> = Ph, R <sup>2</sup> = H	<b>9</b> R <sup>1</sup> , R <sup>3</sup> = Ph, R <sup>2</sup> = H
<b>53</b> R <sup>1</sup> , R <sup>3</sup> = Me, R <sup>2</sup> = H	<b>58</b> R <sup>1</sup> , R <sup>3</sup> = Me, R <sup>2</sup> = H
<b>54</b> R <sup>1</sup> , R <sup>3</sup> = Et, R <sup>2</sup> = H	<b>59</b> R <sup>1</sup> , R <sup>3</sup> = Et, R <sup>2</sup> = H
<b>55</b> R <sup>1</sup> , R <sup>3</sup> = <i>n</i> -Pr, R <sup>2</sup> = H	<b>60</b> R <sup>1</sup> , R <sup>3</sup> = <i>n</i> -Pr, R <sup>2</sup> = H
<b>56</b> R <sup>1</sup> , R <sup>2</sup> = Ph, R <sup>3</sup> = Me	<b>61</b> R <sup>1</sup> , R <sup>2</sup> = Ph, R <sup>3</sup> = Me
<b>57</b> R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = Me	<b>62</b> R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = Me

**Table 7. Palladium-Catalyzed Asymmetric Alkylation of Substrates **7** and **53**–**57** with Dimethyl Malonate **26** Using Ligand **52** (Scheme 8)**

entry	substrate	yield (%)	ee (%) (conf)
1	<b>7</b>	94	98 ( <i>R</i> )
2	<b>53</b>	91	69 ( <i>R</i> )
3	<b>54</b>	90	73 ( <i>R</i> )
4	<b>55</b>	77	74 ( <i>R</i> )
5 <sup>a</sup>	<b>56</b>	83	88 ( <i>R</i> )
6 <sup>a,b</sup>	<b>57</b>	56	92 ( <i>R</i> )

<sup>a</sup> NaCH(CO<sub>2</sub>Me)<sub>2</sub>, THF, 20 °C. <sup>b</sup> 44% of regioisomer **63** formed.



**Table 8. Palladium-Catalyzed Asymmetric Intermolecular Heck Reactions Using Ligand **64**<sup>a</sup>**

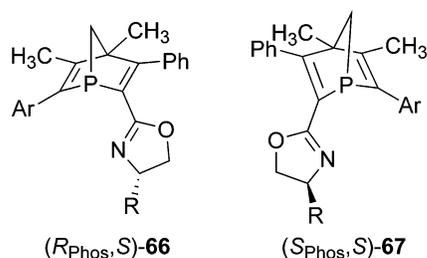
Entry	Olefin	Triflate	Product	Yield (%)	Ee (%) (Conf.)
1	<b>15</b>	<b>16a</b>		81	96 ( <i>R</i> )
2	<b>15</b>	<b>65</b>		64	94 ( <i>R</i> )
3 <sup>b</sup>	<b>15</b>	<b>16b</b>		91	98 ( <i>R</i> )
4	<b>33</b>	<b>16a</b>		37	90 ( <i>R</i> )

<sup>a</sup> 4 mol % [Pd<sub>2</sub>dba<sub>3</sub>.dba], 15 mol % **64**, *i*-Pr<sub>2</sub>NEt, benzene, 5 days, 70 °C. <sup>b</sup> The reaction was carried out at room temperature.

dimethyl-1-indanol, was first reported in 1997 as a highly efficient ligand for the palladium-catalyzed asymmetric amination of 1,3-diphenyl-2-propenyl acetate **7** and 3,3-diphenyl-2-propenyl acetate with benzylamine and potassium phthalimide (up to 99% ee).<sup>27</sup> This ligand also gave high enantioselectivities for the rhodium-catalyzed hydrosilylation of a range of arylalkyl and dialkyl ketones (up to 94% ee).<sup>28</sup> In the asymmetric intermolecular Heck reaction, ligand **64** afforded good to excellent enantioselectivities and moderate to high yields for the reaction of 2,3-dihydrofuran **15** with different aromatic and vinyl triflates **16a**, **16b**, and **65** (Table 8, entries 1–3).<sup>29</sup> This high degree of asymmetric induction was maintained for the bulky substrate 4,7-dihydro-1,3-diox-

epin **33**, but the yield was significantly lowered. Like other phosphinoxazoline ligands, ligand **64** has a low tendency to promote carbon–carbon double-bond migration resulting in the formation of a single regioisomer.

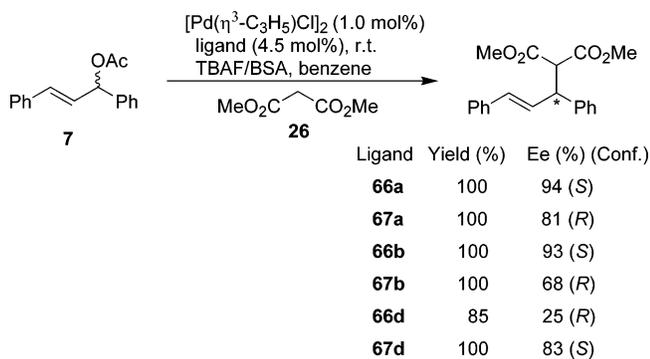
Phosphinoxazoline ligands with stereogenic phosphorus donor atoms have also been investigated in asymmetric catalysis. Gilbertson has reported the synthesis of chiral phosphanorbornadienyl–oxazoline ligands **66** and **67** in which the phosphorus stereocenter is located in the bridgehead of a rigid bicyclic system.<sup>30</sup> These ligands were tested in the palladium-



- a** R = *i*-Pr, Ar = Ph  
**b** R = *t*-Bu, Ar = Ph  
**c** R = *i*-Pr, Ar = phenanthryl  
**d** R = *i*-Pr, Ar = anthracyl

catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** (Scheme 9). Of

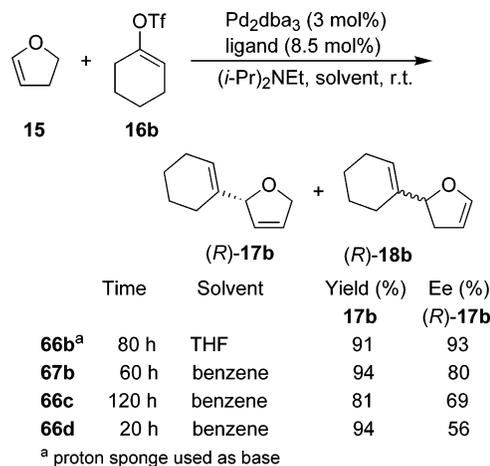
#### Scheme 9



the ligands used, the isopropyl-substituted analogue **66a** afforded the best result of 94% ee in quantitative yield. The results obtained with the diastereomeric ligand pairs indicated that the sense of asymmetric induction in this reaction was determined principally by the configuration of the phosphorus atom. Increasing the size of the aromatic substituent on the bicyclic phosphine resulted, in general, in a decrease in enantiodiscrimination, but with ligand **67d**, a complete reversal of enantioselectivity (compared to **67a**) was obtained (81% ee (*R*) with **67a** and 83% ee (*S*) with **67d**).

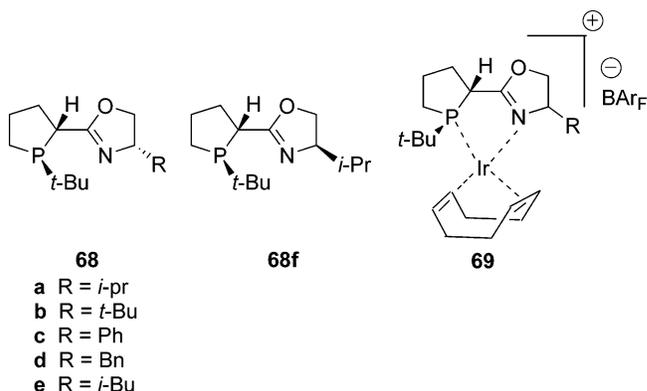
Palladium complexes of ligands **66** and **67** were also effective in the palladium-catalyzed Heck cyclohexenylation of 2,3-dihydrofuran **15**, catalyzing the reaction to completion at room temperature with <10% of the double-bond isomerized product **18b**. Interestingly, for this reaction the oxazoline stereocenter was the dominant stereocontrol element, with the diastereomeric pairs affording the same enantiomeric product. An increase in size of the substitu-

#### Scheme 10



ent on the bicyclic phosphine portion of the ligand caused an increase in the reaction rate but a decrease in enantioselectivity. The *tert*-butyl-substituted oxazolinyl ligand **66b** gave the best results of 93% ee and 91% yield after 80 h at room temperature (Scheme 10).<sup>30</sup>

In 2003 Zhang reported the synthesis of the phospholane–oxazoline ligands **68**, which possess an electron-rich stereogenic phosphorus atom. Their iridium complexes **69** proved to be highly efficient



catalysts for the hydrogenation of a series of both electron-rich and electron-poor methylstilbene derivatives and various substituted (*E*)- $\beta$ -methylcinnamic esters with the catalyst of choice **69c** affording complete reaction and excellent enantioselectivities (90–99% ee) (Table 9, entries 3–5 and 8–16). The diastereomeric complexes **69a** and **69f** gave hydrogenation products of different configuration, therefore indicating that the oxazoline stereocenter determines the sense of enantioselection (Table 9, entries 1 vs 2 and 6 vs 7). Asymmetric hydrogenation of a (*Z*)- $\beta$ -methylcinnamic ester led to a product with a different configuration but a lower enantioselectivity compared to its (*E*)-analogue [80% ee (*S*) vs 98% ee (*R*)] (Table 9, entry 17 vs 10).<sup>31</sup>

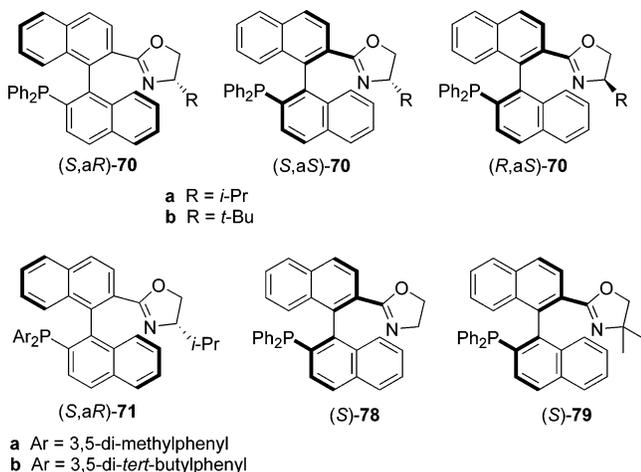
#### 2.1.2. Phosphinoxazoline Ligands with a Stereoaxis

The diastereomeric oxazoline ligands (*S*,*aR*)- and (*S*,*aS*)-**70**, with an axially chiral binaphthyl backbone, have been used independently by the groups

**Table 9. Enantioselective Hydrogenation of Methylstilbene Derivatives and  $\beta$ -Methylcinnamic Esters Using Complexes **69**<sup>a</sup>**

Entry	Substrate	Catalyst	Ee (%) (Conf.)
1		<b>69a</b>	91 ( <i>R</i> )
2		<b>69f</b>	77 ( <i>S</i> )
3		<b>69c</b>	95 ( <i>R</i> )
4		<b>69c</b>	91 ( <i>R</i> )
5		<b>69c</b>	90 ( <i>R</i> )
6		<b>69a</b>	94 ( <i>R</i> )
7		<b>69f</b>	93 ( <i>S</i> )
8		<b>69c</b>	98 ( <i>R</i> )
9		<b>69c</b>	95 ( <i>R</i> )
10		<b>69c</b>	98 ( <i>R</i> )
11		<b>69c</b>	97 ( <i>R</i> )
12		<b>69c</b>	97 ( <i>R</i> )
13		<b>69c</b>	97 ( <i>R</i> )
14		<b>69c</b>	99 ( <i>R</i> )
15		<b>69c</b>	98 ( <i>R</i> )
16		<b>69c</b>	95 ( <i>R</i> )
17 <sup>b</sup>		<b>69c</b>	80 ( <i>S</i> )

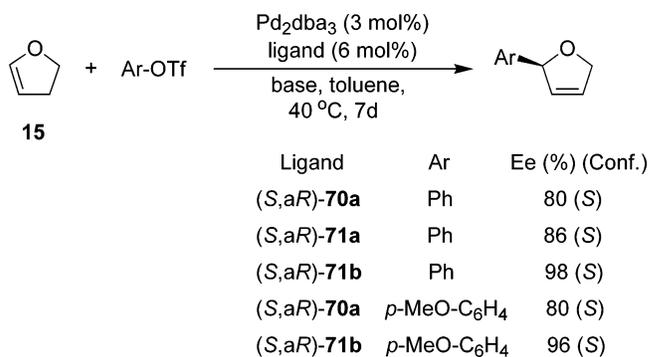
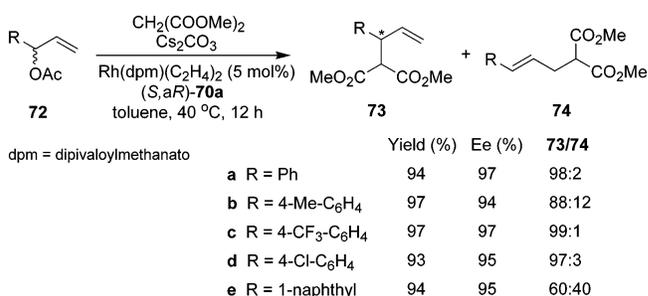
<sup>a</sup> 1 mol % of **69**, 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temperature. <sup>b</sup> (*Z*)- $\beta$ -methylcinnamic ester used.



of Ikeda<sup>32</sup> and Hayashi<sup>33</sup> for the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. The best result [96% ee (*R*), 90% yield at 0 °C] was achieved by Ikeda using the *tert*-butyl-substituted ligand (*S,aR*)-**70b** and employing the BSA/KOAc methodology. The diastereomeric ligands (*S,aR*)- and (*S,aS*)-**70a** afforded high enantioselectivities of the product but opposite enantiomers [90% ee (*R*) and 85% ee (*S*), respectively], thus indicating that the axially chiral binaphthyl skeleton is the more influential stereogenic unit in these ligands and determines the stereochemical outcome of the reaction.<sup>32</sup>

Pregosin has shown that the isopropyl-substituted derivative (*S,aR*)-**70a** is a highly efficient ligand for palladium-catalyzed asymmetric allylic amination, affording good to excellent enantioselectivities (74.9–99.0% ee) for the amination of **7** with a range of amine nucleophiles.<sup>34</sup>

In the palladium-catalyzed asymmetric Heck arylation of 2,3-dihydrofuran **15**, Hayashi obtained **17a** as the single regioisomeric product in 65% yield

**Scheme 11****Scheme 12**

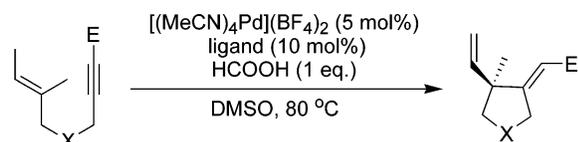
and 88% ee (*R*) using the catalyst (3 mol %) generated in situ from ligand (*S,aS*)-**70a** and Pd<sub>2</sub>(dba)<sub>3</sub>-dba.<sup>35</sup>

Ligands (*S,aR*)-**71** with 3,5-dialkylphenyl groups as phosphorus substituents afforded higher levels of asymmetric induction than the corresponding diphenylphosphino derivative (*S,aR*)-**70a** in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with **26** [99% yield and 97% ee (*R*) with (*S,aR*)-**71a** vs 99% yield and 91% ee (*R*) with (*S,aR*)-**70a**]<sup>36</sup> and in the asymmetric Heck arylation of 2,3-dihydrofuran (Scheme 11).<sup>36,37</sup> Pregosin suggested that this “*meta*-dialkyl effect” arises from restricted rotation around the P–C(*ipso*) bonds, resulting in greater rigidity of the chiral pocket and increased correlation with the substrate.

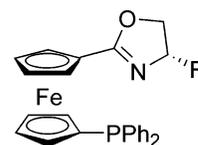
One of the few examples of a highly enantioselective rhodium-catalyzed allylic alkylation has been reported by Hayashi using these ligands.<sup>38</sup> High enantioselectivities (94–97% ee) and regioselectivities (up to 99/1 branched **73**/linear **74**) were obtained for the alkylation of 1-aryl-2-propenyl acetates **72a–e** employing the isopropyl-substituted ligand (*S,aR*)-**70a** (Scheme 12).

The use of axially chiral oxazoline ligands in the enantioselective formation of carbocycles and heterocycles by palladium(II)-catalyzed ene-type carbocyclizations of the 1,6-enynes **75–77** has been investigated by Mikami (Scheme 13).<sup>39</sup> It was found by using ligands (*S,aS*)- and (*R,aS*)-**70a** that the stereocenter at the 4-position of the oxazoline ring is not important in controlling the sense of the asymmetric induction (Table 10, entries 1 and 2), whereas ligand **78** with an unsubstituted oxazoline ring gave only low enantioselectivity for the cyclization of **76** (Table 10, entry 3). These results, X-ray crystal structures of dichloropalladium(II) complexes of ligands (*S,aS*)- and (*R,aS*)-**70a**, and mechanistic studies led to the development of ligand **79**, which possesses an achiral

## Scheme 13



- 75 X = O, E = CO<sub>2</sub>Me  
 76 X = NTs, E = CO<sub>2</sub>Me  
 77 X = C(CO<sub>2</sub>Et)<sub>2</sub>, E = CONMe<sub>2</sub>



83

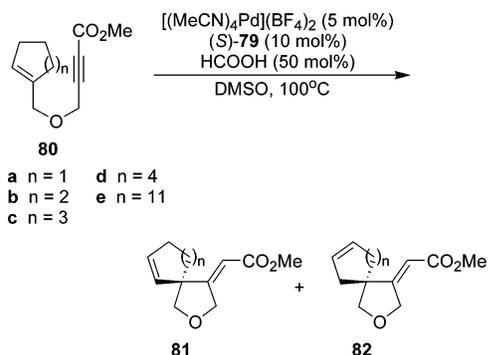
- a R = *i*-Pr  
 b R = *t*-Bu  
 c R = Ph  
 d R = Bn

**Table 10. Enantioselective Palladium-Catalyzed Ene-Type Carbocyclization of 1,6-Enynes 75–77 Using Ligands (*R,a,S*)-70b, (*S,a,S*)-70b, (*S*)-78, and (*S*)-79 (Scheme 13)**

entry	substrate	ligand	reaction time (h)	yield (%)	ee (%) (conf)
1	76	( <i>R,a,S</i> )-70b	3	>99	93 ( <i>S</i> )
2	76	( <i>S,a,S</i> )-70b	3	>99	92 ( <i>S</i> )
3	76	( <i>S</i> )-78	3	>99	35 ( <i>S</i> )
4 <sup>a</sup>	75	( <i>S</i> )-79	24	87	88 ( <i>S</i> )
5	76	( <i>S</i> )-79	3	>99	93 ( <i>S</i> )
6	77	( <i>S</i> )-79	3	>99	95 ( <i>S</i> )

<sup>a</sup> 0.2 equiv of HCOOH used.

## Scheme 14



**Table 11. Enantioselective Palladium-Catalyzed Ene-Type Spirocyclization of Cyclic Allyl Propargyl Ethers 80a–e Using Ligand (*S*)-79 (Scheme 14)**

entry	substrate	reaction time (h)	81		82	
			yield (%)	ee (%)	yield (%)	ee (%)
1	80a	3	88	88	7	
2	80b	22	63	84	20	31
3	80c	3	13	88	78	83
4	80d	6	33	93	61	80
5 <sup>a</sup>	80e	11	>90	83	0	

<sup>a</sup> In the absence of HCOOH.

*gem*-dimethyl oxazoline unit. Using this ligand, carbocyclization of substrates 75–77 proceeded with high enantioselection and almost quantitative yields (up to 95% ee and 99% yield) (Table 10, entries 4–6). This ligand was also amenable to the ene-type spirocyclization of cyclic allyl propargyl ethers 80 of various ring sizes (Scheme 14).<sup>40</sup> In general, high enantioselectivities were achieved for the primary generated spiro-products 81 (83–93% ee) and also for the secondary olefin regioisomers 82 resulting from olefin migrations in some cases (Table 11).

Ikeda has reported the preparation of chiral ferrocene-based *P,N*-ligands, the 1-diphenylphosphino-1'-oxazolinyferrocenes 83a–c, in which the diphenylphosphine and oxazoline groups are attached to

different cyclopentadiene rings.<sup>41</sup> Because of the opposite twists of these cyclopentadiene units, a stable axial chirality can be induced in these ligands on coordination to a metal resulting in the formation of two diastereomeric complexes.

The complexes derived in situ from these ligands and 1 mol % of [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> showed excellent catalytic activities in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate 7 with dimethyl malonate 26 affording product 9 with >96% isolated chemical yield within 30 min at room temperature regardless of the kind of base or solvent used. The optimum enantioselectivity of 91% ee (*S*) was obtained with the isopropyl-substituted ligand 83a using BSA/KOAc and dichloromethane as the base and solvent, respectively. In 1999 Park also reported the application of ligands 83a–c in the palladium-catalyzed alkylation reaction and achieved improved results of 96% yield and 99% ee (*S*) after a reaction time of 10 min using ligand 83a.<sup>42</sup>

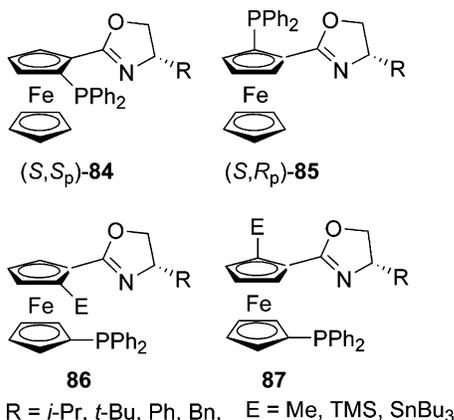
In the palladium-catalyzed intermolecular Heck phenylation of 2,3-dihydrofuran 15, the benzyl-substituted ligand 83d gave the best enantioselectivity [76% ee (*R*)] and the highest catalytic activity, affording 17a as the sole product in 80% yield after 8 h at 60 °C using 3 mol % of Pd(dba)<sub>2</sub>.<sup>43</sup>

### 2.1.3. Phosphino-oxazoline Ligands with a Stereoplane

Of the planar chiral oxazoline ligands used in asymmetric catalysis, those based on ferrocene have attracted the most attention. The applications of planar chiral 2-ferrocenyloxazolines in catalytic asymmetric synthesis up to 2002 have recently been extensively reviewed by Bryce and Sutcliffe.<sup>3</sup> As a consequence, such applications involving mono(oxazoline) *P,N*-ligands will not be discussed in detail here.

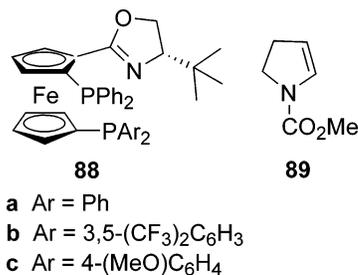
In general, 1,2-disubstituted diphenylphosphino-oxazolinyferrocene compounds 84 and 85 with both stereocenters and stereoplanes have proved to be efficient ligands in numerous asymmetric reactions, affording high levels of asymmetric induction. These reactions include asymmetric palladium(II)-, copper(I)-, and nickel(0)-catalyzed cross-coupling reactions of Grignard reagents, palladium-catalyzed allylic alkylations and aminations, inter- and intramolecular Heck reactions, rhodium(I)-, iridium(I)-, and ruthenium(II)-catalyzed hydrosilylations of ketones, imines, and ketoximes, ruthenium(II)-catalyzed transfer hydrogenation of ketones, and the kinetic resolution of racemic alcohols via the Oppenauer oxidation.<sup>3</sup>

The introduction of a noncoordinating group *ortho* to the oxazoline ring in the 1-diphenylphosphino-1'-



oxazolinylferrocenes **83** brought about the formation of catalysts with three stereogenic units, a stereocenter, a stereoplane, and a stereoaxis, on coordination to a metal. These ligands **86** and **87** have been successfully used in the palladium-catalyzed asymmetric allylic alkylation (up to 98.5% ee) and amination (up to 96.5% ee) of 1,3-diphenyl-2-propenyl acetate **7**<sup>44</sup> and in the intermolecular Heck phenylation of 2,3-dihydrofuran (up to 92.1% ee).<sup>43</sup> The additional stereoplane in these ligands strongly influences both the extent of asymmetric induction and the product configuration by changing or inverting the ratio of the rotamer complexes by steric interaction between the noncoordinating substituent and the coordination site.<sup>3,45</sup>

Recently, Hou and Dai have reported the synthesis of chiral oxazolinylferrocene ligands **88** with the two diarylphosphino moieties located on separate cyclopentadiene rings.<sup>46</sup> It was found by X-ray-crystal-

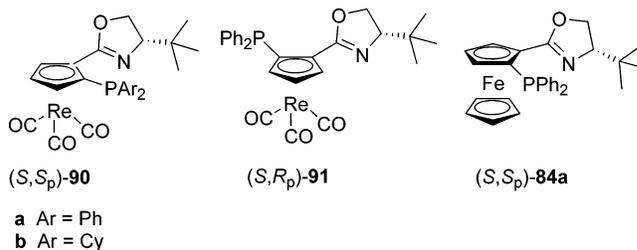


lography and by <sup>31</sup>P NMR spectroscopy that these ligands coordinate to palladium through the two phosphorus donor atoms. In the asymmetric Heck phenylation of 2,3-dihydrofuran **15** (Scheme 2), ligand **88a** gave excellent yields and enantioselectivities of the 2,5-dihydrofuran product **17a** (up to 99% ee) but entirely different regioselectivity profiles with different palladium precursors. With palladium acetate,

**17a** was the major product, whereas in contrast the thermodynamic product **18a** was preferred using Pd(dba)<sub>2</sub> (Table 12, entry 1 vs entry 2). The regiochemical outcome of this reaction could also be tuned by introducing electron-donating and electron-withdrawing substituents onto the aromatic rings of the phosphorus atom. Thus, ligand **88b** with electron-withdrawing trifluoromethyl groups enhanced the regioselectivity in favor of the kinetic product **17a**, whereas ligand **88c** with an electron-donating methoxy group reversed this preference in favor of the thermodynamic product **18a** (Table 12, entries 3–5).<sup>46</sup>

The reaction of both **15** and the 2,3-dihydropyrrole substrate, *N*-methoxycarbonyl-2-pyrroline **89**, with various aryl (2-naphthyl-, 4-methoxyphenyl-, 4-nitrophenyl-, and 4-fluorophenyl) and cyclohexenyl triflates employing ligands **88** also proceeded with good to excellent enantioselectivities (from 40 to >99% ee) with similar regioselectivity trends.<sup>46,47</sup>

Bolm has reported the synthesis of planar chiral phosphinooxazoline ligands **90** and **91** based on η<sup>5</sup>-cyclopentadienyl(tricarbonyl)rhenium(I) (cyrhetrene).



The effectiveness of these ligands in a range of asymmetric reactions was compared to that of the analogous ferrocenyl-based ligand **84a**.<sup>48</sup> In general, it was found that the stereocenter of the oxazoline ring was the dominant factor in controlling the stereochemical outcome of these reactions and that ligand (*S,S<sub>p</sub>*)-**90a** had the matched combination of stereogenic units.

For the alkylation of 1,3-diphenyl-2-propenyl acetate **7**, 2-cyclopentenyl acetate **23** and 2-cycloheptenyl acetate **25** with dimethyl malonate **26**, the best of the cyrhetrenyloxazoline ligands (*S,S<sub>p</sub>*)-**90a** gave slightly lower enantioselectivities than the corresponding ferrocenyl analogue (*S,S<sub>p</sub>*)-**84a** (Table 13, entries 1 and 2, 7 and 8, and 9 and 10). In contrast, for the difficult substrate 4-acetoxy-2-pentene **53**, the mismatched diastereomer (*S,R<sub>p</sub>*)-**91** and the electron-rich dicyclohexylphosphino ligand (*S,S<sub>p</sub>*)-**90b** afforded higher enantioselectivities than both ligand (*S,S<sub>p</sub>*)-**90a** and its ferrocenyl counterpart (*S,S<sub>p</sub>*)-**84a** (Table 13, entries 3–6). The cyrhetrenyl ligands gave no

**Table 12. Regioselectivity Trends in the Enantioselective Heck Phenylation of 2,3-Dihydrofuran **15** Using Ligands **88a–c**<sup>a</sup>**

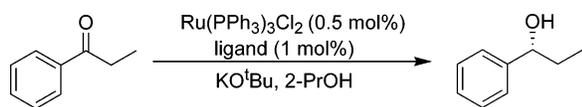
entry	Pd source	ligand	solvent	conversion (%)	<b>17a:18a</b>	ee (%)	<b>17a(R):18a(S)</b>
1	Pd(OAc) <sub>2</sub>	<b>88a</b>	toluene	85	95:5	97	26
2	Pd(dba) <sub>2</sub>	<b>88a</b>	dichloroethane	80	25:75	98	nd <sup>b</sup>
3	Pd(OAc) <sub>2</sub>	<b>88b</b>	toluene	67	99:1	92	nd
4	Pd(OAc) <sub>2</sub>	<b>88c</b>	toluene	65	14:86	86	27
5	Pd(dba) <sub>2</sub>	<b>88c</b>	dichloroethane	68	8:92	nd	19

<sup>a</sup> Pd (1.5 mol %), **88** (3 mol %), *i*-Pr<sub>2</sub>NEt, 60 °C, 36 h. <sup>b</sup> nd, not determined.

**Table 13. Enantioselective Palladium-Catalyzed Allylic Alkylation Using Ligands **84a**, **90**, and **91**<sup>a</sup>**

Entry	Substrate	Nucleophile	Ligand	Time (h)	Yield (%)	Ee (%) (Conf.)
1		CH <sub>2</sub> (CO <sub>2</sub> Me) <sub>2</sub>	( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	4	98	73 ( <i>S</i> )
2			( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	2	99	65 ( <i>S</i> )
3		CH <sub>2</sub> (CO <sub>2</sub> Me) <sub>2</sub>	( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	24	95	34 ( <i>S</i> )
4			( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	24	93	34 ( <i>S</i> )
5			( <i>S,S</i> <sub>p</sub> )- <b>90b</b>	24	91	51 ( <i>S</i> )
6			( <i>S,R</i> <sub>p</sub> )- <b>91</b>	24	92	53 ( <i>S</i> )
7		CH <sub>2</sub> (CO <sub>2</sub> Me) <sub>2</sub>	( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	24	95	64 ( <i>R</i> )
8			( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	24	96	56 ( <i>R</i> )
9		CH <sub>2</sub> (CO <sub>2</sub> Me) <sub>2</sub>	( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	24	97	83 ( <i>R</i> )
10			( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	24	95	79 ( <i>R</i> )
11		BnNH <sub>2</sub>	( <i>S,S</i> <sub>p</sub> )- <b>84a</b>		40	77 ( <i>R</i> )
12			( <i>S,S</i> <sub>p</sub> )- <b>90a</b>		34	97 ( <i>R</i> )

<sup>a</sup> 0.5 mol % [Pd(*η*<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, 1.0 mol % ligand, CH<sub>2</sub>Cl<sub>2</sub>, room temperature.

**Scheme 15**

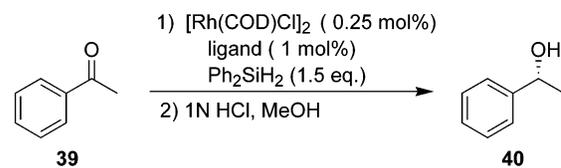
Ligand	Temp. (°C)	Time (h)	Yield (%)	Ee (%) (Conf.)
( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	50	8	99	99.7 ( <i>R</i> )
( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	82	2	86	47 ( <i>R</i> )
( <i>S,S</i> <sub>p</sub> )- <b>90b</b>	82	2	93	64 ( <i>R</i> )
( <i>S,R</i> <sub>p</sub> )- <b>91</b>	82	2	13	9 ( <i>R</i> )

product for the alkylation of 2-cyclohexenyl acetate **24**. In the palladium-catalyzed amination of **7** with benzylamine, only ligand (*S,S*<sub>p</sub>)-**90a** of the cyrhetrenyloxazoline family afforded product. This was achieved with an excellent enantiodiscrimination of 97% ee, albeit in low yield, giving a better result than the corresponding ferrocene ligand (*S,S*<sub>p</sub>)-**84a** (77% ee) (Table 13, entry 11 vs entry 12).<sup>48</sup>

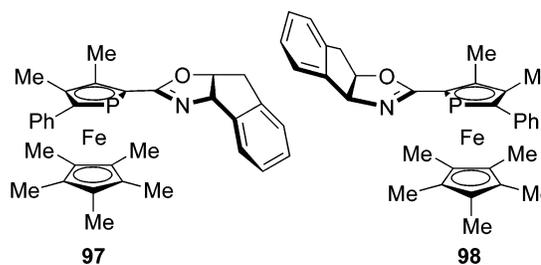
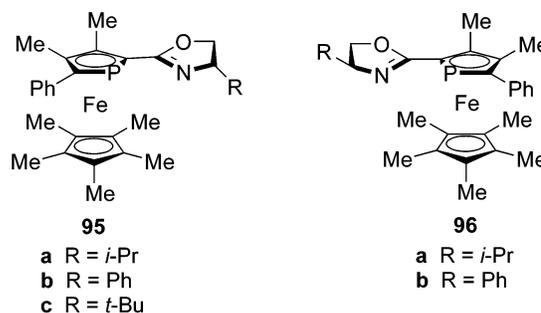
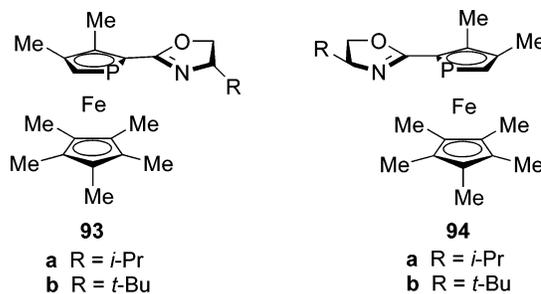
The cyrhetrenyl ligands gave lower reactivities and significantly reduced enantioselectivities [up to 64% ee with (*S,S*<sub>p</sub>)-**90b**] compared to the ferrocene ligand (*S,S*<sub>p</sub>)-**84a** (99.7% ee) for the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of propiophenone **92** (Scheme 15).<sup>48</sup>

Ligand (*S,S*<sub>p</sub>)-**90a** proved to be superior for the rhodium(I)-catalyzed asymmetric hydrosilylation of acetophenone **40**, giving better enantioselectivities (72% ee) and reactivities than the other cyrhetrenyl ligands and the ferrocene analogue (*S,S*<sub>p</sub>)-**84a** (58% ee) (Scheme 16).<sup>48</sup>

Fu has reported the synthesis of novel stereoplanar phosphoferrocene–oxazoline ligands **93**–**98**, in which the phosphorus donor atom is incorporated into one of the cyclopentadiene rings of the ferrocene unit.<sup>49,50</sup> Unlike the sp<sup>3</sup>-hybridized phosphorus of a typical tertiary phosphine ligand, the sp<sup>2</sup>-hybridized phos-

**Scheme 16**

Ligand	Temp. (°C)	Time (h)	Yield (%)	Ee (%) (Conf.)
( <i>S,S</i> <sub>p</sub> )- <b>84a</b>	-20	60	27	58 ( <i>R</i> )
( <i>S,S</i> <sub>p</sub> )- <b>90a</b>	-20	60	55	72 ( <i>R</i> )
( <i>S,S</i> <sub>p</sub> )- <b>90b</b>	-20	60	41	33 ( <i>R</i> )
( <i>S,R</i> <sub>p</sub> )- <b>91</b>	0	60	28	17 ( <i>R</i> )

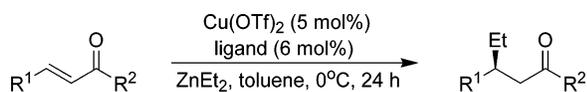


phorus of a phosphoferrocene is stereogenic and can undergo metal to phosphorus  $\pi$ -back-bonding, which can stabilize low-valent metal complexes.

Ligands **93** and **94** were first tested for their enantiodifferentiating ability in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>49</sup> It was found that the stereoplane of the phosphoferrocene and not the stereocenter of the oxazoline was the dominant stereocontrol element. The optimum result of 92% yield and 82% ee was achieved with the matched *tert*-butyl-substituted oxazoline **94b**.

The opposite situation exists in the copper-catalyzed enantioselective conjugate addition of diethylzinc to a range of acyclic enones (Scheme 17), where it is the stereocenter on the oxazoline ring, and not the stereoplane, that exerts control over the stereochemical outcome.<sup>50</sup> Modification of the substituents on both the phospholyl and oxazoline rings led to the

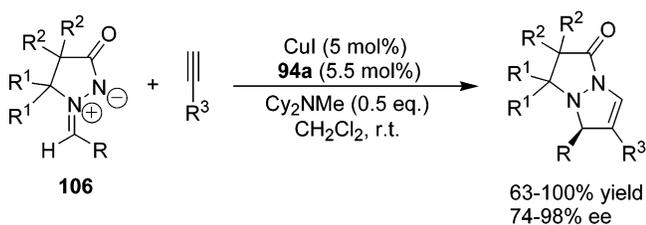
## Scheme 17



**Table 14. Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Acyclic Enones **99–105** in the Presence of Phosphaferrocene–Oxazoline Ligands **95**, **97**, and **98** (Scheme 17)**

Entry	Enone	Ligand	Yield (%)	Ec (%)
1		<b>97</b>	82	87
2		<b>97</b>	82	91
3		<b>95b</b>	89	80
4		<b>95b</b>	89	90
5		<b>98</b>	74	84
6		<b>95b</b>	79	61
7		<b>95b</b>	79	81

## Scheme 18



development of effective ligands **95–98**, which gave high enantioselectivities (61–91% ee) and good yields (74–89%) for the conjugate addition of diethylzinc to electron-rich and electron-poor chalcone derivatives **99–102** (Table 14, entries 1–4),  $\beta$ -alkyl-substituted enones **103** and **104** (Table 14, entries 5 and 6), and the alkyl ketone **105** (Table 14, entry 7). The presence of heterochiral bis- (or higher) ligated complexes in the reaction mixture was suggested by the small negative nonlinear effect obtained for the conjugate addition of diethylzinc to 4-chlorochalcone **101** catalyzed by  $\text{Cu}(\text{OTf})_2/\mathbf{95b}$ .

The phosphaferrocene–oxazoline ligand **94a** was highly effective in a novel copper(I)-catalyzed 1,3-dipolar cycloaddition of azomethine imines to terminal alkynes, generating five-membered nitrogen heterocycles (Scheme 18).<sup>51</sup> Excellent yields (77–100%), complete regioselectivities, and very high levels of enantiodiscrimination (81–98% ee) were achieved for the reaction of a wide range of 3-oxopyrazolidin-1-ium-2-ides **106** (R = aryl, alkenyl, alkyl,  $\text{R}^1, \text{R}^2 = \text{H}$ ,

## Scheme 19



**Table 15. Copper-Catalyzed Asymmetric Intramolecular Kinugasa Reaction Using Ligands **95a** and **95c** (Scheme 19)**

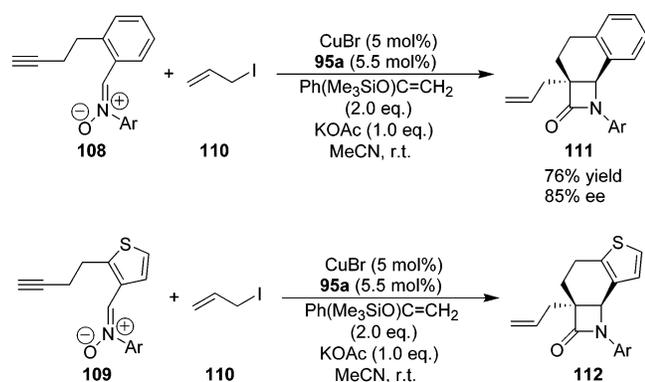
Entry	Product	Ligand	Yield (%)	Ec (%)
1		<b>95a</b>	74	88
2		<b>95a</b>	60	86
3		<b>95a</b>	46	90
4		<b>95c</b>	64	90
5		<b>95c</b>	53	85
6		<b>95c</b>	68	91

Me) and terminal alkynes bearing carbonyl groups or electron-deficient aromatic or heteroaromatic rings. Cycloaddition with simple aryl- or alkyl-substituted alkynes also proceeded with good enantioselectivities (74–88% ee) but at elevated temperatures and with reduced regioselectivity (~6:1).

Fu has also developed a highly enantioselective intramolecular Kinugasa reaction of alkyne–nitrones **107** to produce enantioenriched polycyclic  $\beta$ -lactams employing copper(I) complexes of phosphaferrocene–oxazoline ligands (Scheme 19 and Table 15).<sup>52</sup> The synthesis of a number of 6,4 and 7,4 ring systems was achieved with moderate to good yields (46–74%) and high enantioselectivities (85–91% ee). The isopropyl-substituted ligand **95a** gave superior results for the generation of  $\beta$ -lactams fused to a six-membered ring, whereas the *tert*-butyl-substituted ligand **95c** proved to be optimum for seven-membered rings.

On the basis of the proposed mechanism of the reaction, Fu suggested that a copper enolate intermediate could be intercepted with an electrophile to form an additional carbon–carbon bond and a quaternary stereocenter. The reaction of alkyne–nitrones **108** and **109** with allyl iodide **110** under modified reaction conditions using a mixture of a silyl enol ether and potassium acetate as the base in the presence of ligand **95a** and copper bromide afforded

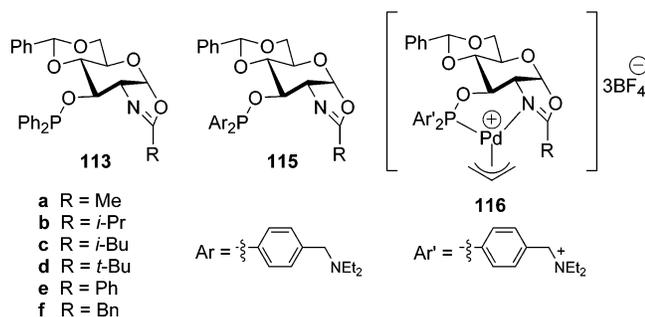
## Scheme 20

Ar = *p*-carboethoxyphenyl

the  $\alpha$ -allylated tricyclic products **111** and **112** in good yield and with high enantioselectivity (Scheme 20).<sup>52</sup>

## 2.1.4. Oxazoline–Phosphinite Ligands

In 1999 Uemura reported the use of D-glucosamine-derived chiral phosphinite–oxazoline ligands **113** in palladium-catalyzed allylic alkylation.<sup>53</sup> Of the vari-

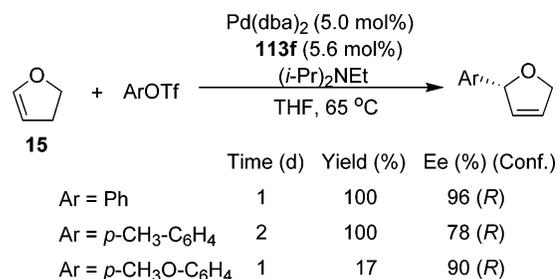


ous substrates examined, the best asymmetric induction was achieved in the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** in the presence of BSA. The optimum result [81% yield and 96% ee (*S*)] was obtained using ligand **113a**, which bears the least sterically demanding substituent at the 2-position of the oxazoline ring. Alkylation of 2-cyclohexenyl acetate **24** [88% yield, 74% ee (*R*) with **113a**] and 4-acetoxy-2-pentene **53** (69% yield and 57% ee with **113a**) with **26** proceeded with lower levels of enantioselection. Using ligand **113d**, high enantioselectivity [90% ee (*S*)] but low regioselectivity (11:89, branched/linear) was obtained in the reaction of 3-phenyl-2-propenyl acetate with **26**. High enantiodiscrimination (94 and 95% ee with ligands **113a** and **113c**) was also found in the allylic amination of a 1,3-diphenyl-2-propenyl carbonate using benzylamine as the nucleophile.

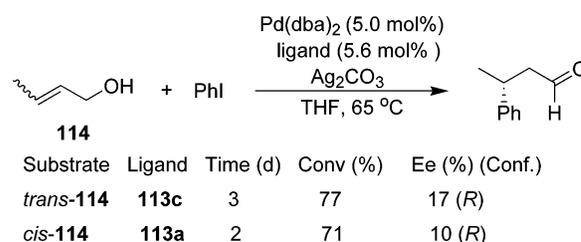
The glucosamine-derived ligands **113a–f** were also examined in the palladium-catalyzed intermolecular Heck reaction between 2,3-dihydrofuran **15** and various aryl triflates (Scheme 21). The best result (100% conversion, 96% ee) was achieved in the phenylation reaction using the benzyl-substituted ligand **113f**.<sup>54</sup>

These ligands also afforded low enantioselectivities (up to 17% ee) in the first example of an enantioselective intermolecular Heck reaction using prochiral acyclic alkenes (*trans*- and *cis*-**114**) (Scheme 22).<sup>54</sup>

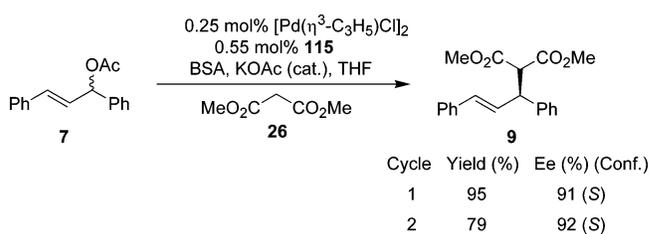
## Scheme 21



## Scheme 22



## Scheme 23

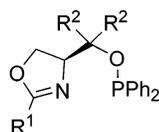


Incorporation of a quarternizable diethylaminomethyl group at the 4-position of the phenyl rings on the phosphorus atom led to the development of a novel amphiphilic chiral ligand **115**.<sup>55</sup> The palladium allyl complex **116** of this ligand is a water-soluble catalyst capable of the alkylation and amination of 1,3-diphenyl-2-propenyl acetate **7** in high yields and enantioselectivities [up to 85% yield and 83% ee (*S*) in biphasic (acetonitrile/water = 4:1 and toluene/water = 1:1) and aqueous solvents. The water-soluble nature of this palladium complex and the easy quarternization and subsequent neutralization of the diethylaminomethyl groups facilitated catalyst recycling in both organic (THF) (Scheme 23) and biphasic (acetonitrile/water) solvents with little loss in reactivity and enantioselectivity.

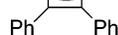
The groups of Richards and Pfaltz have independently reported the synthesis of a new class of modular phosphinite–oxazoline ligands of type **117**.<sup>56,57</sup> These ligands are similar in structure to the JM-Phos ligands **43** and **44** developed by Burgess with the phosphinite moiety being attached to the 4-position of the oxazoline ring.

In the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**, Richards found that the ferrocenyl- and phenyl-substituted ligands **117a** and **117b** afforded the highest enantioselection [90% ee (*S*) with both ligands at 20 °C and 96% ee (*S*) at 0 °C with **117a**]. The reaction of a 1-methyl-2-butenyl carbonate afforded lower enantioselectivities with ligand **117c**, giving the best result of 70% ee (*S*).<sup>56</sup>

Using cationic iridium complexes ([Ir(cod)**117**]-[BARF]) of ligands **117**, Pfaltz achieved high enan-



117

a R<sup>1</sup> = ferrocenyl, R<sup>2</sup> = Hb R<sup>1</sup> = phenyl, R<sup>2</sup> = Hc R<sup>1</sup> = R<sup>2</sup> = Hd R<sup>1</sup> = ferrocenyl, R<sup>2</sup> = *i*-Pre R<sup>1</sup> = ferrocenyl, R<sup>2</sup> = *i*-Buf R<sup>1</sup> = ferrocenyl, R<sup>2</sup> = Bng R<sup>1</sup> = 3,5-*t*-Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R<sup>2</sup> = *i*-Buh R<sup>1</sup> = 3,5-*t*-Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R<sup>2</sup> = Bn

tiaselectivities (85–96% ee) for the hydrogenation of monoaryl-substituted alkenes **118**–**121**, which had proved to be difficult substrates for enantioselective hydrogenation with the phosphinooxazoline ligands **1** (42–84% ee) (Table 16). Of the ligands tested, the ferrocenyl- and 3,5-bis(*tert*-butyl)-phenyl-substituted

**Table 16. Enantioselective Iridium-Catalyzed Hydrogenation Using Ligands 117 and 123<sup>a</sup>**

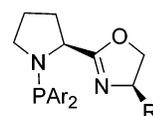
Entry	Substrate	Ligand	Cat. (mol%)	Conv. (%)	Ee (%) (Conf.)
1		117h	0.4	100	98 ( <i>R</i> )
2		123e	0.3	99	92 ( <i>R</i> )
3 <sup>b</sup>		123e	0.2	99	94 ( <i>R</i> )
4		117f	0.1	100	96 ( <i>R</i> )
5		123e	0.3	100	76 ( <i>S</i> )
6		117d	0.4	100	85 ( <i>S</i> )
7		123e	0.3	100	56 ( <i>R</i> )
8		117d	0.5	100	85 ( <i>S</i> )
9		123e	1.0	100	64 ( <i>R</i> )
10		123e	0.3	100	68 ( <i>R</i> )
11		123e	1.0	52	16
12		123e	0.3	100	94
13		117e	0.5	100	90 ( <i>R</i> )
14		123e	0.3	100	88 ( <i>S</i> )
15 <sup>c</sup>		117h	0.1	100	88 ( <i>S</i> )
16		123e	0.2	100	38 ( <i>R</i> )

<sup>a</sup> [Ir(cod)(L)][BARF] (0.1–1.0 mol %), 50 bar H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C. <sup>b</sup> 20 bar of H<sub>2</sub> at 0 °C. <sup>c</sup> 1 bar of H<sub>2</sub> used.

derivatives **117d**–**h** afforded the best results with the nature of the backbone substituents having a minor but significant influence on the stereochemical outcome. It was found that the enantioselectivity for the hydrogenation of the terminal alkene **122** depended strongly on the hydrogen pressure, with the best result of 88% ee being achieved with ligand **117h** at ambient hydrogen pressure (Table 16, entry 15).<sup>57</sup>

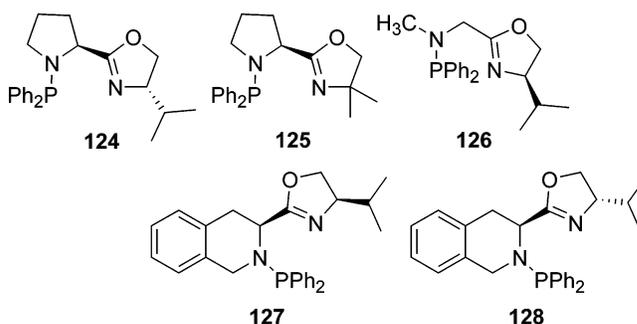
### 2.1.5. Oxazoline Ligands with Phosphorus Bonded to One *N* Atom

Chiral oxazoline ligands in which a diarylphosphino group is directly bonded to a nitrogen atom have been used successfully in asymmetric catalysis. Gilbertson has applied proline-based ligands of this type **123**–**125** in palladium-catalyzed asymmetric



123

a R = Ph, Ar = Ph

b R = *i*-Pr, Ar = Phc R = *t*-Bu, Ar = Phd R = *t*-Bu, Ar = *o*-Tole R = *t*-Bu, Ar = 2-ethylphenylf R = *t*-Bu, Ar = 2,3-dimethylphenylg R = *t*-Bu, Ar = 2,4-dimethylphenyl

allylic alkylation and amination<sup>58</sup> and in the iridium-catalyzed enantioselective hydrogenation of aromatic olefins.<sup>59</sup>

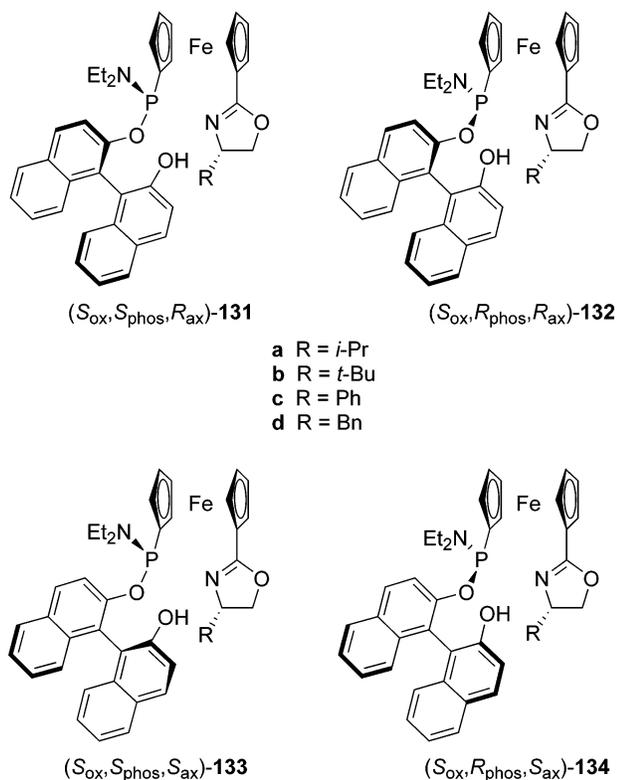
Of the ligands tested, the matched diastereomeric ligand **123b** afforded the best enantioselectivity [94% ee (*R*) in 96% yield] for the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. The strong influence of the stereogenic proline unit on asymmetric induction was demonstrated by the much lower level of enantioselection (41% ee) achieved with the structurally similar ligand **126**, which lacks the structural rigidity of the pyrrolidine ring and the proline-derived stereocenter. The isopropyl-substituted oxazoline **123b** was also the most effective ligand for the addition of the nitrogen-based nucleophiles, benzylamine and potassium phthalimide, to **7**, giving 93 and 91% ee, respectively, the latter albeit in low yield (29%). Like the majority of phosphinooxazoline ligands, significantly lower enantioselectivities (up to 48% ee) were obtained for the alkylation and amination of 4-acetoxy-2-pentene **53** and 2-cyclopentenyl acetate **23**.<sup>58</sup> Agboussou-Niedercorn has also investigated the use of ligands **123** and **124** and the similar tetrahydroisoquinoline ligands **127** and **128**

in palladium-catalyzed allylic alkylation and has observed similar trends.<sup>60</sup>

Gilbertson found that the hydrogenation of the 1-alkyl-1,2-diaryl-substituted alkenes *trans*- $\alpha$ -methyl-stilbene **12** and *p*-methoxymethylstilbene **50** proceeded with high enantioselectivities (>85% ee) using cationic iridium complexes formed from the *tert*-butyl-substituted oxazolines **123c–g** with a BARF counterion (Table 16, entries 2 and 3). Lower enantioselectivities were afforded by the catalyst derived from ligand **123e** for the hydrogenation of 1-aryl-1,2-dimethyl-substituted alkenes (up to 76% ee) (Table 16, entries 5 and 7), cyclic alkenes (up to 68% ee) (Table 16, entries 9 and 10), and the terminal olefin **122** (38% ee) (Table 16, entry 16). Using the same ligand, the tetrasubstituted alkene **130** gave both low enantioselectivity (16% ee) and low conversion (52%) (Table 16, entry 11), whereas high enantioselectivities (up to 94% ee) were afforded for the functionalized alkenes **13** and **121** (Table 16, entries 12 and 14).<sup>59</sup>

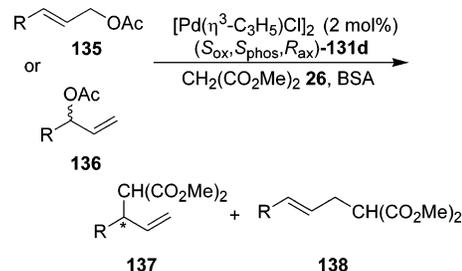
### 2.1.6. Oxazoline–Phosphoramidate Ligands

Dai and Hou have applied the diastereomeric phosphoramidate ligands **131–134** in the palladium-catalyzed allylic alkylation and amination of unsymmetrical 1- and 3-monosubstituted-2-propenyl acetates **135** and **136**, respectively.<sup>45,61</sup> These ferrocenyl-



based ligands have three stereogenic units: the stereogenic center of the oxazoline unit, the stereocenter of the BINOL moiety, and a stereogenic phosphorus atom. Of the various oxazoline-substituted diastereomers, ( $S_{ox}, S_{phos}, R_{ax}$ )-**131d** was found to be the ligand of choice for the alkylation of substrates of type **135** and **136**, affording branched products **137** with high regioselectivity (up to >99:1) and enanti-

### Scheme 24

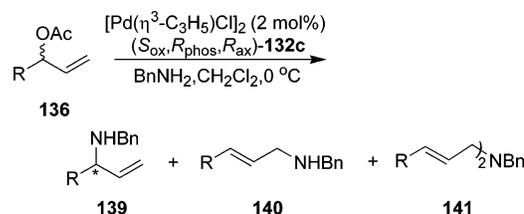


**Table 17. Palladium-Catalyzed Alkylation of Unsymmetrical Monosubstituted 2-Propenyl Acetates of Types 135 and 136 Using Ligand ( $S_{ox}, S_{phos}, R_{ax}$ )-131d (Scheme 24)<sup>a</sup>**

Entry	Substrate	Yield (%)	Regioselectivity		Ee (%)
			137:138		
1		R = H	98	95:5	95
		R = Me	91	98:2	92
		R = CN	96	90:10	95
2		98	98:2	89	
3		95	>99:1	93	
4		83	97:3	94	

<sup>a</sup> Np = 1-naphthyl.

### Scheme 25



**Table 18. Palladium-Catalyzed Amination of Unsymmetrical Monosubstituted 2-Propenyl Acetates of Type 136 Using Ligand ( $S_{ox}, R_{phos}, R_{ax}$ )-132c (Scheme 25)**

entry	substrate	yield (%)	regioselectivity		ee (%)
			139:140:141		
1	R = Ph	94	95:3:2	98	
2	R = 1-naphthyl	87	94:6:–	97	
3	R = 4-MeC <sub>6</sub> H <sub>4</sub>	89	94:6:–	95	
4	R = 2-thienyl	85	90:9:1	98	
5	R = methyl	78	>97:3:–	84	

oselectivity (89–95% ee) (Scheme 24 and Table 17). Allylic amination of substrates of type **136** with benzylamine occurred with high regio- and enantioselectivity using the diastereomeric ligands ( $S_{ox}, R_{phos}, R_{ax}$ )-**132** and ( $S_{ox}, S_{phos}, S_{ax}$ )-**133**, with the phenyl-substituted ligand ( $S_{ox}, R_{phos}, R_{ax}$ )-**132c** giving the best results (Scheme 25 and Table 18). Only moderate regioselectivity was achieved with substrates of type **135**. Surprisingly, all of the diastereomers ( $S_{ox}, S_{phos}, R_{ax}$ )-**131** and ( $S_{ox}, R_{phos}, S_{ax}$ )-**134** that gave excellent results in the alkylation reaction provided linear products **140** with high regioselectivity in the amination reaction. It was suggested that this difference in regioselectivity is a consequence of the presence

**Table 19. Enantioselective Palladium-Catalyzed Alkylation of Substrates of Type 135 with Dimethyl Malonate 26 Using Ligands 142–144, 146, and 147A<sup>a</sup>**

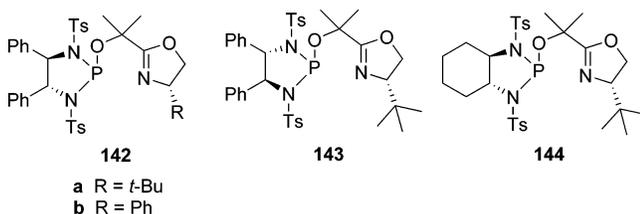
Entry	Substrate	Ligand	Conv. (%)	Regioselectivity 137:138	Ee (%) (Conf.)
1		142a	100	84:16	94 (S)
2		143	100	53:47	93 (S)
3		144	100	60:40	95 (S)
4 <sup>b</sup>		146	84 <sup>c</sup>	69:31	86 (S)
5		147a	100	26:74	87 (S)
6		142a	100	98:2	98 (S)
7		143	100	93:7	99.4 (S)
8		146	93 <sup>c</sup>	90:10	95 (S)
9		147a	100	66:34	94 (S)
10		142a	100	55:45	60 (S)
11 <sup>b</sup>		146	75 <sup>c</sup>	30:70	43 (S)
12		147a	100	38:62	23 (S)

<sup>a</sup> [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (1 mol %), ligand (2.5 mol %), **26**, BSA/KOAc, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 20 h. Np = 1-naphthyl.  
<sup>b</sup> Reaction carried out at 50 °C for 2 h. <sup>c</sup> Isolated yields.

of a free hydroxy group in these ligands. It is thought that the amine nucleophile hydrogen bonds to this hydroxy group and thus attacks the allyl substrate in an intramolecular fashion. Depending on the orientation of the hydroxy group in the ligand, this intramolecular attack may favor either linear or branched products.

### 2.1.7. Oxazoline–Phosphoramidate Ligands

In 1999 Pfaltz reported the synthesis of the phosphoramidate ligands **142–144** from chiral 1,2-diamines.<sup>62</sup> These ligands, and in particular the *tert*-butyl-substituted analogue **142a**, proved to be highly



effective for the palladium-catalyzed alkylation of monosubstituted-2-propenyl acetates of type **135** with dimethyl malonate **26** in terms of both enantioselectivity (up to 99% ee) and regioselectivity (up to 98:2 de) (Table 19). However, reactions with 1,3-diphenyl-2-propenyl acetate **7** [88% ee (*S*) with **142b**], 4-acetoxy-2-pentene **53** (20% ee with **142a**), and 2-cyclohexenyl acetate **24** [71% ee (*R*) with **142a**] gave enantioselectivities that were significantly lower than the best results reported in the literature.<sup>62</sup>

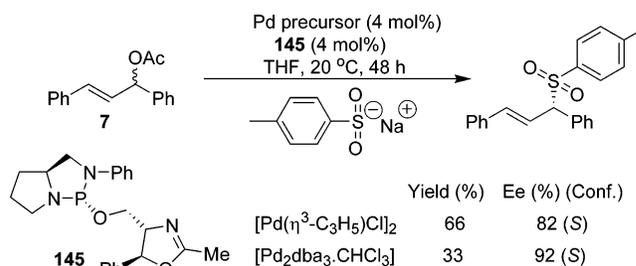
Iridium complexes of ligands **142–144** were also applied in the enantioselective hydrogenation of a range of olefins (Table 20). In contrast to allylic alkylation, ligand **143** was more effective than its diastereomer **142a**, achieving better results [87 vs 80% (*R*) ee and 49 vs 16% conversion] for the

**Table 20. Enantioselective Hydrogenation of Olefins Using [Ir(cod)(ligand)][BARF] Catalysts<sup>a</sup>**

Entry	Substrate	Ligand	Conv. (%)	Ee (%) (Conf.)
1		143	57	92 ( <i>R</i> )
2		144	19	41 ( <i>R</i> )
3		147a	98	62 ( <i>R</i> )
4		143	49	87 ( <i>R</i> )
5		144	15	94 ( <i>R</i> )
6		147a	100	75 ( <i>R</i> )
7		143	43	86 ( <i>R</i> )
8		144	32	91 ( <i>R</i> )
9	<b>121</b>	147a	100	75 ( <i>R</i> )
10		143	100	85 ( <i>R</i> )
11		144	65	84 ( <i>R</i> )
12		147a	100	76 ( <i>R</i> )
13		143	100	35 ( <i>R</i> )
14		144	55	42 ( <i>R</i> )
15		147a	100	90 ( <i>S</i> )
16		143	3	-
17		144	4	-
18		147a	52	78 ( <i>R</i> )

<sup>a</sup> 4 mol % [Ir(cod)(L)][BARF], CH<sub>2</sub>Cl<sub>2</sub>, 100 bar H<sub>2</sub>, room temperature, 2 h.

### Scheme 26



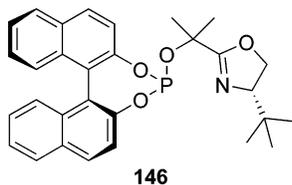
hydrogenation of (*E*)-1,2-diphenylpropene **13**. In general, ligands **143** and **144** gave lower conversions but similar enantioselectivities compared to the phosphinoxazoline ligands **1**; however, for the hydrogenation of ethyl  $\beta$ -methylcinnamate **121** and (*E*)-2-(4-methoxyphenyl)but-2-ene **118** higher enantioselectivities [up to 91 and 85% ee (*R*), respectively] were obtained.<sup>62</sup>

Bondarev and co-workers have reported the synthesis of an oxazoline-containing phosphoramidate ligand **145** with a stereogenic center at the phosphorus atom. This ligand was tested in the palladium-catalyzed asymmetric allylic sulfonylation of 1,3-diphenyl-2-propenyl acetate **7** and gave moderate conversions (up to 66% yield) and high enantioselectivities (up to 92% ee) (Scheme 26).<sup>63</sup>

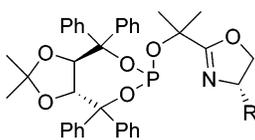
### 2.1.8. Oxazoline–Phosphite Ligands

Oxazoline ligands containing phosphite moieties have been used with some success in asymmetric catalysis. The first reported of these, the axially chiral ligand **146**, was designed by Pfaltz specifically to control enantioselectivity and regiochemistry in the allylic alkylation of 1- and 3-monosubstituted allyl substrates.<sup>64</sup>

In 1999 Pfaltz reported the preparation of the TADDOL-derived phosphite–oxazoline ligand **147a**.<sup>62</sup>



146



147

a R = *t*-Bu  
b R = (*R*)-*i*-Pr

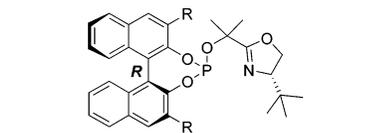
This ligand was tested in palladium-catalyzed allylic alkylation and gave comparable enantioselectivities but significantly lower regioselectivities for the reaction of 3-substituted-2-propenyl acetates with dimethyl malonate **26** compared to ligand **146** (Table 19, entries 5, 9 and 12 vs entries 4, 8, and 11). Using this ligand, alkylation of 1,3-diphenyl-2-propenyl acetate **7** [20% ee (*S*)], 4-acetoxy-2-pentene **53** (61% ee), and 2-cyclohexenyl acetate **24** (46% ee (*R*)) with **26** proceeded with complete conversion but low to moderate enantioselectivity.

The iridium complex derived from [Ir(cod)Cl]<sub>2</sub> and ligand **147a** was highly active in the enantioselective hydrogenation of various olefins, giving high conversions and moderate to good enantiodiscriminations (62–90% ee) (Table 20). The best result with this ligand was achieved in the hydrogenation of (*Z*)-2-(4-methoxyphenyl)but-2-ene **119**, giving a much improved enantioselectivity of 90% ee compared to the best result obtained by the phosphinooxazoline ligands **1** (42% ee).<sup>62</sup>

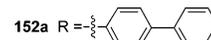
Seebach has found that the catalyst derived in situ from [Rh(cod)Cl]<sub>2</sub> and the (*R*)-isopropyl-substituted TADDOL-derived ligand **147b** was highly effective for the asymmetric hydrosilylation of a range of arylalkyl and aliphatic ketones, affording high yields (69–91%) and moderate to excellent enantioselectivities (42–95% ee).<sup>65</sup>

Pfaltz has prepared a series of ligands **149–156** by introducing substituents at the 3- and 3'-positions of the binaphthyl backbone of ligand **146** and by varying the structure of the biaryl skeleton.<sup>66</sup> Copper complexes of these ligands were tested in the conjugate addition of diethylzinc to cyclic enones of various ring sizes (Scheme 27). For the reaction with cyclohexenone **158** and cycloheptenone **159**, all of the ligands formed highly active catalysts, giving yields >95% and enantioselectivities up to 94% ee (Table 21, entries 5–12). The results show that the stereoaxis of the phosphite moiety had the most influence on the stereochemical outcome of the reaction. Only moderate yields (up to 69%) were reported for diethylzinc addition to the cyclopentenone **157** (Table 21, entries 1–4). This reaction is complicated by the tendency of the reactive enolate, resulting from the conjugate addition, to undergo a Michael reaction. Ligand **149a** gave moderate to good enantioselectivities (70–87% ee) but low conversions (up to 41%) for the 1,4-addition of a functionalized diorganozinc reagent to enones **157–159**. The 1,4-addition of diethylzinc to the acyclic substrate, *trans*-4-phenyl-3-buten-2-one, was also examined. Of the ligands tested, **152b** with a biphenyl oxazoline substituent gave by far the best result of 99% yield and 87% ee.<sup>66</sup>

Gladioli has reported the preparation of novel atropisomeric oxazoline ligands **160** consisting of an



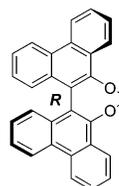
146 R = H  
149a R = Me  
150a R = Ph



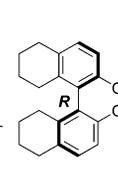
152a

151a

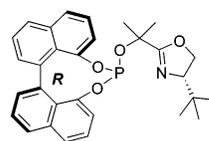
153a



154a



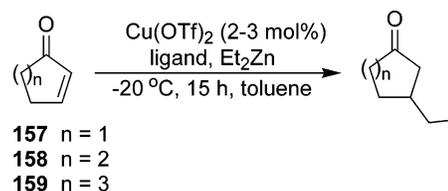
155a



156a

All ligands above are the (*aR,S*)-diastereomers; the (*aS,S*)-diastereomers **146b**, **149b–156b** were also prepared but are not shown above for the sake of clarity.

### Scheme 27

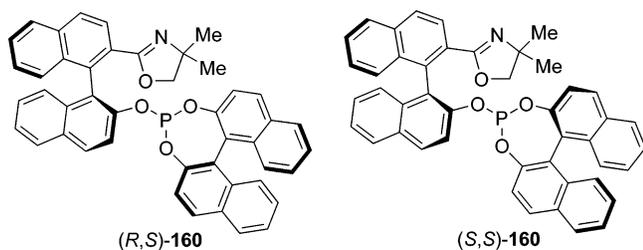


**Table 21. Asymmetric Copper-Catalyzed 1,4-Addition of Diethylzinc to Cyclic Enones **157–159** Using Ligands **149–156** (Scheme 27)<sup>a</sup>**

entry	ligand	substrate	yield (%)	ee (%) (conf)
1	<b>152a</b>	<b>157</b>	41	94 ( <i>R</i> )
2	<b>152b</b>	<b>157</b>	44	83 ( <i>S</i> )
3	<b>156a</b>	<b>157</b>	69	90 ( <i>R</i> )
4	<b>156b</b>	<b>157</b>	63	32 ( <i>S</i> )
5 <sup>b</sup>	<b>149a</b>	<b>158</b>	96	90 ( <i>R</i> )
6 <sup>b</sup>	<b>149b</b>	<b>158</b>	99	40 ( <i>S</i> )
7	<b>152a</b>	<b>158</b>	95	48 ( <i>R</i> )
8	<b>152b</b>	<b>158</b>	97	86 ( <i>S</i> )
9	<b>154a</b>	<b>159</b>	99	14 (–)
10	<b>154b</b>	<b>159</b>	97	94 (+)
11	<b>156a</b>	<b>159</b>	92	81 (–)
12	<b>156b</b>	<b>159</b>	96	12 (–)

<sup>a</sup> Ligands **149a–156a** have (*aR,S*)-configuration and ligands **149b–156b** have (*aS,S*)-configuration. <sup>b</sup> Reaction stopped after 3 h.

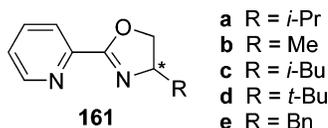
axially chiral phosphite moiety linked to a binaphthalene fragment bearing an achiral *gem*-dimethyl oxazoline ring.<sup>67</sup> Rhodium complexes of the (*R,S*)- and (*S,S*)-diastereomers of this ligand were tested in the hydroformylation and hydroboration of styrene and in the hydrogenation of methyl acetamidoacrylate, but in all cases only very low enantioselectivities were obtained. The ligands (*R,S*)- and (*S,S*)-**160** were also tested in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. Although complete conversions were at-



tained, the enantioselectivities achieved were moderate at best (up to 43% ee).

## 2.2. Mono(oxazoline) *N,N*-Ligands

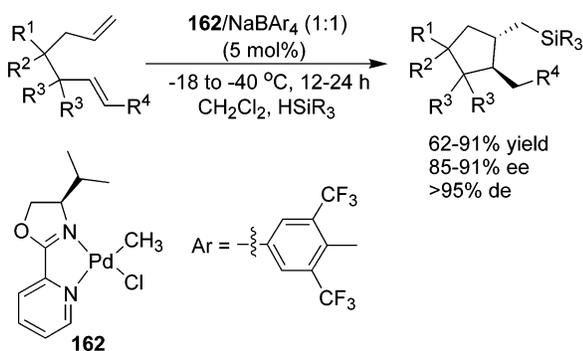
The best-known mono(oxazoline) ligands with two coordinating nitrogen donor atoms are the pyridinyl-oxazoline ligands **161**. Since being first applied in



asymmetric catalysis in 1986<sup>4</sup> and subsequently with some success in rhodium(I)-catalyzed hydrosilylation,<sup>68</sup> these ligands and their many structural derivatives have been used successfully in a range of asymmetric reactions. In this section, only those applications reported since 1998 are discussed in detail.

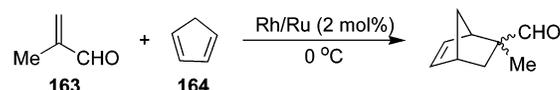
Widenhofer has reported the first examples of the asymmetric formation of functionalized carbocycles by the cyclization/hydrosilylation of functionalized 1,6-dienes using palladium complexes of the pyridinyl-oxazoline ligands (*R*)-**161a–d** (Scheme 28).<sup>69,70</sup>

### Scheme 28



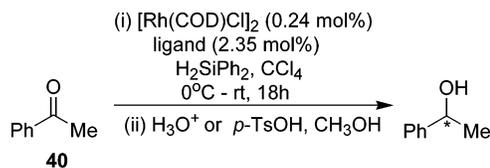
It was found that the palladium complex **162** of the isopropyl-substituted ligand (*R*)-**161a** was the optimum catalyst, affording high yields (62–91%), enantioselectivity (>85% ee) and diastereoselectivity [>95% de (*trans*)] for the reaction of a wide range of substrates (diesters, protected diols, monoesters, and dienes with terminal and olefinic substituents) with various trialkylsilanes.<sup>69</sup> The use of benzhydryldimethylsilane (HSiMe<sub>2</sub>CHPh<sub>2</sub>) as the silane source allowed the oxidation of the resulting silylated carbocycles to the corresponding alcohols in good yields (81–100%), maintaining high levels of diastereoselectivity (≥50:1) and enantioselectivity (86–95% ee).<sup>70</sup>

### Scheme 29



Catalyst	Time (h)	Yield (%)	exo:endo	Ee (%)
[( $\eta$ -C <sub>5</sub> Me <sub>5</sub> )Rh(( <i>S</i> )- <b>161a</b> )] [SbF <sub>6</sub> ] <sub>2</sub>	72	81	95:5	68
[(mesitylene)Ru(( <i>S</i> )- <b>161d</b> )] [SbF <sub>6</sub> ] <sub>2</sub>	5	94	96:4	83

### Scheme 30

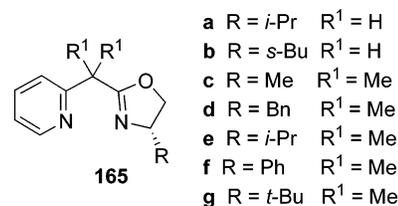


Chiral half-sandwich rhodium and ruthenium complexes of pyridinyl-oxazoline ligands **161** have been tested in the asymmetric Diels–Alder reaction.<sup>71</sup> A dicationic rhodium complex ([( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)Rh((*S*)-**161a**)] [SbF<sub>6</sub>]<sub>2</sub>) (2 mol %) gave good *exo/endo* (95:5) selectivity and moderate enantioselectivity (68% ee) in good yield (81%) at a temperature of 0 °C for the reaction of methacrolein **163** with cyclopentadiene **164** (Scheme 29).

Davies also found that the mesitylene ruthenium complexes ([mesitylene)RuCl((*S*)-**161**)] [SbF<sub>6</sub>]) exist as a single diastereomer in dichloromethane and that their corresponding dicationic catalyze Diels–Alder reactions with high *exo/endo*- and enantioselectivity.<sup>72</sup> The ruthenium catalyst derived from the *tert*-butyl-substituted ligand (*S*)-**161d** gave the best result (94% yield, 83% ee, and *exo/endo* 96:4) for the reaction of **163** and **164** (Scheme 29). Of the other dienes and dienophiles tested, the reaction between isoprene and **163** furnished both the highest enantioselectivity (90% ee) and *exo/endo* ratio (>98% 1,4) using the ruthenium catalyst derived from (*S*)-**161a**.<sup>72a</sup>

A number of pyridinyl-oxazoline ligands of modified structure have been tested in the rhodium(I)-catalyzed asymmetric hydrosilylation of acetophenone **40** (Scheme 30).

Ligands **165a** and **165b**, with a methylene group linking the oxazoline and pyridine rings, were investigated to examine the influence of a six-membered chelate to rhodium.<sup>73</sup> The catalytic system of [Rh(COD)Cl]<sub>2</sub> (0.5 mol %), the isopropyl-substituted ligand **165a** and CCl<sub>4</sub> (which significantly increases



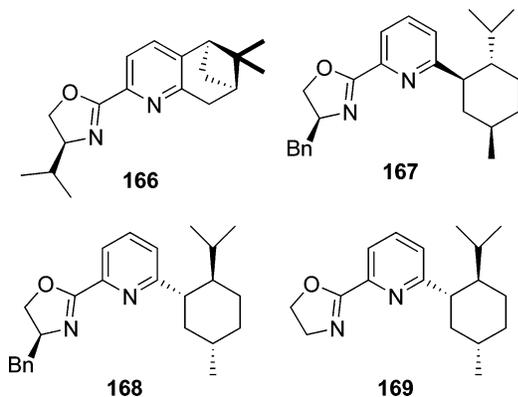
enantioselectivity) gave the best enantiodiscrimination of 42% ee (Table 22, entry 1). This modest enantioselectivity was thought to be a consequence of a boat conformation of the chelate ring, which orients the stereogenic substituent away from the metal center as was evident in the X-ray crystal structure of the rhodium complex.

**Table 22. Rhodium(I)-Catalyzed Hydrosilylation of Acetophenone **40** Using Ligands **165**–**172** (Scheme 30)**

entry	ligand	yield (%)	ee (%) (conf)
1 <sup>a</sup>	<b>165a</b>	70	42 ( <i>R</i> )
2	<b>166</b>	90	80 ( <i>S</i> )
3	( <i>S</i> )- <b>161a</b>	87	63 ( <i>R</i> )
4	<b>167</b>	58	rac
5	<b>168</b>	54	1 ( <i>R</i> )
6	<b>169</b>	81	9 ( <i>R</i> )
7	( <i>S</i> )- <b>161e</b>	96	63 ( <i>R</i> )
8	<b>171b</b>	91	67 ( <i>R</i> )
9	<b>171c</b>	94	74 ( <i>R</i> )
10	<b>171e</b>	94	68 ( <i>R</i> )
11 <sup>b</sup>	<b>171e</b>	65	10 ( <i>R</i> )
12 <sup>c</sup>	<b>172e</b>	93	64 ( <i>R</i> )
13 <sup>c</sup>	<b>172c</b>	90	71 ( <i>R</i> )
14 <sup>c,d</sup>	<b>172c</b>	83	75 ( <i>R</i> )

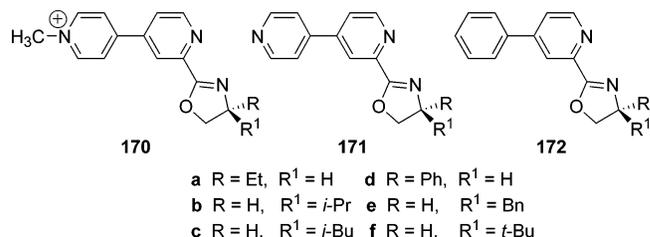
<sup>a</sup> Ligand (5 mol %), reaction time = 48 h. <sup>b</sup> No CCl<sub>4</sub> added, reaction time = 90 h. <sup>c</sup> CCl<sub>4</sub> added with H<sub>2</sub>SiPh<sub>2</sub>. <sup>d</sup> [Rh(COD)-**172c**]PF<sub>6</sub> used with 1.9 mol % **172c**, reaction time = 42 h.

Brunner reported the preparation of ligands **166**–**169** in which two different optically active substituents were incorporated at the 2- and 6-positions of the pyridine ring.<sup>74</sup> In the rhodium-catalyzed hy-



drosilylation of acetophenone **40** with diphenylsilane, the pinane-derived ligand **166** gave higher enantioselectivities (80% vs 63% ee) but opposite product configuration compared to the 2-(2-pyridinyl)oxazoline ligand (*S*)-**161a** (Table 22, entries 2 vs 3). This inversion of configuration has been previously reported when 2-(2-pyridinyl)oxazolines, unsubstituted on the pyridine ring, were replaced by the corresponding picoline- or quinoline-oxazolines containing substituents in the 5- and/or 6-position of the pyridine ring.<sup>68b,75</sup> The menthyl-substituted ligands **167**–**169** gave very low levels of enantioselection compared to the corresponding pyridinyl-oxazoline ligand (*S*)-**161e** (Table 22, entries 4–6 vs 7), which may be a result of the inability of these ligands to coordinate to rhodium due to the extra bulk.<sup>74</sup>

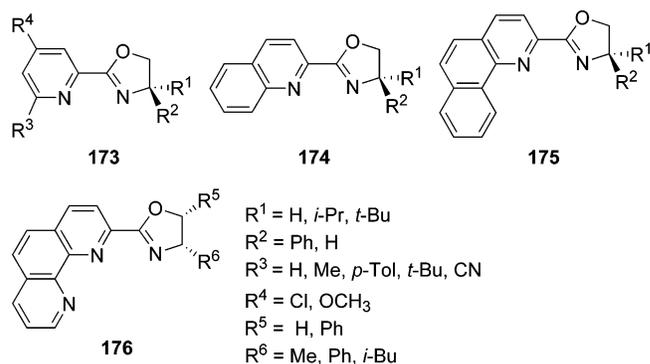
Brunner has also reported the synthesis of *N*-methylated 2-(4,4'-bipyridinyl-2-yl)oxazoline ligands **170** with potential charge-transfer properties for the possible preorientation of a metal-bound prochiral ketone, which may result in higher enantiodiscrimination.<sup>76</sup> It was found that although these ligands give higher enantioselectivities than the corresponding nonmethylated analogues **171** (e.g., 44% ee with **170c** vs 7% ee with **171c**) under the same conditions for the rhodium(I)-catalyzed hydrosilylation of the



electron-rich 2,5-dimethoxyacetophenone with diphenylsilane, other results indicate that the desired charge-transfer interactions, if present at all, had little influence on the stereochemical outcome.

In the rhodium(I)-catalyzed hydrosilylation of acetophenone **40**, ligands **171** showed, with one exception, comparable enantioselection (32–74% ee) with respect to the corresponding pyridinyl-oxazoline ligands of type **161** (Table 22, entries 8 and 10 vs 3 and 7, respectively). Significantly higher enantioselectivities were obtained when the reactions were carried out in the presence of carbon tetrachloride (“CCl<sub>4</sub> effect”) than in the solvent-free reaction, with the highest increase of 58% being obtained with ligand **171e** (Table 22, entries 10 vs 11). The time of addition of CCl<sub>4</sub> proved to be vital for the attainment of good asymmetric induction using ligands **172**. Good enantioselectivities (71 and 64% ee with **172c** and **172e**, respectively) (Table 22, entries 12 and 13) were obtained when CCl<sub>4</sub> was added after in situ catalyst formation, whereas the catalyst was rendered inactive if CCl<sub>4</sub> was added prior to catalyst formation. An optimum enantioselectivity of 75% ee was achieved when the preformed complex [Rh(COD)-**172c**]PF<sub>6</sub> was used with a 4-fold amount of free ligand (Table 22, entry 14).<sup>77</sup>

By using a wide range of ligands **173**–**175**, Chelucci investigated the steric and electronic effects of pyridinyl-oxazoline ligands in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>78,79</sup> An

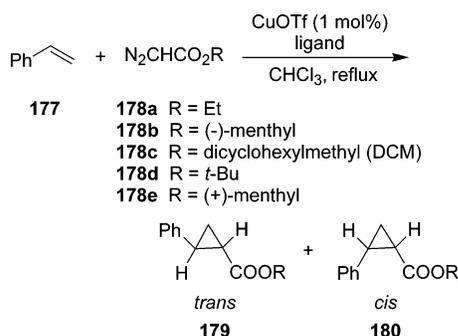


examination of the steric effects of these ligands revealed that the enantioselectivity of the reaction increased with increasing size of the oxazoline substituent and with the introduction of a methyl group or a fused benzene ring at the 6-position of the pyridine. Ligands **173** (R<sup>1</sup> = *t*-Bu, R<sup>3</sup> = Me, and R<sup>2</sup>, R<sup>4</sup> = H) and **174** (R<sup>1</sup> = *t*-Bu and R<sup>2</sup> = H) afforded the best results of 92% yield and 91% ee (*S*) and 93% yield and 92% ee (*S*), respectively.<sup>78</sup> The catalytic activity of this reaction was highly dependent on the

**Table 23. Asymmetric Copper(I)-Catalyzed Cyclopropanation of Styrene **177** with Diazoacetates **178a–d** Using Ligands **173**, **176**, **181**, **165**, and **191** (Scheme 31)**

entry	diazoacetate	ligand	yield (%)	<i>trans/cis</i> <b>179/180</b>	ee (%) <i>trans</i>	ee (%) <i>cis</i>
1 <sup>a</sup>	<b>178a</b>	<b>173</b> (R <sup>1</sup> , R <sup>3</sup> = <i>t</i> -Bu R <sup>2</sup> , R <sup>4</sup> = H)	89	62:38	60 (1 <i>S</i> ,2 <i>S</i> )	51 (1 <i>R</i> ,2 <i>S</i> )
2 <sup>a</sup>	<b>178a</b>	<b>176</b> (R <sup>5</sup> = Ph, R <sup>6</sup> = Me)	77	58:42	2 (1 <i>R</i> ,2 <i>R</i> )	41 (1 <i>R</i> ,2 <i>S</i> )
3	<b>178a</b>	<b>181g</b>	65	68:32	54 (1 <i>R</i> ,2 <i>R</i> )	54 (1 <i>R</i> ,2 <i>S</i> )
4	<b>178b</b>	<b>181g</b>	86	74:26	69 (1 <i>R</i> ,2 <i>R</i> )	83 (1 <i>R</i> ,2 <i>S</i> )
5	<b>178a</b>	<b>181e</b>	77	65:35	45	26
6 <sup>b</sup>	<b>178a</b>	<b>165g</b>	66	65:35	16	4
7 <sup>c</sup>	<b>178a</b>	( <i>a,S,S</i> )- <b>191c</b>	60	60:40	66 (1 <i>R</i> ,2 <i>R</i> )	62 (1 <i>S</i> ,2 <i>R</i> )
8 <sup>c</sup>	<b>178a</b>	( <i>a,S,R</i> )- <b>191c</b>	66	61:39	45 (1 <i>R</i> ,2 <i>R</i> )	18 (1 <i>S</i> ,2 <i>R</i> )
9 <sup>c</sup>	<b>178c</b>	( <i>a,S,S</i> )- <b>191c</b>	82	79:21	74 (1 <i>R</i> ,2 <i>R</i> )	82 (1 <i>S</i> ,2 <i>R</i> )
10 <sup>c</sup>	<b>178b</b>	( <i>a,S,S</i> )- <b>191c</b>	96	75:25	83 (1 <i>R</i> ,2 <i>R</i> )	87 (1 <i>S</i> ,2 <i>R</i> )
11 <sup>c</sup>	<b>178e</b>	( <i>a,S,S</i> )- <b>191c</b>	81	81:19	78 (1 <i>S</i> ,2 <i>S</i> )	70 (1 <i>R</i> ,2 <i>S</i> )

<sup>a</sup> Reaction carried out at 25 °C in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> CH<sub>2</sub>Cl<sub>2</sub> was used. <sup>c</sup> 3 mol % CuOTf used, reaction time = 10 h.

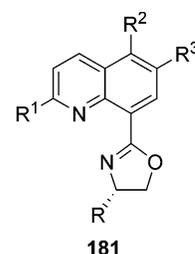
**Scheme 31**

electronic properties of the ligands. Pyridinyl-oxazoline ligands of type **173** with an electron-donating methoxy group at the 4-position of the pyridine increased the reaction rate, and those with an electron-withdrawing chloro group dramatically decreased the rate of the reaction with little change in the enantioselectivity compared to ligands with unsubstituted pyridine rings.<sup>79</sup> Ligand **173** (R<sup>3</sup> = CN and R<sup>4</sup> = H) with an electron-withdrawing cyano group at the 6-position of the pyridine ring gave a high enantioselectivity [94% ee (*S*) with R<sup>1</sup> = *t*-Bu and R<sup>2</sup> = H] but at a much reduced reaction rate (77% yield after 168 h at room temperature).<sup>80</sup>

Chelucci and Gladiali also screened ligands **173–175** in the asymmetric Cu(I)-catalyzed cyclopropanation of styrene **177** with ethyl diazoacetate **178a** (Scheme 31).<sup>81</sup> In general, the enantioselectivity seemed to increase with the increasing steric bulk of the substituents on the oxazoline ring and at the 6-position of the pyridine. Electron-withdrawing substituents had little effect, but the enantiodiscrimination was significantly enhanced with the presence of an electron-donating methoxy group at the 4-position of the pyridine ring. Moderate enantioselectivities were attained in general, with ligand **173** (R<sup>1</sup>, R<sup>3</sup> = *t*-Bu and R<sup>2</sup>, R<sup>4</sup> = H) giving the best results [*trans/cis* ratio = 62:38, 60% ee (*trans*) and 51% ee (*cis*)] (Table 23, entry 1). The potentially tridentate oxazolinylphenanthroline ligands **176** were poor inducers of asymmetry (up to 41% ee, <9% ee in most cases) (Table 23, entry 2), and it was suggested that the oxazoline nitrogen donor is not involved in the coordination at the metal center.

Several derivatives of the 8-quinolinyl-oxazoline class of ligands **181** were prepared by Zhou and co-

workers. These ligands were tested in the asymmetric copper(I)-catalyzed cyclopropanation of styrene **177** with diazoacetates **178a–d**.<sup>82</sup> In the reaction

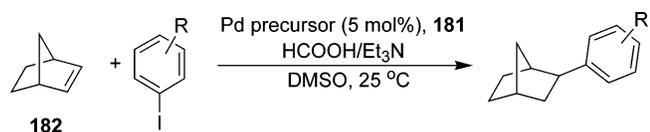


- |   |   |
|---|---|
| <b>a</b> R = Me, R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = H               | <b>h</b> R = Ph, R <sup>1</sup> = Me, R <sup>2</sup> , R <sup>3</sup> = H                     |
| <b>b</b> R = Bn, R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = H               | <b>i</b> R = <i>t</i> -Bu, R <sup>1</sup> = Me, R <sup>2</sup> , R <sup>3</sup> = H           |
| <b>c</b> R = <i>i</i> -Pr, R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = H     | <b>j</b> R = Bn, R <sup>1</sup> = <i>n</i> -Bu, R <sup>2</sup> , R <sup>3</sup> = H           |
| <b>d</b> R = Ph, R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = H               | <b>k</b> R = <i>t</i> -Bu, R <sup>1</sup> = <i>i</i> -Bu, R <sup>2</sup> , R <sup>3</sup> = H |
| <b>e</b> R = <i>t</i> -Bu, R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup> = H     | <b>l</b> R = Bn, R <sup>1</sup> = <i>i</i> -Bu, R <sup>2</sup> , R <sup>3</sup> = H           |
| <b>f</b> R = Bn, R <sup>1</sup> = Me, R <sup>2</sup> , R <sup>3</sup> = H           | <b>m</b> R = Bn, R <sup>1</sup> = H, R <sup>2</sup> , R <sup>3</sup> = OMe                    |
| <b>g</b> R = <i>i</i> -Pr, R <sup>1</sup> = Me, R <sup>2</sup> , R <sup>3</sup> = H | <b>n</b> R = Bn, R <sup>1</sup> , R <sup>2</sup> = H, R <sup>3</sup> = NO <sub>2</sub>        |

with ethyl diazoacetate **178a**, the 2-methyl-substituted ligands performed better than their unsubstituted analogues, with ligand **181g** affording the optimum result (54% ee for both *cis* and *trans* isomers) (Table 23, entry 3). A double-asymmetric induction effect was evident in the reaction with (–)-menthyl diazoacetate **178b**, with the enantioselectivity increasing to 83% ee for the *cis*-isomer (Table 23, entry 4). A comparison of the results achieved with ligands **181** with the high yields and low enantiodiscrimination afforded by the pyridinyl ligands **165c–g** suggested that conjugation between the heteroaryl ring and oxazoline unit is necessary for good enantiocontrol with these ligand types (Table 23, entry 5 vs 6).<sup>83</sup>

Quinolinyl-oxazoline ligands **181b** and **181c** with a medium-sized oxazoline substituent proved to be effective ligands for the palladium-catalyzed asymmetric hydroarylation of norbornene **182** with phenyl iodide, yielding the *exo*-product exclusively in 73 and 74% ee respectively (Scheme 32).<sup>84</sup> It was found that the nature of the hydroarylation reagent had a significant influence on this reaction. The common arylating agents phenyl bromide and phenyl triflate were inactive, and whereas phenyl iodide analogues with an electron-donating substituent increased the enantioselectivity, those with electron-withdrawing

## Scheme 32



	R	Yield (%)	Ee (%) (Conf.)
Pd(dba) <sub>2</sub> /181b	H	40	73 (1 <i>R</i> ,2 <i>R</i> )
Pd(dba) <sub>2</sub> /181c	H	54	74 (1 <i>R</i> ,2 <i>R</i> )
Pd(OAc) <sub>2</sub> /181b	H	52	67 (1 <i>R</i> ,2 <i>R</i> )
Pd(OAc) <sub>2</sub> /181b	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	59	75 (1 <i>R</i> ,2 <i>R</i> )
Pd(OAc) <sub>2</sub> /181b	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	29	53 (1 <i>R</i> ,2 <i>R</i> )

**Table 24. Palladium-Catalyzed Alkylation of 1,3-Diphenyl-2-propenyl Acetate 7 with Dimethyl Malonate 26 Using Ligands 181 and 184<sup>a</sup>**

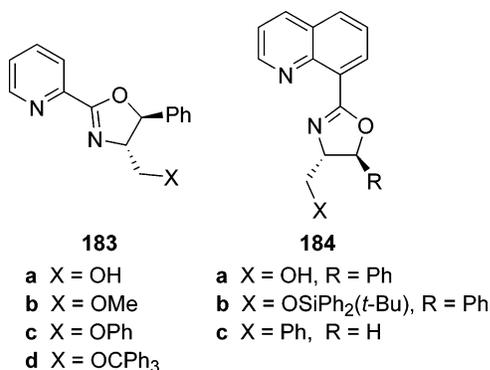
entry	ligand	time (h)	yield (%)	ee (%) (conf)
1	181g	60	86	76 ( <i>R</i> )
2	181c	0.5	96	42 ( <i>S</i> )
3	181i	50	79	78 ( <i>R</i> )
4	181e	2	94	77 ( <i>S</i> )
5 <sup>b</sup>	184c	3	98	69 ( <i>R</i> )

<sup>a</sup> [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (2.5 mol %), 10 mol % ligand, BSA, KOAc (cat.), CH<sub>2</sub>Cl<sub>2</sub>, room temperature. <sup>b</sup> [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (1 mol %), 2.5 mol % ligand.

groups substantially decreased both the enantiodiscrimination and yield.

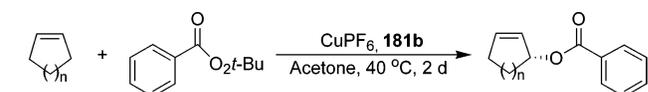
The 2-alkyl-substituted quinolinyl-oxazoline ligands 181f–i were less active but gave slightly higher enantioselectivities (53–78% ee vs 42–77% ee) than their unsubstituted analogues 181b–e in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate 7 with dimethyl malonate 26 (Table 24, entries 1 and 3 vs 2 and 4).<sup>85</sup> An interesting reversal of enantioselectivity was observed on introduction of an alkyl group at the 2-position of the quinoline ring and was explained by the relative steric interactions between the ligand substituents and a product-like allyl in a late transition state.

Pyridinyl and quinolinyl ligands 183 and 184 with functionalized oxazoline substituents were investigated in the reaction of dimethyl malonate with a range of allylic substrates.<sup>86</sup> In all cases the catalysts



derived from the quinolinyl ligands 184 were more active than their pyridinyl analogues 183, and of the substrates tested, the reaction with 1,3-diphenyl-2-propenyl acetate 7 proceeded with the highest enantioselectivity (up to 69% ee with 184c) (Table 24, entry 5). The reactions with the unsymmetrical substrate (*E*)-3-acetoxy-1-phenyl-1-propene were re-

## Scheme 33

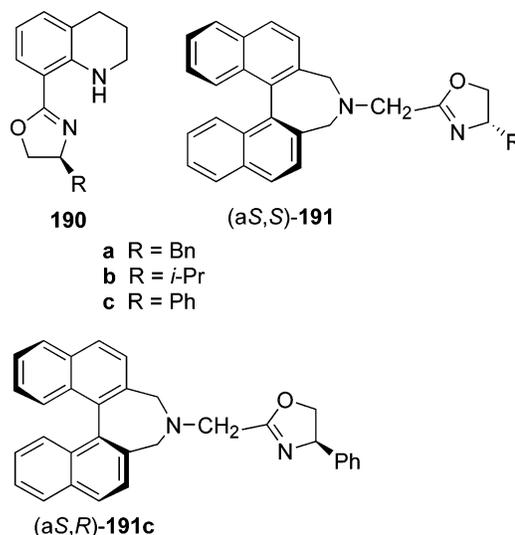


	Yield (%)	Ee (%) (Conf.)
185 n = 1	55	6 ( <i>S</i> )
186 n = 2	49	43 ( <i>S</i> )
187 n = 3	37	48 ( <i>S</i> )
188 n = 4	trace	-

gioselective for the achiral linear product (9:1 linear/branched, in all cases), whereas those with 2-cyclohexenyl acetate 24 occurred with low catalytic activity and low enantioselectivity (up to 12% ee with 183c). Moderate enantioselectivities (up to 31% ee with ligand 184a) and low reactivities were also obtained for the amination of 1,3-diphenyl-2-propenyl acetate 7 with benzylamine.<sup>86</sup>

Ligands 181a–e were also tested in the copper(I)-catalyzed asymmetric allylic oxidation of cyclic olefins 185–188 with *tert*-butylperbenzoate 189 (Kharasch–Sosnovsky reaction).<sup>87</sup> The best results were attained in the oxidation of cyclohexene 186 and cycloheptene 187, with the ligand of choice, 181b, furnishing moderate enantioselectivities and yields after 2 days at 40 °C (Scheme 33).

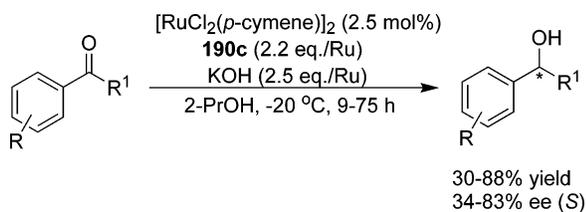
In 2002 Zhou reported the synthesis of the chiral 1,2,3,4-tetrahydroquinolinyl-oxazoline ligands 190 and their application in ruthenium-catalyzed asymmetric transfer hydrogenation.<sup>88</sup> Under optimized



reaction conditions, the catalyst formed from [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> and the phenyl-substituted ligand 190c achieved moderate to good enantioselectivities (34–83% ee) in moderate yields (30–88%) for the reduction of a range of aromatic ketones (Scheme 34). The importance of the NH group in this ligand, which is thought to play an important role in the mechanism of transfer hydrogenation,<sup>89</sup> was demonstrated by the poor enantioselectivity for the reduction of acetophenone 40 afforded by the analogous quinolinyl-oxazoline ligand 181d, which lacks an NH moiety (25% ee at 25 °C vs 73% ee with 190c).

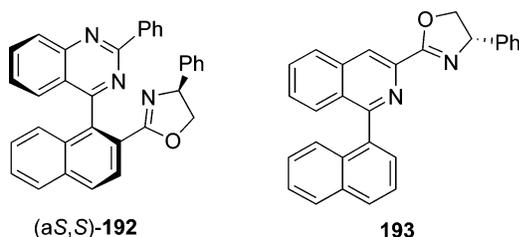
Zhou and co-workers have also used the chiral dihydrodinaphthazepinyl-oxazoline ligands 191,

## Scheme 34



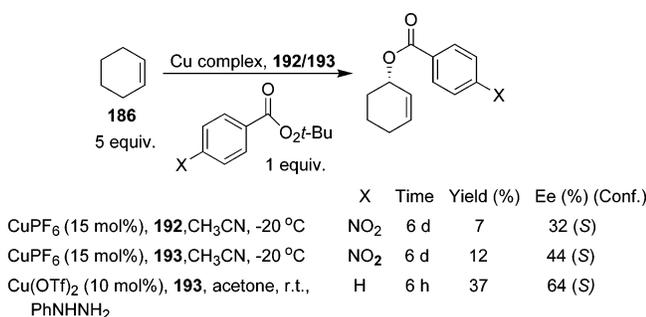
which contain both an  $sp^2$  and an  $sp^3$  coordinating nitrogen atom, in the copper(I)-catalyzed asymmetric cyclopropanation of styrene **177** with diazoacetates **178a–c** and **178e**.<sup>90</sup> Of the ligands tested, the matched diastereomeric compound (a*S,S*)-**191c** afforded the best enantiodiscrimination [62% ee (*cis*) and 66% ee (*trans*)] for the reaction with ethyl diazoacetate **178a**. The sense of asymmetric induction was thought to be controlled mainly by the stereoaxis of the binaphthyl unit because the diastereomeric ligands (a*S,S*)- and (a*S,R*)-**191c** gave the same enantiomeric products (Table 23, entries 7 and 8). A much improved enantioselectivity [82% ee (*cis*) and 74% ee (*trans*)] was obtained for the reaction with the bulky dicyclohexylmethyl diazoacetate (DCM) **178c** (Table 23, entry 9), whereas a double-asymmetric induction effect from the catalyst and the substrate was evident using (–)-menthyl diazoacetate **178b** (Table 23, entries 10 and 11). Good enantioselectivities were also obtained for the reaction of a number of styrene derivatives with (–)-menthyl diazoacetate.

Andrus has prepared novel stereoaxis-containing oxazoline *N,N*-ligands **192** and **193** with a 4-(1-naphthyl)-2-phenylquinazoline and a 1-naphthylisoquinoline skeleton, respectively. These ligands were



investigated in the copper-catalyzed allylic oxidation of cyclohexene **186** (Scheme 35).<sup>91</sup> The oxazolinyliso-

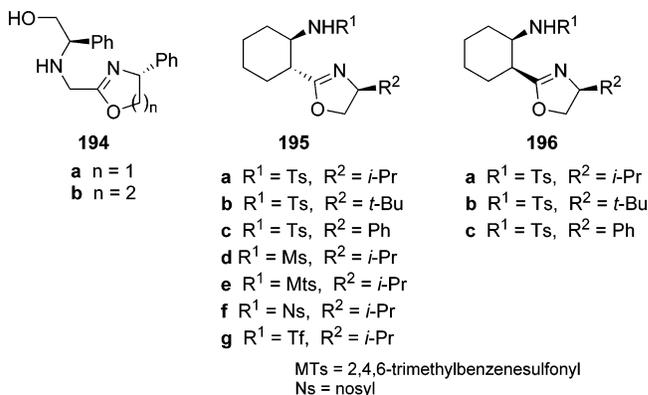
## Scheme 35



quinoline ligand **193** was used as the diastereomeric mixture as it was found to exist as inseparable rapidly interconverting atropisomers. Using the catalytic system of copper(I) hexafluorophosphate with

*tert*-butyl *p*-nitroperbenzoate as the oxidant, low yields (7 and 12%) and low enantiomeric excesses of 32 and 44% ee were obtained for ligands **192** and **193**, respectively. Much improved reactivities and enantioselectivities (37% yield and 64% ee) were achieved with ligand **193** by employing copper(II) triflate, *tert*-butyl perbenzoate, and the reducing additive phenylhydrazine.

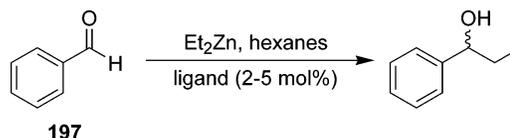
Zhang has used mono(oxazoline) *N,N*-ligands of type **194** in the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones.<sup>92</sup> The catalyst derived from [RuCl<sub>2</sub>(C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>] and ligand **194b** was the



most effective, giving good conversions (70–99%) and poor to good enantioselectivities (8–79% ee) for the reduction of a range of arylalkyl ketones and pinacolone. It was shown that *ortho*-substituted acetophenones facilitated a significantly higher level of enantioselectivity than their *para*-substituted analogues.

Wipf has prepared a range of chiral cyclohexane-based amino oxazoline ligands **195** and **196** with different oxazoline substituents and sulfonyl nitrogen groups. These ligands were screened for asymmetric induction in the addition of diethylzinc to benzaldehyde **197** (Scheme 36).<sup>93</sup>

## Scheme 36



The best result of 91% yield and 86% ee was achieved with ligand **195d** at a catalyst loading of 2 mol % (Table 25, entry 1). The absence of a nonlinear

**Table 25. Asymmetric Diethylzinc Addition to Aldehydes Using Ligand 195d<sup>a</sup>**

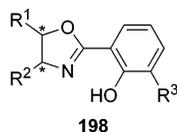
entry	substrate	time (h)	yield (%)	ee (%) (conf.)
1	PhCHO	22	91	86 ( <i>R</i> )
2	( <i>p</i> -Cl)PhCHO	52	79	72 ( <i>R</i> )
3	( <i>p</i> -MeO)PhCHO	43	81	80 ( <i>R</i> )
4	( <i>E</i> )-PhHC=CHCHO	45	47	41 ( <i>R</i> )
5	BnO(CH <sub>2</sub> ) <sub>2</sub> C≡CCHO	21	91	11 ( <i>R</i> )
6	PhCH <sub>2</sub> CH <sub>2</sub> CHO	23	97	83 ( <i>R</i> )
7	<i>c</i> -C <sub>6</sub> H <sub>11</sub> CHO	25	68	>98 ( <i>R</i> )
8	<i>n</i> -C <sub>7</sub> H <sub>15</sub> CHO	23	95	92 ( <i>R</i> )
9	( <i>S</i> )-citronellal	26	80	91 ( <i>R</i> )
10	( <i>R</i> )-citronellal	28	80	94 ( <i>R</i> )

<sup>a</sup> 2 mol % ligand, 0 °C.

effect with this ligand indicated that dimeric zinc complex formation does not occur. As a consequence, a high level of asymmetric induction (85–88% ee) was maintained over a 50-fold ligand loading range from 5 to 0.1 mol %.<sup>94</sup> Using this optimum ligand, it was found that substitution at the phenyl ring of aromatic aldehydes led to decreased reaction rates and enantioselectivities (Table 25, entries 2 and 3) but that diethylzinc addition to the aliphatic aldehydes hydrocinnamaldehyde, cyclohexanecarboxaldehyde, and octanal proceeded with high levels of enantioinduction (83–>98% ee) (Table 25, entries 6–8). The high diastereoselectivities (91 and 94% de) obtained with enantiomeric (*S*)- and (*R*)-citronellal demonstrated predominant reagent control over substrate diastereoselectivity in the addition process (Table 25, entries 9 and 10).<sup>93</sup>

### 2.3. Mono(oxazoline) *N,O*-Ligands

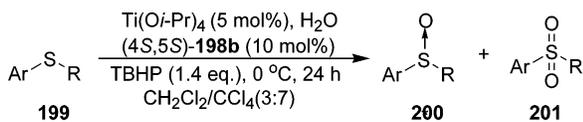
Metal complexes bearing 2-(oxazoliny)phenolato ligands have been utilized in a number of asymmetric reactions including Baeyer–Villiger oxidations,<sup>95</sup> cyclopropanations,<sup>96</sup> allylic functionalizations,<sup>97</sup> and Lewis-acid-catalyzed C–C bond formations.<sup>98</sup> In 2001 Feng reported the synthesis of the new derivatives **198** and used these phenolic oxazoline ligands in the



(4*S*,5*R*)-**a** R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = *t*-Bu (4*S*,5*S*)-**d** R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = H  
 (4*S*,5*S*)-**b** R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = *t*-Bu (4*S*)-**e** R<sup>1</sup> = H, R<sup>2</sup> = Ph, R<sup>3</sup> = *t*-Bu  
 (4*S*,5*R*)-**c** R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = H (4*S*)-**f** R<sup>1</sup> = H, R<sup>2</sup> = PhCH<sub>2</sub>, R<sup>3</sup> = *t*-Bu

titanium-catalyzed oxidation of prochiral sulfides **199** into chiral sulfoxides **200** using *tert*-butyl hydroperoxide (TBHP) (Scheme 37).<sup>99</sup>

#### Scheme 37



Ligand (4*S*,5*S*)-**198b** induced significantly higher enantioselectivities [72% ee (*R*)] than the other members of the ligand class for the oxidation of methyl phenyl sulfide with 1.1 equiv of TBHP in CH<sub>2</sub>-Cl<sub>2</sub>/CCl<sub>4</sub> at 0 °C for 24 h. An increase in enantioselectivity with increasing amounts of oxidant used [up to 96% ee (*R*) with 2.0 equiv of TBHP] was thought to be due to a concomitant kinetic resolution of the product sulfoxide by further oxidation to the sulfone **201** (Table 26, entries 1–3). Moderate chemoselectivities and isolated yields of the sulfoxides, but good enantioselectivities, were obtained for the oxidation of a number of arylalkyl sulfides using catalysts derived from Ti(*i*-PrO)<sub>4</sub> and ligand (4*S*,5*S*)-**198b** (Table 26, entries 4–6).

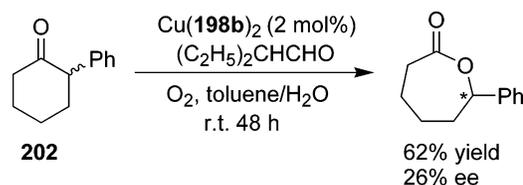
Copper complexes of ligands (4*S*,5*R*)-**198a** and (4*S*,5*S*)-**198b** were tested in the asymmetric Baeyer–Villiger reaction of 2-phenylcyclohexanone **202** using 2-ethylbutanal as the co-oxidant. The best results

**Table 26. Catalytic Enantioselective Oxidation of Sulfides Using Ti(*i*-PrO)<sub>4</sub> and Ligand (4*S*,5*S*)-**198b** (Scheme 37)**

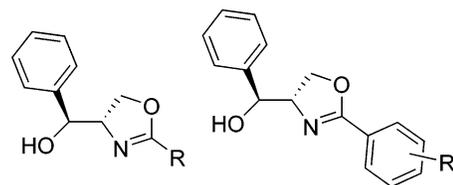
entry	Ar	R	TBHP (equiv)	yield (%)	<b>200:201</b>	ee (%) (conf)
1	Ph	Me	1.1	66	48:52	72 ( <i>R</i> )
2	Ph	Me	1.4	87	38:62	80 ( <i>R</i> )
3	Ph	Me	2.0	95	17:83	96 ( <i>R</i> )
4	Ph	Et	1.4	79	41:59	72 ( <i>R</i> )
5	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	Me	1.4	78	34:66	75 ( <i>R</i> )
6	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	1.4	90	42:58	81 ( <i>R</i> )

were afforded by ligand (4*S*,5*S*)-**198b**, but only modest enantioselectivity (26% ee) was achieved (Scheme 38).<sup>100</sup>

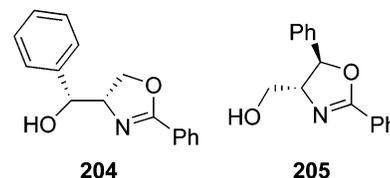
#### Scheme 38



On the basis of the conformationally restricted and structurally rigid amino alcohols that give excellent enantioselectivities for the addition of diethylzinc to imines, Gong has developed a series of *N,O*-oxazoline ligands **203–205**.<sup>101</sup>

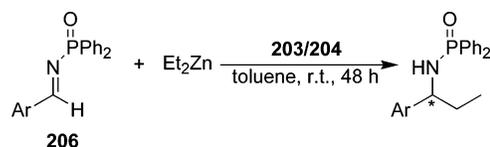


**203**  
**a** R = Ph  
**b** R = *i*-Pr  
**c** R = Naphthyl  
**d** R = Bn  
**e** R = CH<sub>2</sub>Naphthyl  
**203**  
**f** R' = 2-Br  
**g** R' = 4-Br  
**h** R' = 2-Me  
**i** R' = 3-Me  
**j** R' = 4-Me  
**k** R' = 4-MeO



In general, high enantioselectivities (81–93% ee) were obtained for the addition of diethylzinc to *N*-diphenylphosphinoyl benzalimine **206a** (Ar = Ph) promoted by stoichiometric amounts of ligands **203** and **204** (Scheme 39).

#### Scheme 39



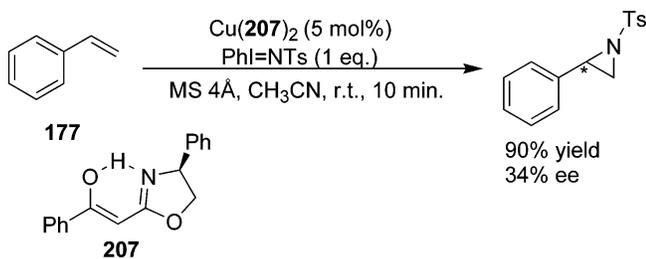
It was found that the stereocenter at the carbon atom bearing the hydroxy group was crucial for high

**Table 27. Asymmetric Diethylzinc Addition to *N*-Diphenylphosphinoylimines **206** Promoted by Ligands **203a** and **203k** (Scheme 39)**

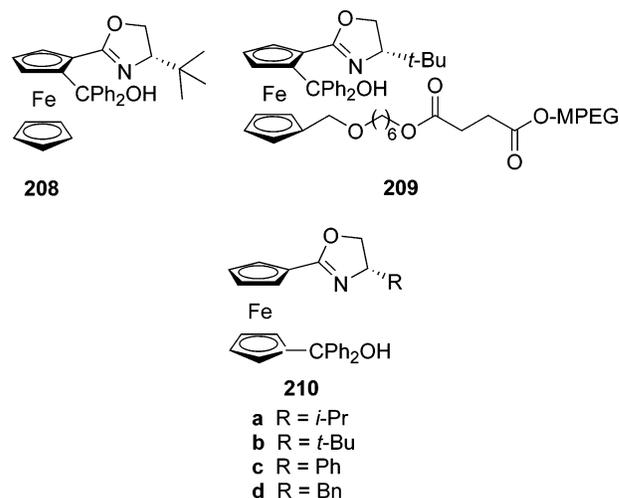
entry	imine		ligand	yield (%)	ee (%) (conf)
	<b>206</b>	Ar			
1	<b>a</b>	C <sub>6</sub> H <sub>5</sub> -	<b>203s</b>	77	91 ( <i>S</i> )
2	<b>a</b>	C <sub>6</sub> H <sub>5</sub> -	<b>203k</b>	72	93 ( <i>S</i> )
3	<b>b</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> -	<b>203a</b>	82	92 ( <i>S</i> )
4	<b>c</b>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> -	<b>203a</b>	83	90 ( <i>S</i> )
5	<b>c</b>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> -	<b>203k</b>	75	95 ( <i>S</i> )
6	<b>d</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> -	<b>203a</b>	84	90 ( <i>S</i> )
7	<b>e</b>		<b>203a</b>	75	90 ( <i>S</i> )
8	<b>e</b>		<b>203k</b>	83	94 ( <i>S</i> )
9	<b>f</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> -	<b>203a</b>	72	93 ( <i>S</i> )
10	<b>f</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> -	<b>203k</b>	80	92 ( <i>S</i> )
11	<b>g</b>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> -	<b>203a</b>	68	93 ( <i>S</i> )
12	<b>g</b>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> -	<b>203k</b>	75	93 ( <i>S</i> )

asymmetric induction (ligand **205** lacking this stereocenter gave only 23% ee) and also determined the configuration of the product [92% ee (*S*) with **203a** vs 76% ee (*R*) with **204**]. Generally, oxazolines bearing an *ortho*-substituted phenyl ring provided lower levels of enantiodiscrimination than their corresponding *para*- and *meta*-analogues (e.g., 84% ee with **203h** compared to 93 and 91% ee with **203i** and **203j**, respectively). Ligands **203a** and **203k** were used to promote the addition of diethylzinc to a range of diphenylphosphinoylimines **206a–g** giving high enantioselectivities (90–93% ee) for all of the imine substrates tested (Table 27).

Andersson has reported that a copper(II) complex [Cu(**207**)<sub>2</sub>] of the diphenyl-substituted *N,O*-bidentate anionic ligand **207** is a highly active catalyst precursor for the asymmetric aziridination of styrene **177**, affording 90% yield (after 10 min at room temperature) and a moderate enantioselectivity of 34% ee (Scheme 40).<sup>102</sup>

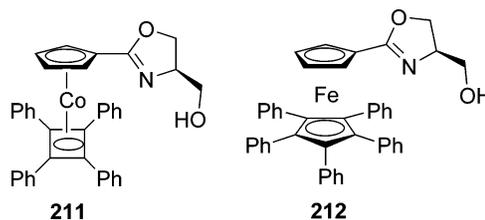
**Scheme 40**

The application of stereoplanar ferrocenyl-based mono(oxazoline) *N,O*-ligands in asymmetric catalysis has been discussed in a recent review by Bryce and Sutcliffe.<sup>3</sup> In brief, Bolm has achieved good yields (83–99%) and high enantioselectivities (78–93% ee) for the addition of diethylzinc to various aromatic and aliphatic aldehydes mediated by the chiral hydroxy-(diphenyl)methyl-2-ferrocenyloxazoline ligand **208** (5 mol %).<sup>103</sup> Using a modified diphenylzinc reagent (formed in situ from diphenylzinc and diethylzinc in a ratio of 1:2) to limit a competitive uncatalyzed reaction pathway, high enantioselectivities (up to 98% ee) were also obtained using ligand **208** for the transfer of a phenyl group to aliphatic and aromatic aldehydes.<sup>104</sup> High catalytic activity and enantioselectivity (97% ee) were retained for the addition of



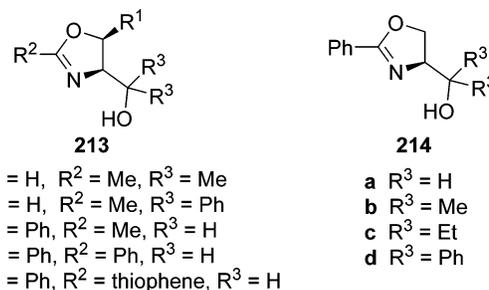
diphenylzinc to *p*-chlorobenzaldehyde using ligand **209** in which the ferrocenyloxazoline **208** is bound to a soluble poly(ethylene glycol) monomethyl ether polymer (MeO-PEG).<sup>105</sup> The use of this polymer-supported ligand facilitated the easy recovery and recycling of the catalyst, maintaining excellent asymmetric induction of 95% ee after five cycles. Hou has shown that ligands **210**, in which the hydroxy-(diphenyl)methyl and oxazoline groups are located on separate cyclopentadiene rings, are also effective in the addition of diethylzinc to aldehydes, affording high yields and moderate to good enantioselectivities (64–91% ee).<sup>106</sup>

Richards reported the synthesis of the stereoplanar mimetics **211** and **212**. In these ligands, the tetra- or pentaphenyl-substituted lower rings of the metallocenes serve to block one face of the oxazoline ring



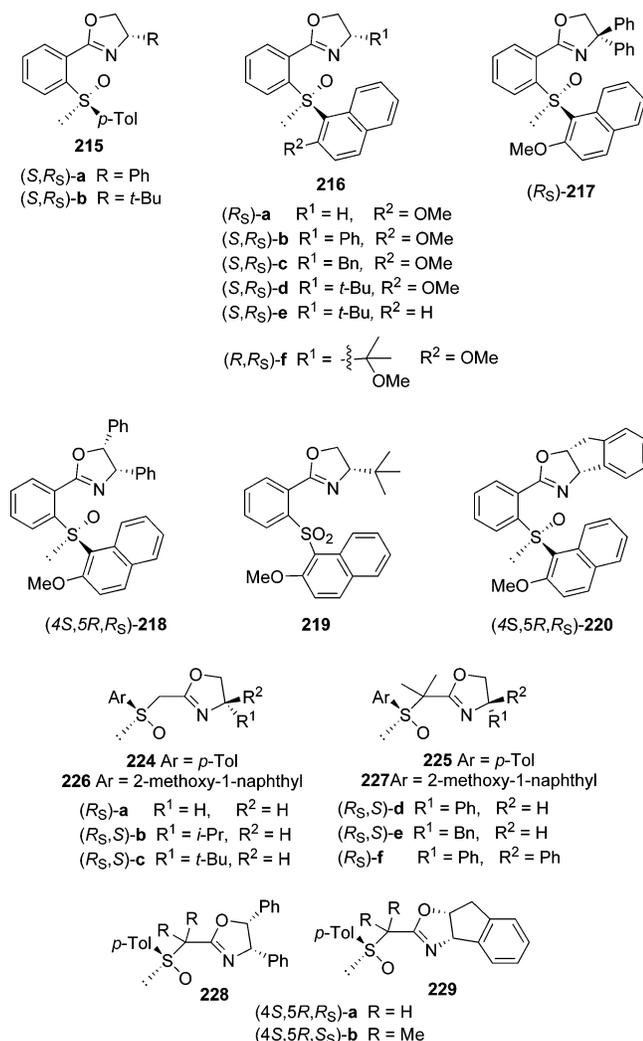
by an unfavorable steric interaction with the oxazoline substituent. Ligands **211** and **212** were applied in the addition of diethylzinc to benzaldehyde **197**, providing enantioselectivities of 68 and 75% ee (*R*), respectively.<sup>107</sup>

Structural modification of the hydroxymethyl oxazoline ligands **213**, first prepared by Williams,<sup>108</sup> led to the development, by Braga, of analogues **214**, which are effective catalysts in the asymmetric addition of diethylzinc to aldehydes.<sup>109</sup> The least



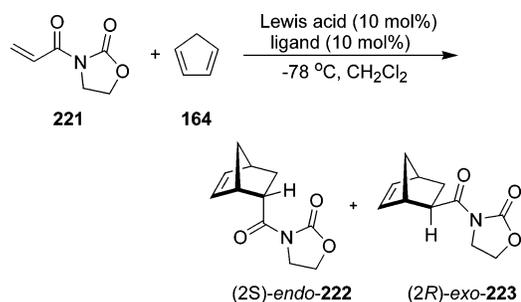
sterically hindered derivative **214a** was the ligand of choice, affording 91% yield and 95% ee (*R*) for the reaction with benzaldehyde **197**. In general, the enantioselectivity decreased for the addition to benzaldehydes with electron-donating groups (40–89% ee), whereas the presence of electron-withdrawing substituents facilitated excellent levels of enantioinduction [ $>99\%$  ee (*R*) with *o*- and *p*-chlorobenzaldehyde]. For aliphatic aldehydes, both catalytic activity and enantiodiscrimination were highly dependent on the chain length, with the best result of 67% yield and  $>99\%$  ee (*R*) being achieved using hexanal.

Hiroi has investigated the use of chiral oxazoline-sulfoxides **215**–**220** as ligands in the asymmetric Lewis acid-catalyzed Diels–Alder reaction of *N*-acryloyl-1,3-oxazolidinone **221** with cyclopentadiene **164**



(Scheme 41).<sup>110</sup> Of the various Lewis acids examined, magnesium iodide proved to be the most effective, affording good *endo/exo* selectivity (94:6) and achieving up to 92% ee in combination with the 2-methoxyisopropyl-substituted oxazoline **216f** (Table 28, entry 5). This high enantioinduction was thought to arise from a double-asymmetric acceleration provided by the two chiral centers because the absence of chirality on the oxazoline or the sulfoxide led to low enantioselectivities as shown by ligands **216a**, **217**, and **219**, respectively (Table 28, entries 2, 6, and 8). It was

### Scheme 41



**Table 28. Lewis Acid-Catalyzed Asymmetric Diels–Alder Reaction of *N*-Acryloyl-1,3-oxazolidinone **221** with Cyclopentadiene **164** Using Ligands **215**–**220** and **224**–**229** (Scheme 41)**

entry	Lewis acid	ligand	time (h)	yield (%)	<i>endo/exo</i> <b>222:223</b>	% ee of <b>222</b> (conf)
1	MgI <sub>2</sub>	<b>215b</b>	24	86	94:6	46 ( <i>S</i> )
2	MgI <sub>2</sub>	<b>216a</b>	24	82	94:6	17 ( <i>S</i> )
3	MgI <sub>2</sub>	<b>216d</b>	24	90	97:3	81 ( <i>S</i> )
4	MgI <sub>2</sub>	<b>216e</b>	24	81	93:7	36 ( <i>S</i> )
5	MgI <sub>2</sub>	<b>216f</b>	24	90	94:6	92 ( <i>S</i> )
6	MgI <sub>2</sub>	<b>217</b>	24	96	84:16	36 ( <i>S</i> )
7	MgI <sub>2</sub>	<b>218</b>	36	90	94:6	42 ( <i>S</i> )
8	MgI <sub>2</sub>	<b>219</b>	36	62	92:8	6 ( <i>S</i> )
9	MgI <sub>2</sub>	<b>220</b>	24	52	96:4	37 ( <i>S</i> )
10	Cu(OTf) <sub>2</sub>	<b>224e</b>	22	86	89:11	39 ( <i>R</i> )
11	Cu(ClO <sub>4</sub> ) <sub>2</sub>	<b>224e</b>	22	90	88:12	34 ( <i>R</i> )
12	Cu(SbF <sub>6</sub> ) <sub>2</sub>	<b>224e</b>	10	85	94:6	66 ( <i>R</i> )
13	Cu(SbF <sub>6</sub> ) <sub>2</sub>	<b>224b</b>	6	96	94:6	10 ( <i>S</i> )
14	Cu(SbF <sub>6</sub> ) <sub>2</sub>	<b>224c</b>	8	89	97:3	34 ( <i>S</i> )
15	Cu(SbF <sub>6</sub> ) <sub>2</sub>	<b>226c</b>	8	83	89:11	75 ( <i>R</i> )

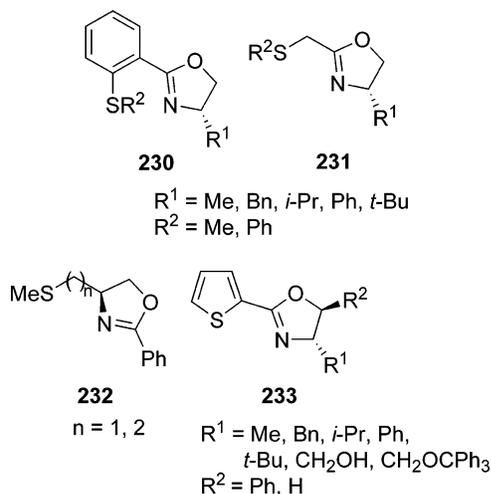
postulated that these ligands coordinate to magnesium by the oxazolyl nitrogen and the sulfinyl oxygen and that the enantiomeric product observed results from attack at the *Re*-face of the dienophile.

The 2-(*p*-tolylsulfinylmethyl)- and 2-[(2-methoxy-1-naphthyl)sulfinylmethyl]-1,3-oxazoline ligands **224**–**229** were also tested in the asymmetric Diels–Alder reaction (Scheme 41).<sup>111</sup> It was found that copper(II) salts were the optimum Lewis acids and that the magnitude of asymmetric induction and the sense of the enantiomeric product depended on the steric bulk of the oxazoline substituent and the counterion used (Table 28, entries 10–14). The highest enantioselectivity (75% ee) was obtained using ligand **226c** and hexafluoroantimonate as the counterion (Table 28, entry 15).

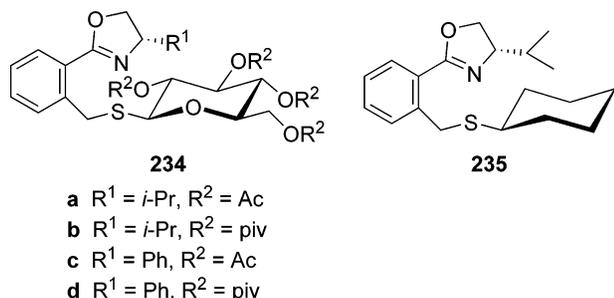
### 2.4. Mono(oxazoline) *N,S*-Ligands

The bidentate oxazoline *N,S*-ligands **230**–**233** developed by Williams were among the first mono(oxazoline) ligands containing an auxiliary sulfur donor atom to be applied in asymmetric catalysis and have given high enantioselectivities (up to 96% ee) for the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>112</sup> In recent years, a number of mono(oxazoline) *N,S*-ligands of varying structure have been developed and utilized successfully in asymmetric catalysis.

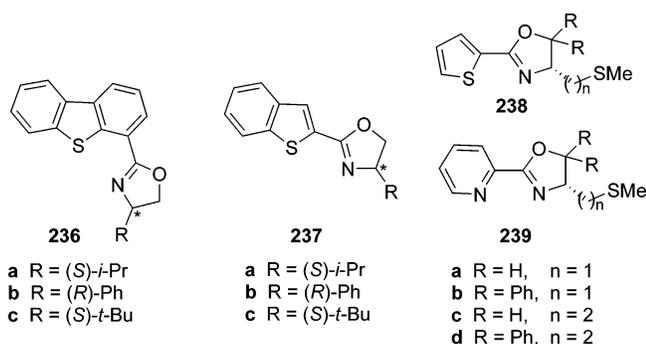
In 1998 Pregosin applied the thioglucose-derived oxazoline ligands **234** in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>113</sup> Ligands **234b** and **234d**,



with bulky pivalate protecting groups, provided the best enantioselectivities of 97 and 96% ee in **40** and **62%** yield, respectively. The lower enantiodiscrimination (75% ee) obtained with the cyclohexane thioether **235** indicated that the sugar moiety was important in the enantioinduction.



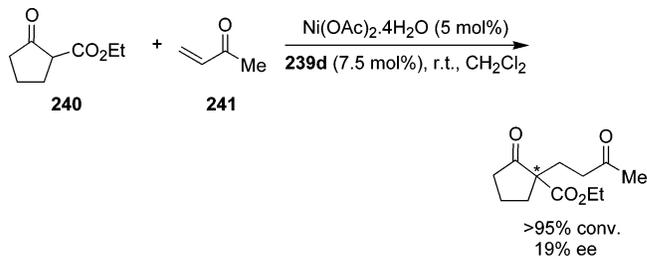
The dibenzothiophene (DBT-MOx)- and benzothiophene (BT-MOx)-derived ligands **236** and **237** were also investigated in the asymmetric palladium-catalyzed alkylation of **7** with **26**.<sup>114</sup> Both ligand



classes afforded moderate conversions and modest enantioselectivities (up to 41% ee), with the six-membered chelate ring-forming DBT-MOx ligands **236** giving slightly better results.

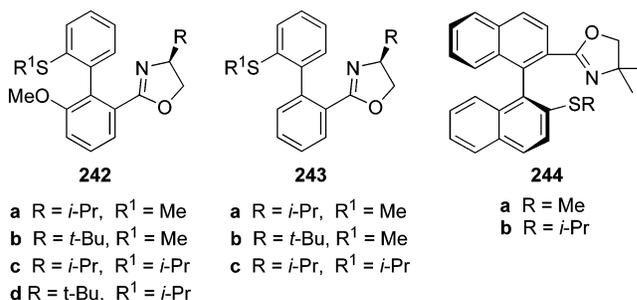
Christoffers has prepared a number of chiral tridentate oxazoline ligands **238** and **239** with heteroaryl (pyridine or thiophene) and thioether donor groups. Screening of these ligands with 13 different metal salts in the asymmetric Michael reaction of the  $\beta$ -keto ester **240** with the methyl vinyl ketone **241** revealed that only those catalysts derived from the pyridine-based ligands **239** induced asymmetry, with

## Scheme 42



the best result of 19% ee being achieved with nickel(II) acetate and ligand **239d** (Scheme 42).<sup>115</sup>

Ikeda reported the synthesis of sulfur-oxazoline ligands **242** and **243** with an axis-fixed or unfixed biphenyl backbone, respectively.<sup>116</sup> Of the axis-fixed



ligands, only those containing an isopropyl thioether group, **242c** and **242d**, could be successfully separated into their component diastereomers. Ligands **243** exist as an equilibrium diastereomeric mixture because their two *ortho* substituents are insufficient to prevent rotation around the biaryl axis. Upon coordination of ligands **243** to palladium(II), only **243a** and **243b**, bearing a methylthioether group, exclusively formed one of the two possible diastereomeric complexes. These ligands were tested in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26** and afforded good yields and enantioselectivities (up to 82% ee with ligand **243a**). It was found that the stereoaxis of the biphenyl backbone exerted considerable influence on the catalytic activity, with ligands (*S,aR*)-**242c** and (*S,aR*)-**242d** being significantly more active than their respective (*S,aS*)-diastereomers (Table 29, entries 1 and 3 vs 2 and 4). For both ligand classes, the nature of the alkylthio group similarly affected the enantioselectivity, with ligands bearing a methyl thioether achieving higher enantiodiscrimination than those with an isopropyl group (Table 29, entry 7 and 8 vs 9 and entries 5 and 6 vs 1–4).

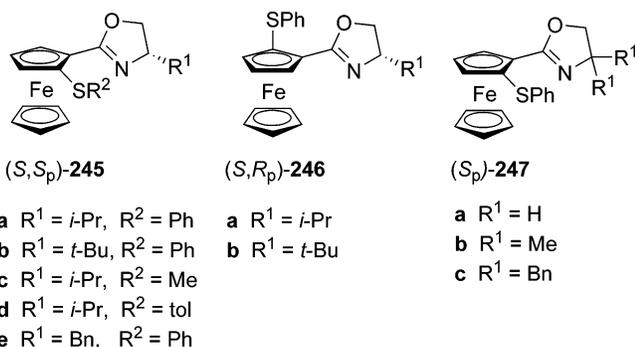
Gladiali has prepared the stereoaxis-containing ligands **244**, which possess both an achiral oxazoline pendant and an arylalkyl sulfide substituent.<sup>67</sup> A rhodium(I) complex of ligand **244a** gave good conversions but racemic products for both the hydroboration and hydroformylation of styrene and was inactive in the hydrogenation of methyl acetamidoacrylate and in the transfer hydrogenation of acetophenone **40**. In the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethylmalonate **26**, ligand **244a** gave an optimum enantioselectivity of 66% ee (Table 29, entry 10).

**Table 29. Palladium-Catalyzed Asymmetric Alkylation of 1,3-Diphenyl-2-propenyl Acetate **7** with Dimethyl Malonate **26** Using Ligands **242**–**247**<sup>a</sup>**

entry	ligand	time (h)	yield (%)	ee (%) (conf)
1	( <i>S,aR</i> )- <b>242c</b>	48	92	20 ( <i>S</i> )
2	( <i>S,aS</i> )- <b>242c</b>	96	trace	
3	( <i>S,aR</i> )- <b>242d</b>	48	91	19 ( <i>S</i> )
4	( <i>S,aS</i> )- <b>242d</b>	96	18	18 ( <i>S</i> )
5	<b>242a</b> ( <i>aR</i> : <i>aS</i> 17:83)	72	90	74 ( <i>S</i> )
6	<b>242b</b> ( <i>aR</i> : <i>aS</i> 22:78)	72	89	71 ( <i>S</i> )
7	<b>243a</b>	48	93	82 ( <i>S</i> )
8	<b>243b</b>	48	91	73 ( <i>S</i> )
9	<b>243c</b>	48	87	18 ( <i>S</i> )
10 <sup>b</sup>	<b>244a</b>	36	70	66 ( <i>S</i> )
11 <sup>c</sup>	<b>245a</b>	3	98	89 ( <i>S</i> )
12 <sup>c</sup>	<b>245b</b>	10	98	98 ( <i>S</i> )
13 <sup>c</sup>	<b>245c</b>	3	98	82 ( <i>S</i> )
14 <sup>c</sup>	<b>245e</b>	5	98	88 ( <i>S</i> )
15 <sup>c</sup>	<b>246a</b>	3	98	90 ( <i>S</i> )
16 <sup>c</sup>	<b>246b</b>	1	98	90 ( <i>S</i> )
17 <sup>c</sup>	<b>247a</b>	48	90	8 ( <i>R</i> )
18 <sup>c</sup>	<b>247b</b>	48	92	12 ( <i>R</i> )
19 <sup>c</sup>	<b>247c</b>	5	98	72 ( <i>S</i> )

<sup>a</sup> 1.25 mol % [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, ligand (3 mol %), BSA/KOAc(cat.), THF, room temperature. <sup>b</sup> 3 mol % [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, ligand (10 mol %), CHCl<sub>3</sub>, 0 °C. <sup>c</sup> 2 mol % [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, ligand (6 mol %), CH<sub>2</sub>Cl<sub>2</sub>.

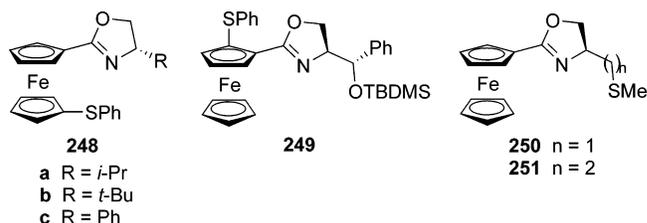
Dai and Hou have prepared a number of stereoplanar oxazolinylferrocenylthioethers **245**–**247** and have shown that these are highly effective ligands for the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**, affording high catalytic efficiency and good to excellent enantioselectivities (82–98% ee) (Table 29, entries 11–18).<sup>117</sup> Ligands with an aryl thioether



group gave better enantioselectivities than those with a methyl thioether (Table 29, entry 11 vs 13), and *tert*-butyl-substituted oxazolines were superior to their isopropyl and benzyl analogues (Table 29, entry 12 vs 11). The diastereomeric ligand pairs **245a/246a** and **245b/246b** provided the same enantiomeric product, suggesting that it is the stereocenter of the oxazoline ring that determines the stereochemical outcome of the reaction (Table 29, entries 11 and 12 vs 15 and 16). The low enantioselectivities (8 and 12% ee) obtained with ligands **247a** and **247b** (Table 29, entries 17 and 18), which have only planar chirality, were thought to be a consequence of the formation of a stereocenter on the sulfur atom upon coordination to the metal center. In the absence of a stereogenic substituent (as in **245** and **246**) or bulky groups (as in **247c**) on the oxazoline ring both configurations of the stereogenic sulfur atom are viable, leading to

almost no diastereoselectivity in the formation of the metal complexes and low enantioselectivities.

Ferrocenyloxazoline ligands **248**, in which the oxazoline and thioether groups are located on separate cyclopentadiene rings, generated relatively inactive palladium complexes for the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**, giving 28% yield (after 6 days at room temperature, 2 mol % Pd) and 75% ee (*S*) with the optimum ligand **248c**.<sup>118</sup> In the same palladium-catalyzed

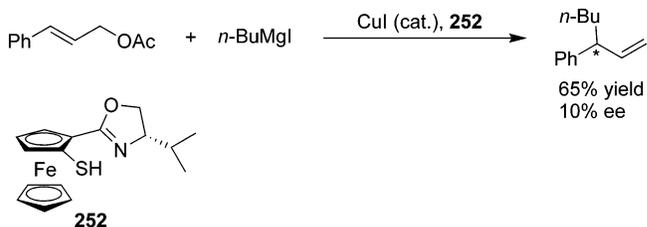


allylic alkylation reaction, the *N,S*-ligand **249** gave very high enantioselectivities (92–95% ee) with almost quantitative chemical yields, employing both the sodium dimethyl malonate and BSA/KOAc protocols.<sup>119</sup>

Ferrocenyloxazolines **250** and **251**, containing a secondary chelating sulfur moiety, were reported by Bryce and investigated in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7**.<sup>120</sup> The best result (98% yield and 93% ee) was obtained in dichloromethane using ligand **251** and BSA/KOAc to generate the dimethyl malonate nucleophile. Whereas previous *N,S*-oxazoline ligands have shown poor enantiocontrol in polar solvents such as DMF due to ligand displacement by the solvent, ligand **251** afforded reasonable results (76% yield, 79% ee) using sodium dimethyl malonate as the nucleophile.

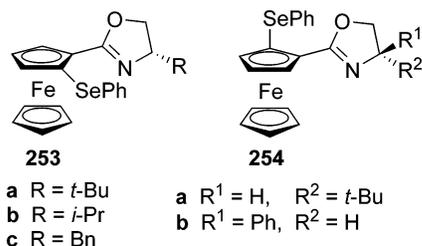
Bäckvall reported the synthesis in low yield of the relatively unstable ferrocenyloxazoline thiol **252**. The catalyst formed by the reaction of this ligand with CuI was used in the allylic substitution of 3-phenyl-2-propenyl acetate with *n*-BuMgI, giving product in 65% yield and 10% ee (Scheme 43).<sup>121</sup>

#### Scheme 43



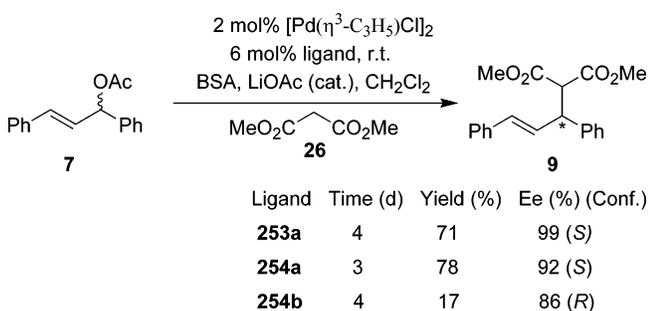
### 2.5. Miscellaneous Mono(oxazoline) Ligands

Hou prepared 2-ferrocenyloxazolines **253** and **254** possessing a stereoplane and selenium-containing *ortho*-substituents.<sup>122</sup> By analogy with the oxazolinylferrocenylthioethers **245** and **246**, these ligands were tested in the asymmetric palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. In general, high enantioselectivities (71–99% ee) and variable yields (17–80%) were obtained with the *tert*-butyl-substituted ligand

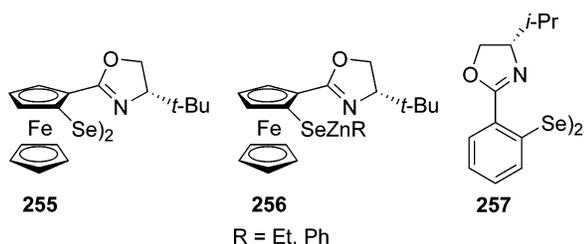


**253a**, proving to be the ligand of choice. The diastereomeric ligand pair **253a** and **254a** afforded the same enantiomeric product, indicating that the stereo-center of the oxazoline ring determined the sense of asymmetric induction. This was also evident by the opposite enantiomeric product afforded by ligand **254b** compared to ligand **254a** (Scheme 44).

#### Scheme 44



The bis(2-ferrocenyloxazoliny)diselenide **255** was used by Bolm as a chiral ligand in the asymmetric addition of diethylzinc to aldehydes. The best results

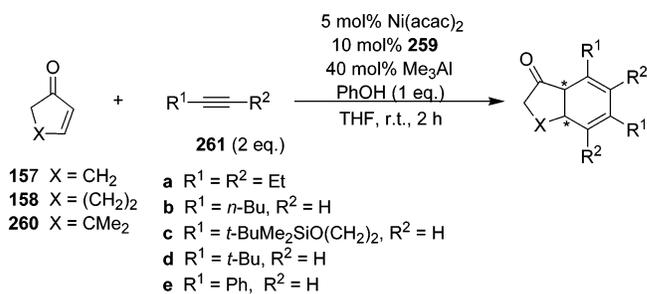


of 65–96% yield and 76–85% ee were obtained using a mixture of diethylzinc and diphenylzinc-modified diarylzinc. It was suggested that the catalytically active species is the zinc selenide **256** formed by heterolytic cleavage of the diselenide **255**.<sup>123</sup>

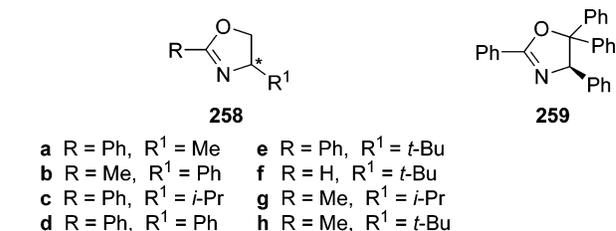
Similarly, the active ligand in the chiral diselenide oxazoline **257**-mediated copper(I)-catalyzed enantioselective addition of Grignard reagents to enones was thought to be the oxazolinylselenide formed from the in situ cleavage of **257** by the Grignard reagent.<sup>124</sup> In general, the enantioselectivity for the addition of isopropyl and *n*-butyl Grignard reagents (RMgCl) to cyclic enones **157**–**159** increased with increasing ring size with the optimum result of 94% yield and 85% ee being obtained for the addition of an isopropyl group to cycloheptenone **159**. The addition of the isopropyl Grignard reagent to chalcone, however, proceeded with a low enantioselectivity of 5% ee.

In 2002 Ikeda reported the first example of a catalytic enantioselective intermolecular [2+2+2]

#### Scheme 45



cycloaddition of one molecule of alkene and two molecules of alkyne using a binary metal catalytic system consisting of a nickel complex modified by monodentate oxazoline ligands of type **258a–d** or **259** and an aluminum phenoxide (Scheme 45).<sup>125</sup> Of



the ligands investigated, the 2,4,5,5-tetraphenyl derivative **259** was optimal, giving perfect regioselection (except for the reaction of **157** with **261b**) and moderate enantioselection (40–62% ee) for the cycloaddition of cyclopentenones **157** and **260** with various alkynes **261a–e** (Table 30, entries 1–7). The

**Table 30. Ni/Al-Catalyzed Enantioselective [2+2+2] Cycloaddition of Cyclic Enones **157**, **158**, and **260** with Alkynes **261** in the Presence of Ligand **259** (Scheme 45)**

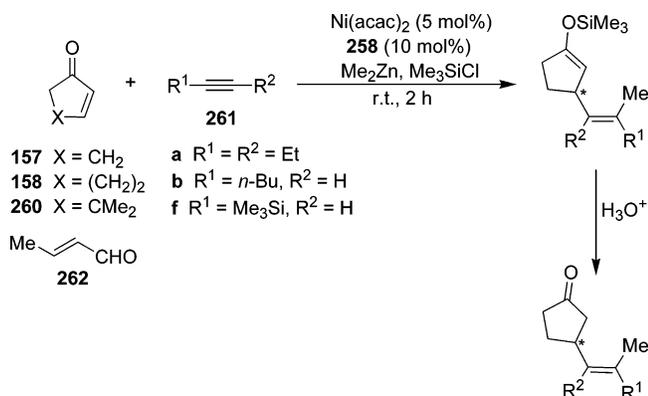
entry	enone	alkyne	yield (%)	ee (%)
1	<b>157</b>	<b>261a</b>	22	45
2	<b>157</b>	<b>261b</b>	66 <sup>a</sup>	48
3	<b>157</b>	<b>261c</b>	77	62
4	<b>157</b>	<b>261d</b>	72	58
5	<b>157</b>	<b>261e</b>	65	55
6	<b>260</b>	<b>261a</b>	21	44
7	<b>260</b>	<b>261d</b>	25	40
8	<b>158</b>	<b>261b</b>	65	4

<sup>a</sup> 95% regioselectivity.

reaction of cyclohexenone **158** with alkyne **261b** proceeded with a significantly lower level of enantioinduction (4% vs 48% ee) compared to that of cyclopentenone **157** (Table 30, entry 8 vs entry 2).

Nickel complexes of the monodentate oxazoline ligands **258c–h** were also found to catalyze a multi-component tandem coupling reaction between an enone, an alkyne, dimethylzinc, and chlorotrimethylsilane (Scheme 46).<sup>126</sup> Of the ligands tested, 2-methyl-4-*tert*-butyl-oxazoline **258h** afforded the best results, giving moderate to good enantioselectivities (31–81% ee) and poor to good yields (5–78%) with both cyclic (**157**, **158**, and **260**) and aliphatic (**262**) enones and different alkynes **261a**, **261b**, and **261f** in a range of reaction solvents (Table 31).

## Scheme 46

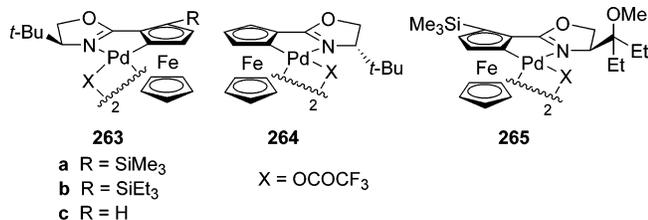


**Table 31. Nickel-Catalyzed Enantioselective Tandem Coupling Using Ligand 258h (Scheme 46)**

entry	enone	alkyne	solvent	yield (%)	ee (%)
1	157	261a	THF	57	78
2	260	261a	triglyme	78	81
3	158	261a	triglyme	39	38
4 <sup>a</sup>	157	261f	diglyme	51	66
5 <sup>b</sup>	157	261b	DME	32	67
6 <sup>c</sup>	262	261b	DME	28	49

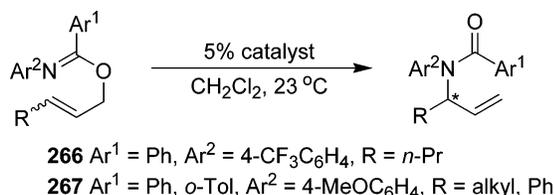
<sup>a</sup> 100% regioselectivity. <sup>b</sup> 89% regioselectivity. <sup>c</sup> Yield and enantiomeric excess is of the alcohol obtained after NaBH<sub>4</sub> reduction of the aldehydic product.

The ferrocenyloxazoline palladacycles **263–265**, prepared in situ by the reaction of the corresponding iodide-bridged complexes with silver trifluoroacetate,



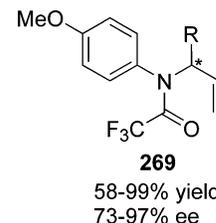
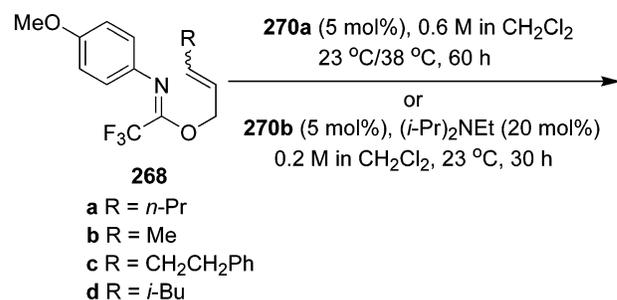
were utilized by Overman as catalysts for the asymmetric rearrangement of allylic imidates to allylic amides (Scheme 47).<sup>127</sup>

## Scheme 47



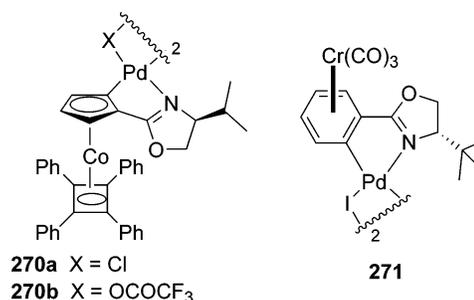
In general, it was determined that a ferrocenyl silyl substituent was important for high enantiocontrol [91% ee with **263a** vs 49% ee with **263c** for the reaction of (*Z*)-**266**] and that the size of the oxazoline substituent and the silyl group had little effect on the enantioselectivity. Rearrangement of (*Z*)-allylic imidates proceeded with higher enantiodiscrimination and opposite product configuration compared to the corresponding (*E*)-isomers. Of the two substrate types used, the allylic *N*-(4-methoxyphenyl)arylimidates **267** facilitated higher reaction rates but similar levels of enantioselection compared to 2-hexenyl-*N*-

## Scheme 48



(4-trifluoromethylphenyl)benzimidate **266**. The ligand of choice, **263a**, afforded excellent enantioselectivities (75–96% ee) in generally high yields for the rearrangement of a range of (*Z*)-allylic imidates **267**, with the highest enantioselectivities being obtained when the 3-alkyl substituent was primary and  $\beta$ -branched.

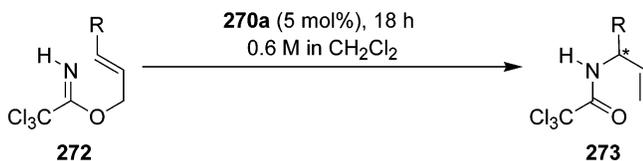
To increase the synthetic utility of the asymmetric rearrangement of allylic imidates to allylic amides, Overman investigated the reaction of *N*-(4-methoxyphenyl)trifluoroacetimidates **268** (Scheme 48), the *N*-(4-methoxyphenyl)-trifluoroacetamide products **269** of which can be deprotected by a two-step sequence to give useful yields of allylic amines.<sup>128</sup> In addition to the ferrocenyl oxazoline palladacycle **263a**, the ( $\eta^5$ -cyclopentadienyl)( $\eta^4$ -tetraphenylcyclobutadiene)cobalt oxazoline complex **270b**, generated by the reac-



tion of the corresponding chloride-bridged complex **270a** with silver trifluoroacetate, and the ( $\eta^6$ -arene)-tricarboxylchromium(0) oxazoline complex **271**, which was activated prior to use by reaction with thallium triflate, were screened for both activity and enantioselectivity in the asymmetric rearrangement of (*E*)- and (*Z*)-2-hexenyl-*N*-(4-methoxyphenyl)trifluoroacetimidates **268a** in the presence of 20 mol % of 1,8-bis(dimethylamino)naphthalene at room temperature.

The cobalt oxazoline palladacycle complex (COP trifluoroacetate) **270b**, which gave yields of 84 and 71% and enantioselectivities of 84% ee (*S*) and 94% ee (*R*) for the reaction of (*E*)-**268a** and (*Z*)-**268a**, respectively, was the catalyst of choice and was investigated together with its chloride-bridged dimer precursor (COP-Cl) **270a**, which gave comparable

## Scheme 49



**Table 32. Asymmetric Rearrangement of (*E*)-Allylic Trichloroacetimidates **272** to Allylic Trichloroacetamides **273** Using Catalyst **270a** (Scheme 49)**

entry	<b>272</b>	R	temp (°C)	yield (%)	ee (%) (conf)
1	<b>a</b>	n-Pr	38	99	95 ( <i>S</i> )
2	<b>b</b>	i-Bu	38	95	96 ( <i>S</i> )
3 <sup>a</sup>	<b>b</b>	i-Bu	38	92	98 ( <i>S</i> )
4	<b>c</b>	Me	rt <sup>c</sup>	85	92 ( <i>S</i> )
5 <sup>b</sup>	<b>d</b>	cyclohexyl	38	82	96 ( <i>S</i> )
6	<b>e</b>	CH <sub>2</sub> CH <sub>2</sub> Ph	38	93	93 ( <i>S</i> )
7	<b>f</b>	(CH <sub>2</sub> ) <sub>3</sub> OAc	38	97	92 ( <i>S</i> )
8	<b>g</b>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	rt	73	95 ( <i>S</i> )
9	<b>h</b>	(CH <sub>2</sub> ) <sub>3</sub> (OCH <sub>2</sub> CH <sub>2</sub> O)	rt	85	95 ( <i>S</i> )
10	<b>i</b>	(CH <sub>2</sub> ) <sub>2</sub> COMe	38	98	95 ( <i>S</i> )
11	<b>j</b>	CH <sub>2</sub> OTBDMS	38	98	96 ( <i>R</i> )
12	<b>k</b>	CH <sub>2</sub> OH	rt	84	80 ( <i>R</i> )
13	<b>l</b>	(CH <sub>2</sub> ) <sub>3</sub> NBn(Boc)	38	96	95 ( <i>S</i> )
14	<b>m</b>	(CH <sub>2</sub> ) <sub>9</sub> NBn <sub>2</sub>	rt	82	97 ( <i>S</i> )

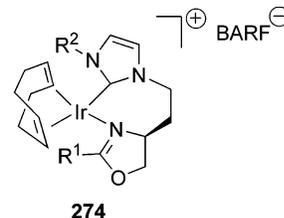
<sup>a</sup> 1 mol % **270a**, 1.2 M in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> 1 M in CH<sub>2</sub>Cl<sub>2</sub>. <sup>c</sup> rt, room temperature.

enantioselectivity [93% ee (*S*)] at a reduced reaction rate (93% yield after 60 h at 23 °C vs 93% yield after 30 h) for the reaction of (*E*)-**268d**, in the rearrangement of a number of (*E*)- and (*Z*)-allylic *N*-(4-methoxyphenyl)trifluoroacetimidates **268a–d**. In general, it was found that with the proper choice of the cobalt oxazoline palladacycle complex, the allylic amide products **269a–d** were formed with enantiomeric excesses >92% from (*E*)- and (*Z*)-imidates containing both branched and unbranched alkyl chains (Scheme 48).

Using the cobalt oxazoline palladacycle complex **270a**, Overman extended this asymmetric methodology to the rearrangement of prochiral (*E*)-allylic trichloroacetimidates **272** (readily prepared from allylic alcohols and trichloroacetonitrile) to allylic trichloroacetamides **273** in order to develop a practical method for the transformation of prochiral allylic alcohols to enantioenriched allylic amines and their analogues because the trichloroacetamide group can be easily cleaved or transformed to other functional arrays (Scheme 49 and Table 32).<sup>129</sup> The rearrangement of (*E*)-allylic trichloroacetimidates **272**, containing branched and unbranched substituents, proceeded with high yields (82–99%) and excellent enantiodiscrimination (92–96% ee) employing catalyst **270a** (5 mol %) in dichloromethane (Table 32, entries 1–6). An increase in the substrate concentration from 0.6 to 1.2 M facilitated a decrease in the catalyst loading to 1 mol % accompanied by a slight increase in enantioselection (Table 32, entry 3 vs entry 2). Ester, acetal, ketone, and silyl ether substituents were well tolerated, with the corresponding allylic trichloroacetamide products **273** being formed in 80–96% ee and excellent yields (Table 32, entries

7–12). Substrates with nitrogen-containing substituents also afforded high enantioselectivities (95–97% ee) but in general proved to be more problematic (Table 32, entries 13 and 14).

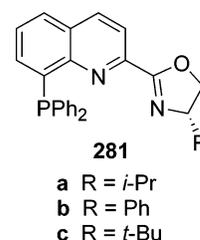
Cationic iridium complexes **274** of *N*-heterocyclic carbene–oxazoline ligands have been applied by Burgess in the asymmetric hydrogenation of trisubstituted and tetrasubstituted alkenes, which possess



R<sup>1</sup> = 1-adamantyl, *t*-Bu, CHPh<sub>2</sub>, Ph  
R<sup>2</sup> = *t*-Bu, CHPh<sub>2</sub>, cyclohexyl, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 3,5-*t*-Bu<sub>2</sub>-4-MeOC<sub>6</sub>H<sub>2</sub>, 2,5-Et<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,5-*t*-Bu<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 1-adamantyl

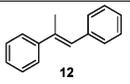
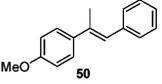
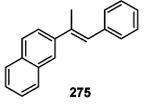
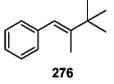
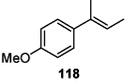
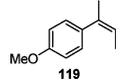
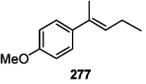
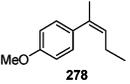
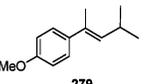
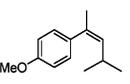
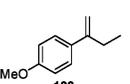
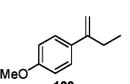
little or no coordinating functionality.<sup>130</sup> The optimum catalyst, derived from the ligand containing 2,6-diisopropylphenyl and 1-adamantyl groups as the imidazolylidene and oxazoline substituents, respectively, afforded moderate to excellent enantioselectivities (37–98% ee) in generally high yields for the reduction of a range arylalkenes, with (*E*)-alkenes generally providing better results than their (*Z*)-analogues (Table 33). Variations in enantioselectivity were observed for some substrates at different hydrogen pressures and reaction temperatures. This was exemplified by the reduction of the 1,1-disubstituted alkene **122**, which afforded the (*S*)-product at –15 °C and 85 bar (high hydrogen concentration) and the (*R*) product at 25 °C and 1 bar (low hydrogen concentration) (Table 33, entries 11 and 12). This change in asymmetric induction was attributed to two or more competing reaction mechanisms, which predominate at different hydrogen concentrations. Deuterium-labeling experiments excluded the possibility that one of these reaction mechanisms was due to double-bond migrations.

Phosphino(oxazolonyl)quinoline (DPOQ) ligands **281**, prepared by Ahn, have been applied in ruthenium(II)-catalyzed asymmetric inter- and intramolecular cyclopropanation.<sup>131</sup> Low enantiodiscriminations and



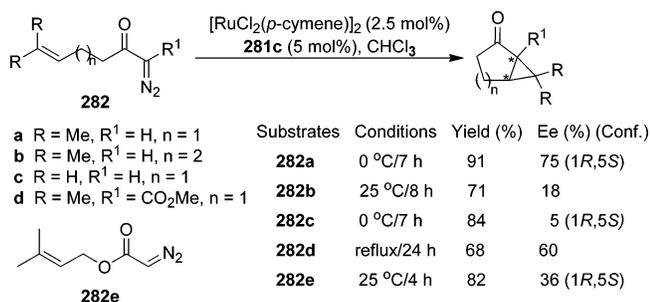
moderate *trans/cis* selectivities were obtained for the intermolecular reaction between styrene **177** and ethyl diazoacetate **178a**. For the intramolecular cyclopropanation of diazo-ene **282a**, the sense and extent of the asymmetric induction was highly dependent on the ligand used, with the *tert*-butyl-substituted ligand **281c** affording the optimum result

**Table 33. Asymmetric Hydrogenation of Alkenes Using the Iridium Complex **274** ( $R^1 = 1\text{-Adamantyl}$ ,  $R^2 = 2,6\text{-i-Pr}_2\text{C}_6\text{H}_3$ )<sup>a</sup>**

Entry	Substrate	Yield (%)	Ee (%)
1		99	98
2		99	97
3		90	93
4 <sup>b</sup>		13	75
5		99	96
6		99	79
7		95	84
8		58	49
9		100	89
10		54	37
11 <sup>c</sup>		100	64 (S)
12 <sup>d</sup>		100	89 (R)

<sup>a</sup> H<sub>2</sub> (50 bar), 25 °C, 2 h, CH<sub>2</sub>Cl<sub>2</sub>, 0.6 mol % **274**. <sup>b</sup> H<sub>2</sub> (1 bar), 23 °C. <sup>c</sup> -15 °C, 85 bar. <sup>d</sup> 25 °C, 1 bar.

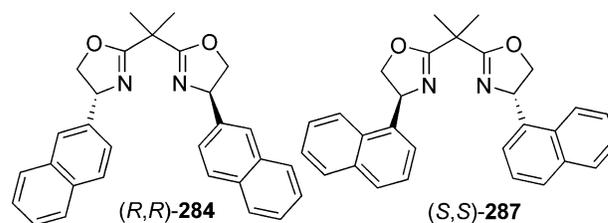
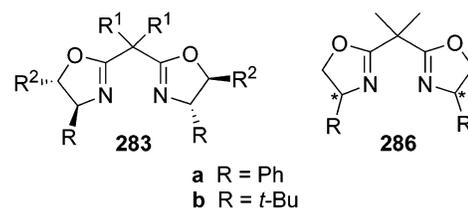
of 91% yield and 75% ee (1*R*,5*S*). Using this ligand, poor to moderate enantioselectivities (5–60% ee) were attained for the cyclopropanation of a number of diazo-enes **282b–e** (Scheme 50).

**Scheme 50****3. Bis(oxazoline) Ligands**

Since the publication in 1998 of a review by Ghosh on the application of *C*<sub>2</sub>-symmetric chiral bis(oxazoline) ligands in metal-catalyzed asymmetric synthesis,<sup>1</sup> a vast number of novel bis(oxazoline) ligands that are capable of coordinating to a metal complex in a bidentate, tridentate, or tetradentate fashion have been reported. In addition, chiral ligands discussed in Ghosh's review have since been applied in an extensive range of new metal-catalyzed transformations with considerable success. In this section, only applications of new bis(oxazoline) ligands reported since 1998 will be reviewed in detail.

**3.1. Bidentate Bis(oxazoline) Ligands****3.1.1. Bis(oxazoline) Ligands with Only a Stereocenter**

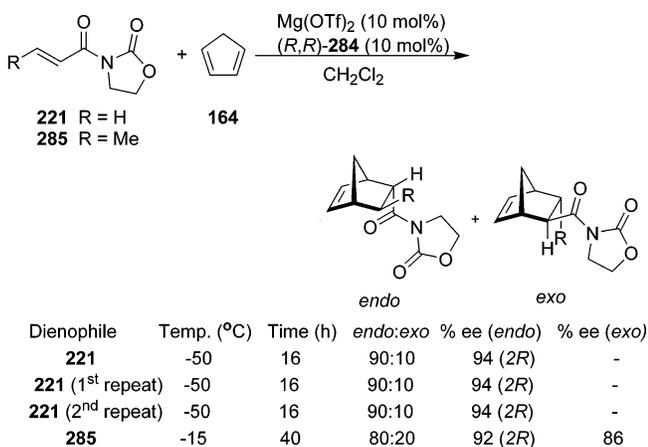
Of the bidentate bis(oxazoline) (box) ligands used in asymmetric catalysis, those (**283**) with a one carbon spacer as the link between the two oxazoline rings are the most frequently utilized, affording high



enantioselectivities in a range of metal-catalyzed reactions.<sup>1</sup> Variation of the nature, size, and flexibility of the link between the two oxazoline rings and the introduction and modification of oxazoline substituents have led to the development of novel chiral bidentate ligands and these are described here.

In 1998 Desimoni prepared both enantiomers of the bis(oxazoline) ligand **284**, with bulky 2-naphthyl groups at the 4-position of the oxazoline rings.<sup>132</sup> This ligand was examined in the Lewis acid-catalyzed Diels–Alder reaction of cyclopentadiene **164** and the *N*-alkenoyl-oxazolidin-2-ones **221** and **285** in an attempt to increase the enantiocontrol displayed by the (*R*)-Ph-box ligand **286a**. This aim was achieved by using different metal salts [Mg(HClO<sub>4</sub>)<sub>2</sub>, Mg(OTf)<sub>2</sub>, and Cu(OTf)<sub>2</sub>] as Lewis acid catalysts with ligand (*R,R*)-**284**. The catalyst derived from magnesium(II) triflate provided the *endo*-product with the highest levels of asymmetric induction giving 94 and 92% ee (*R*) for the reaction of **221** and **285**, respectively (Scheme 51). The opposite enantiomeric product [(*S*)-*endo*] was obtained in 77% ee when the counterion was changed to perchlorate. This reversal of enantioselectivity was attributed to the formation of a tetrahedral complex with magnesium(II) perchlorate

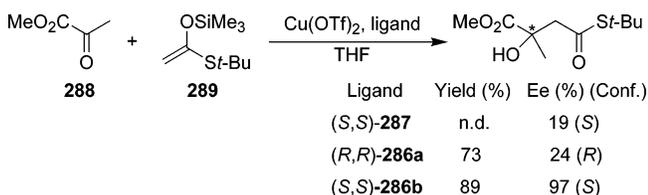
## Scheme 51



and an octahedral complex with magnesium(II) triflate. The low solubility of the ligand in polar aprotic solvents (ethyl acetate and diisopropyl ether) allowed for its easy recovery and subsequent reuse, giving reproducible results for the reaction of dienophile **221** in a further two catalytic reactions.

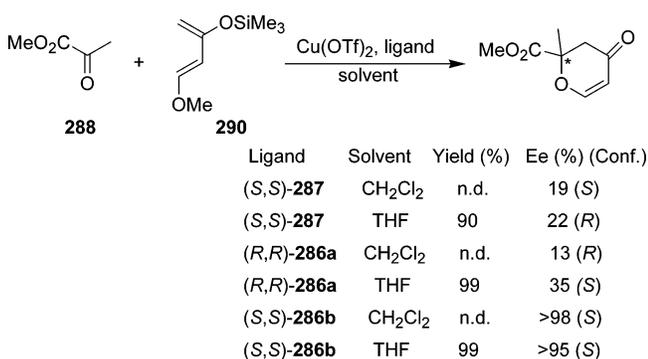
Rutjes investigated the influence of the oxazoline 4-substituent on enantiocontrol in a number of reactions by preparing the ligand (*S,S*)-**287**, which contains 1-naphthyl oxazoline substituents, and comparing the effectiveness of its Cu(II) complex as a Lewis acid catalyst to that of the analogous bis(oxazoline) ligands (*R,R*)-**286a** and (*S,S*)-**286b** bearing phenyl and *tert*-butyl groups, respectively.<sup>133</sup> In the Mukaiyama aldol reaction of methyl pyruvate **288** with the silyl ketene acetal **289** (Scheme 52) and

## Scheme 52



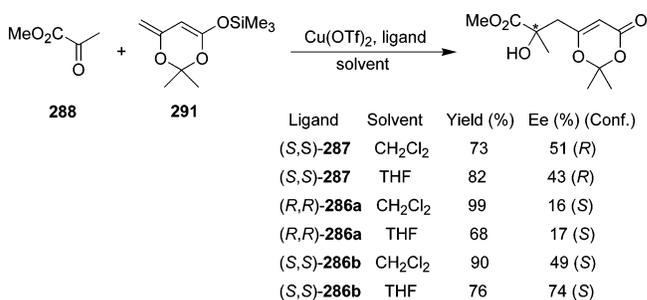
in the hetero-Diels–Alder reaction of **288** with Danishefsky's diene **290** [*E*]-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene] (Scheme 53), the Cu(OTf)<sub>2</sub>

## Scheme 53

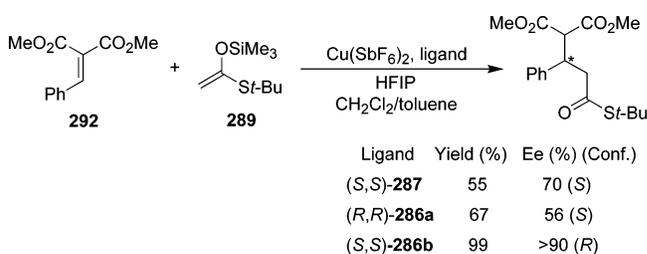


complexes of the 4-aryl-substituted ligands (*S,S*)-**287** and (*R,R*)-**286a** gave similar enantioselectivities (19–35% ee), but these were significantly lower than those obtained using the 4-alkyl-substituted ligand (*S*)-*t*

## Scheme 54



## Scheme 55



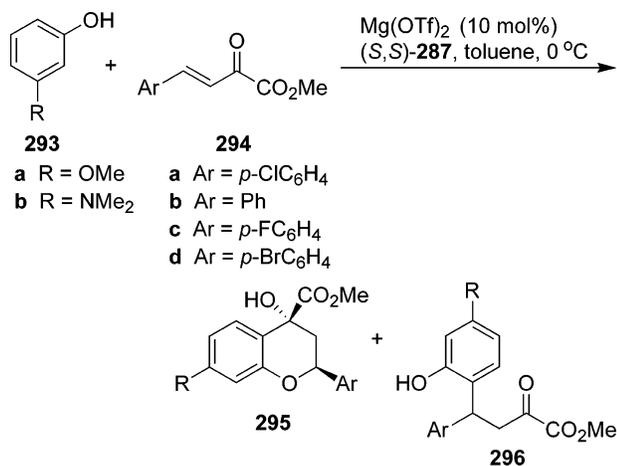
Bu-box **286b** (95–98% ee). In the hetero-Diels–Alder reaction, the sense of enantioinduction afforded by the aryl-substituted ligands was dependent on the solvent used.

The Cu(II) complex of the 1-naphthyl-substituted ligand (*S,S*)-**287** afforded higher levels of enantio-discrimination than that of the phenyl-substituted ligand (*R,R*)-**286a** in both the addition of the large silyl enol ether **291** to methyl pyruvate **288** (Scheme 54) and in the Mukaiyama–Michael addition of the silyl ketene acetal **289** to diester **292** (Scheme 55). However, these optimum enantioselectivities (51 and 70% ee) were still significantly lower than those obtained using the *tert*-butyl-substituted ligand (*S,S*)-**286b**. In the above two reactions and in the hetero-Diels–Alder reaction, a reversal of enantioselectivity with the 1-naphthyl-substituted ligand (*S,S*)-**287** compared to the alkyl-substituted ligand (*S,S*)-**286b** was observed. This effect was also seen in some cases with the phenyl-substituted ligand (*R,R*)-**286a**.<sup>133</sup> This reversal in the sense of asymmetric induction with aryl- and alkyl-substituted bis(oxazoline) ligands has been previously reported in the literature by Jørgensen and is thought to be due to differences in the flexibility and dynamics of the ligand.<sup>134</sup>

Ligand (*S,S*)-**287** was also applied in the novel enantio- and diastereoselective catalytic tandem reaction involving a Lewis acid-catalyzed oxa-Michael addition of phenols **293** to the  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **294** and a subsequent intramolecular Friedel–Crafts alkylation to form the chiral functionalized chromanes **295** (Scheme 56).<sup>135</sup>

Under optimized reaction conditions using magnesium(II) triflate as the Lewis acid catalyst and in the presence of the additive *p*-methyl-*N,N*-dimethylaniline (10 mol %), the 1-naphthyl-substituted bis(oxazoline) ligand (*S,S*)-**287** gave product **295** as a single diastereomer in 89% yield and 73% ee with <5% of the Friedel–Crafts *C*-alkylation side-product **296** for the reaction of *m*-methoxyphenol **293a** with the *p*-chlorophenyl-substituted  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester **294a**. Reactions of **293a** with a range of  $\beta,\gamma$ -

## Scheme 56

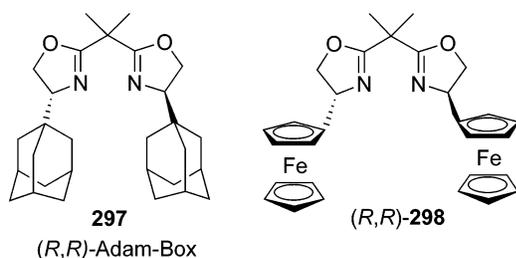
Table 34. Enantioselective Tandem Reaction Using Ligand  $(S,S)$ -**287** (Scheme 56)

entry	nucleophile	electrophile	yield (%) of <b>295</b>	ee (%)
1 <sup>a</sup>	<b>293a</b>	<b>294a</b>	89	73
2	<b>293a</b>	<b>294b</b>	67	73
3 <sup>a</sup>	<b>293a</b>	<b>294b</b>	77	80
4 <sup>a</sup>	<b>293a</b>	<b>294c</b>	43	74
5 <sup>a</sup>	<b>293a</b>	<b>294d</b>	45	66
6	<b>293b</b>	<b>294a</b>	>95	<18
7	<b>293b</b>	<b>294b</b>	>95	13

<sup>a</sup> 10 mol % of *p*-methyl-*N,N*-dimethylaniline added.

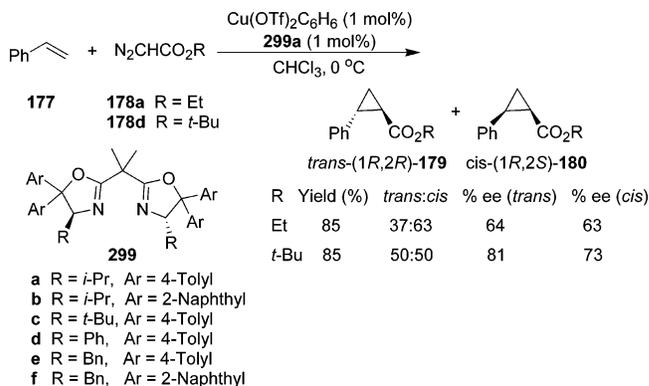
unsaturated  $\alpha$ -ketoesters **294b–c** proceeded with moderate yields (43–77%) but good enantioselectivities (66–80% ee), whereas the use of *m*-*N,N*-dimethylaminophenol **293b** as the nucleophile gave high yields of the product chromane but low enantioselectivities (13–18% ee) (Table 34). With *m*-methoxy-*N*-methylaniline as the nucleophile, the desired tetrahydroquinoline product was obtained exclusively but with no enantioselectivity.

Moreno-Mañas synthesized the bis(oxazoline) ligand  $(R,R)$ -Adam-Box **297**, which contains bulky adamantyl groups at the 4-position of the oxazoline rings.



Copper complexes of this ligand were tested in a number of reactions and gave similar results but enantiomeric products compared to those of the very efficient  $(S)$ -*t*-Bu-box **286b**.<sup>136</sup> Excellent enantioselectivities were obtained in the copper(I)-catalyzed cyclopropanation of 1,1-diphenylethene [75% yield and >98% ee (*S*)] and styrene **177** (56% yield, *trans/cis* 75:25, 94% ee ( $(S,S)$ -*trans*)] with ethyl diazoacetate **178a**, in the copper(II)-catalyzed Diels–Alder reaction of *N*-acryloyloxazolidin-2-one **221** with cyclopentadiene **164** [66% yield, *endo/exo* 92:8, 98% ee ( $(R,R,R)$ -*endo*)] and in the copper(I)-catalyzed allylic

## Scheme 57

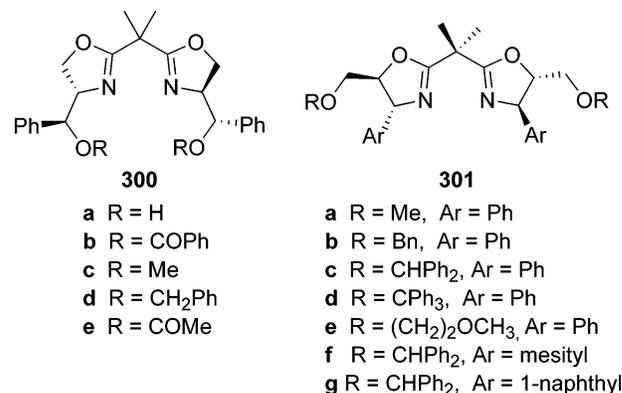


oxidation of cyclopentene **185** with *tert*-butyl perbenzoate **189** [82% ee (*R*)].

Moyano has applied the ferrocenyl-substituted bis(oxazoline) ligand **298** in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. Although high enantioselectivities were obtained (up to 92% ee), the activity of the palladium catalyst (4 mol %) (either preformed or generated in situ) was relatively low (20% yield after 92 h at room temperature).<sup>25</sup>

As part of a program aimed at generating *cis*-cyclopropanes, Gibson prepared a number of 5,5-diaryl-substituted bis(oxazoline) ligands **299** and investigated their application in the *cis*-selective cyclopropanation of styrene **177** with both ethyl and *tert*-butyl diazoacetate (**178a** and **178d**) using different copper(I) and copper(II) salts (Scheme 57).<sup>137</sup> The best results were obtained using copper(I) triflate and the isopropyl-substituted 5,5-ditoly ligand **299a** at  $0\text{ }^\circ\text{C}$ . Reaction with ethyl diazoacetate **178a** afforded a *trans*:*cis* ratio of 37:63 with enantioselectivities of 64 and 63% ee for the *trans* and *cis* isomers, respectively. Higher enantiodiscrimination, but lower isomer selectivity, was afforded with *tert*-butyl diazoacetate **178d**, giving *trans*- and *cis*-cyclopropane in a 1:1 ratio with ee values of 81 and 73%, respectively.

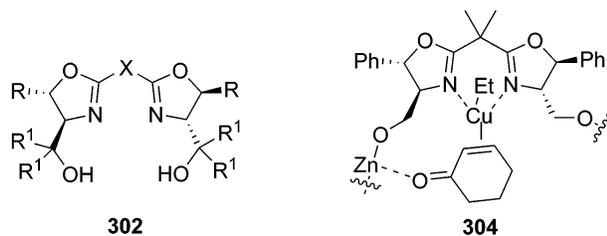
Bis(oxazoline) ligands **300**, which possess hydroxyalkyl and alkoxyalkyl groups at the stereogenic 4-position of the oxazoline rings, were used by Aït-Haddou in palladium-catalyzed allylic alkylation.<sup>138</sup> Moderate to high enantioselectivities (77–92% ee) and excellent yields (up to 99%) were obtained for the alkylation of 1,3-diphenyl-2-propenyl acetate **7** with sodium dimethyl malonate **8**. Surprisingly, the hydroxyalkyl-substituted ligand **300a** afforded a dif



ferent enantiomeric product [(*S*)-**9** in 92% ee and 98% yield] from the alkoxyalkyl-substituted ligands **300b–e** [(*R*)-**9** in 90% ee and 98% yield with **300b**]. From mechanistic investigations, the authors suggested that this reversal of enantioselectivity was due to hydrogen bonding between the dimethyl malonate anion and the hydroxy group of ligand **300a** inducing a change in the regioselectivity of the nucleophilic attack.

Using a range of chiral amino alcohols generated by the Sharpless asymmetric epoxidation of allylic alcohols and subsequent azide ring-opening and reduction, Pericàs prepared the bis(oxazoline) ligands **301** with aryl and alkoxyalkyl substituents at the 4- and 5-positions of the oxazoline rings, respectively. In general, these ligands provided excellent enantioselectivities (93–96% ee) in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with the nucleophile generated from dimethyl malonate **26**, BSA, and a catalytic amount of potassium acetate.<sup>139</sup> It was found that by increasing the steric bulk of both oxazoline substituents in these ligands, the catalytic activity of the respective palladium complexes increased [up to 100% conversion after 48 h at room temperature with [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)**301g**]PF<sub>6</sub> (2 mol %)]. It was suggested that the increased steric bulk of the oxazoline substituents causes an increased interaction of the C-4 substituent with the allyl substrate resulting in the allyl group desymmetrizing with respect to palladium, leading to a more electrophilic carbon atom which is more efficiently attacked by the malonate nucleophile.

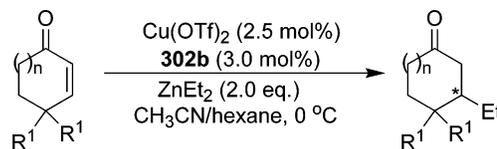
Because of the failure of the bis(oxazoline) ligand (*S,S*)-**286b** to induce asymmetry in the copper-catalyzed addition of diethylzinc to cyclohexenone **158**, Reiser suggested that a ligand capable of providing an asymmetric environment for both the copper and zinc atoms could be beneficial for enantioselective. Thus, ligands **302**, with a hydroxyalkyl



- 302**
- a** R = Ph, R<sup>1</sup> = H, X = CH<sub>2</sub>  
**b** R = Ph, R<sup>1</sup> = H, X = CMe<sub>2</sub>  
**c** R = *p*-MeS-Ph, R<sup>1</sup> = H, X = CMe<sub>2</sub>  
**d** R = H, R<sup>1</sup> = Me, X = CMe<sub>2</sub>  
**e** R = H, R<sup>1</sup> = Ph, X = CMe<sub>2</sub>  
**f** R = Ph, R<sup>1</sup> = H, X = (CH<sub>2</sub>)<sub>2</sub>

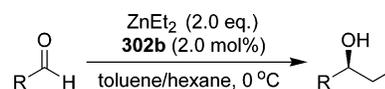
group as the oxazoline 4-substituent, which could provide two spatially separated coordination sites for zinc and copper, were prepared. These ligands promoted the addition of diethylzinc to cyclohexenone **158** with moderate yields (43–93%) and greatly varied enantioselectivities (0–94% ee), with the best result of 93% yield and 94% ee being attained by

### Scheme 58



	<b>158</b> n = 1, R <sup>1</sup> = H	Enone	Time (h)	Yield (%)	Ee (%)
	<b>159</b> n = 2, R <sup>1</sup> = H	<b>158</b>	20	93	94 ( <i>S</i> )
	<b>303</b> n = 1, R <sup>1</sup> = Me	<b>159</b>	21	71	41
		<b>303</b>	140	42	8

### Scheme 59



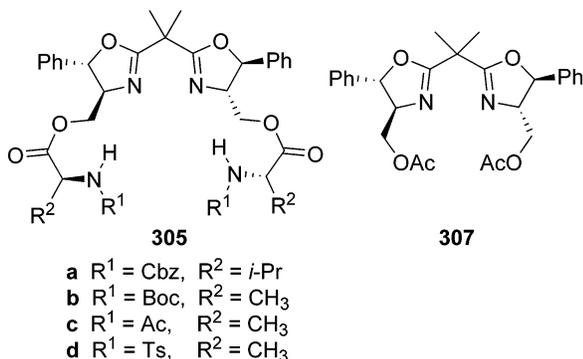
**Table 35. Asymmetric Diethylzinc Addition to Aldehydes Using Ligand 302b (Scheme 59)**

entry	R	<i>n</i> -BuLi (mol %)	time (h)	yield (%)	ee (%) (conf)
1	Ph	0	45	96	93 ( <i>S</i> )
2	<i>p</i> -MeOPh	0	50	99	95 ( <i>S</i> )
3	<i>p</i> -ClPh	0	45	76	83 ( <i>S</i> )
4	<i>p</i> -ClPh	4	90	92	87 ( <i>S</i> )
5	<i>p</i> -FPh	0	89	74	88 ( <i>S</i> )
6	<i>p</i> -FPh	4	90	84	87 ( <i>S</i> )
7	<i>n</i> -Hex	0	90	31	36 ( <i>S</i> )
8	<i>n</i> -Hex	2	100	60	66 ( <i>S</i> )
9	<i>n</i> -Hex	4	25	78	75 ( <i>S</i> )
10	<i>n</i> -Hex	6	25	68	47 ( <i>S</i> )
11	<i>n</i> -Hex	7	25	61	38 ( <i>S</i> )

ligand **302b** at 0 °C (Scheme 58).<sup>140</sup> The importance of ligand binding to both copper and zinc was apparent from the low enantioselectivities (0 and 32% ee) obtained with additives (TMSCl or water) capable of disturbing the coordination of the hydroxy group of the ligand to zinc. Ligand **302b** showed a low substrate tolerance, giving significantly lower enantiodiscrimination of 41 and 8% ee for the addition of diethylzinc to cycloheptenone **159** and the 4,4-dimethyl-substituted cyclohexenone **303**, respectively. In addition, 1,4-phenylation of cyclohexenone **158** was achieved in 73% yield and 74% ee (*S*) using Cu(OTf)<sub>2</sub> (10 mol %), ligand **302b** (15 mol %), and a 1:3 mixture of diphenyl- and dimethylzinc at 0 °C. Reiser postulated that the restricted coordination in the bimetallic complex **304**, in which the cyclohexenone substrate is locked in a two-point binding mode via a zinc and copper atom, could explain the high enantiocontrol in the alkyl transfer along with the limited substrate tolerance.

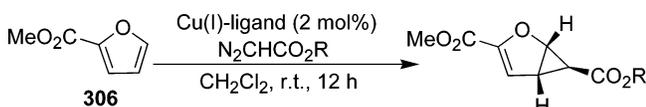
Ligand **302b** was also effective in the asymmetric addition of diethylzinc to a range of aldehydes. High enantioselectivities (83–95% ee) were obtained with aromatic aldehydes, whereas both the yield and enantioselectivity, in the case of the aliphatic hexanal, increased with the addition of catalytic amounts of butyllithium (up to 78% yield and 75% ee with 4 mol % of *n*-BuLi) (Scheme 59 and Table 35).<sup>140</sup>

In 2003 Reiser investigated the use of ligands **302b** and **305**, which possess secondary binding sites, in copper(I)-catalyzed asymmetric cyclopropanation.<sup>141</sup> With methyl furancarboxylate **306** as the substrate, cyclopropanation with methyl or ethyl diazoacetate



took place at the lesser substituted (more electron rich) double bond, yielding the *exo*-product exclusively in moderate yields (33–46%) and good enantioselectivities (62–91% ee) (Scheme 60 and Table 36). It was

#### Scheme 60

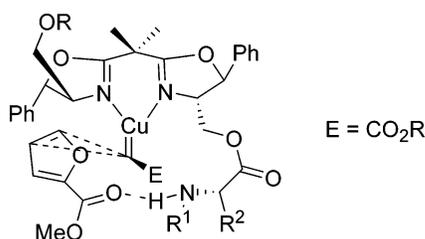


**Table 36. Asymmetric Copper(I)-Catalyzed Cyclopropanation of 306 with Methyl and Ethyl Diazoacetate Using Ligands 302b, 305, and 307 (Scheme 60)**

entry	ligand	diazoacetate	yield (%)	ee (%)
1	<b>302b</b>	methyl	45	69
2	<b>307</b>	methyl	46	45
3	<b>305a</b>	methyl	41	62
4	<b>305b</b>	methyl	43	77
5	<b>305d</b>	methyl	39	88
6	<b>305b</b>	ethyl	42	83
7	<b>305c</b>	ethyl	33	85
8	<b>305d</b>	ethyl	36	91

suggested that the hydrogen donor groups (hydroxy and amino groups) of the oxazoline 4-substituents of ligands **302b** and **305** can form a hydrogen bond with the carbomethoxy group of the furan substrate, thus controlling the direction of approach of the substrate to the metal active site and differentiating between the enantiotopic faces of the double bond (Scheme 61).

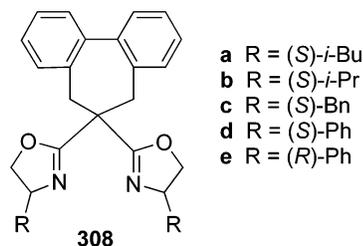
#### Scheme 61



This was evident by the increase in the asymmetric induction obtained using ligands **305** with hydrogen-bonding groups of increasing strength (Table 36, entries 3–5 and 6–8) and by the lower enantioselectivity obtained using ligand **307** (compared to **302b**) in which the possibility of hydrogen bonding was removed (Table 36, entry 2 vs entry 1). Much lower levels of enantiocontrol were afforded by ligands **302b**, **305**, and **307** for the cyclopropanation (with methyl diazoacetate) of styrene **177** [up to 46% ee

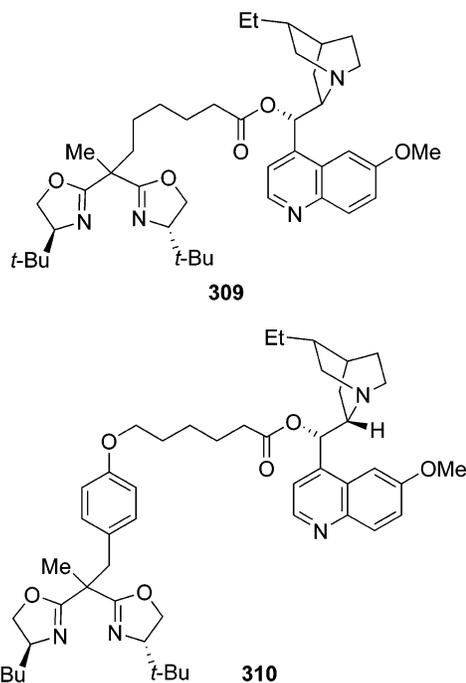
(*trans*) and 58% ee (*cis*)] and the heterocyclic substrates 2,3-dihydrofuran **15** [up to 25% ee (*exo*) and 37% ee (*endo*)] and *N*-BOC-pyrrole [up to 46% ee (*endo*)], substrates that lack directing carbomethoxy groups adjacent to the heteroatom.

Du has reported the synthesis of ligands **308** in which the two oxazoline rings are linked by a dibenzo[*a,c*]cycloheptadiene unit. These ligands were employed in the copper(I)-catalyzed asymmetric cyclopropanation of styrene **177** with different diazoacetates.<sup>142</sup> The isobutyl-substituted derivative **308a** was the



ligand of choice, giving the *trans* and *cis*-products in 68 and 55% ee, respectively, with a *trans/cis* ratio of 62:38 for the reaction with ethyl diazoacetate **178a**. Higher levels of asymmetric induction were obtained using the bulkier *tert*-butyl diazoacetate **178d** [76% ee (*trans*) and 61% ee (*cis*), *trans/cis* 66:34] and with the enantiopure *l*-menthyl diazoacetate **178b** [82% ee (*trans*) and 64% ee (*cis*), *trans/cis* 68:32].

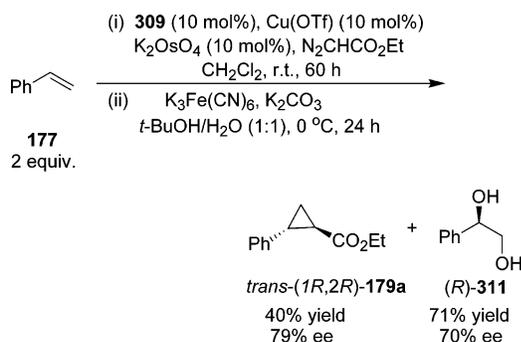
Benaglia has reported the synthesis of the bifunctional ligands **309** and **310** containing a bis(oxazoline) moiety connected to a dihydroquinidine residue and has applied these ligands in sequential asymmetric catalysis.<sup>143,144</sup>



Ligand **309** was employed in the presence of Cu(I) and Os(VIII) species to promote the cyclopropanation and dihydroxylation of different molecules of styrene **177** in a single reaction flask, affording cyclopropane

**179a** and diol **311** in 79 and 70% ee, respectively (Scheme 62).<sup>143</sup>

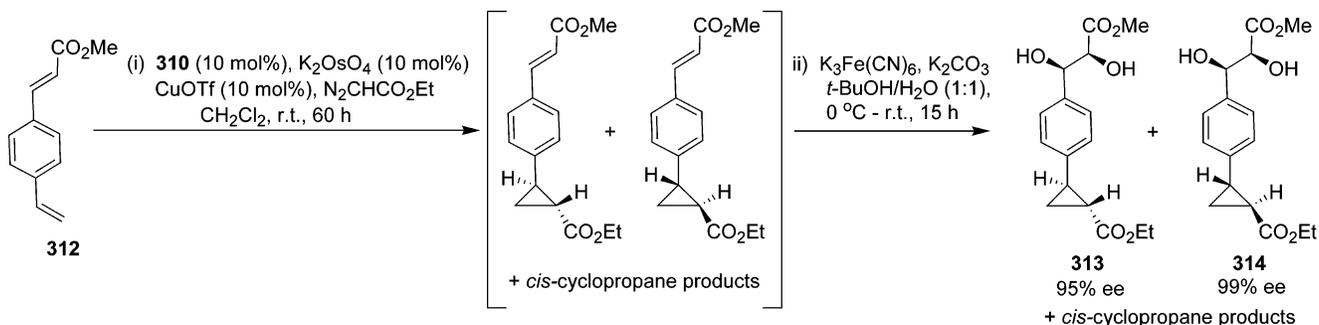
### Scheme 62



Ligand **310**, on coordination with potassium osmate and copper(I) triflate, was used to promote asymmetric cyclopropanation and dihydroxylation at different sites of the substrate, methyl (*E*)-3-(4-vinylphenyl)propenoate **312**, in a sequential fashion (Scheme 63). In a one-flask procedure, substrate **312** first underwent copper(I)-catalyzed cyclopropanation at the electron-rich double bond and then dihydroxylation at the electron-poor alkene to afford a product containing four stereocenters with complete regio-control and high stereoselectivity. The *trans*-cyclopropane products were isolated in 20% yield as a 75:25 mixture of diastereomers (**313** and **314**) with excellent enantiodiscrimination of 95 and 99% ee, respectively. In addition, ligand **310** was recovered unchanged in 91% yield during the chromatographic separation of the products.<sup>144</sup>

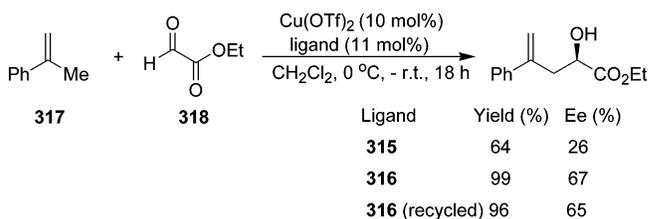
By introducing perfluoroalkyl-substituted groups into the backbone of bis(oxazoline) ligands, Benaglia also prepared derivatives **315** and **316**, with different fluorine contents and solubility properties, which could easily be recycled in two different catalytic asymmetric reactions.<sup>145</sup> These ligands were investigated in both the copper(II)-catalyzed ene reaction between  $\alpha$ -methylstyrene **317** and ethyl glyoxylate **318** (Scheme 64) and in the copper(I)-catalyzed cyclopropanation of styrene **177** with ethyl diazoacetate **178a** (Scheme 65) and in both cases ligand **316**, with the fewer number of perfluorinated ponytails, afforded the highest levels of enantioselection [67% ee and 78% ee (*trans*), respectively]. Recovery of these

### Scheme 63

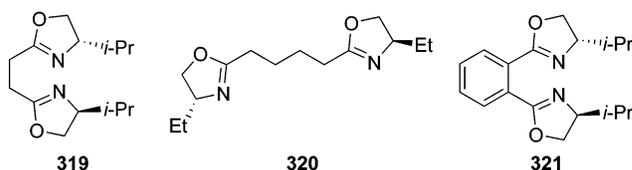
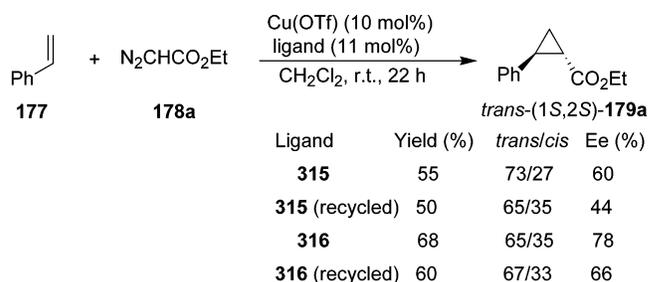


perfluorinated ligands was achieved by either filtration through silica gel (ligand **316**) or extraction into a perfluorinated solvent (ligand **315**). Recycling of ligand **316** in the ene reaction was successful, resulting in little change in both the yield and enantioselectivity, whereas the decrease in enantioselectivity and yield observed in the cyclopropanation using recycled ligands was attributed to ligand contamination by ethyl diazoacetate decomposition products.

### Scheme 64

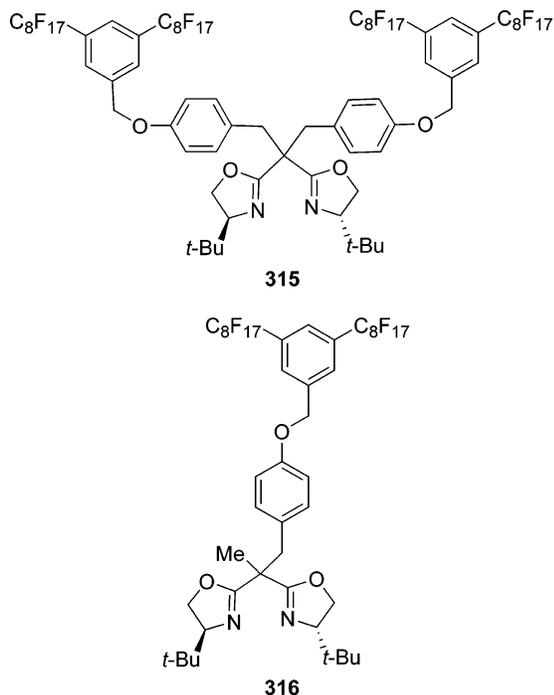


### Scheme 65



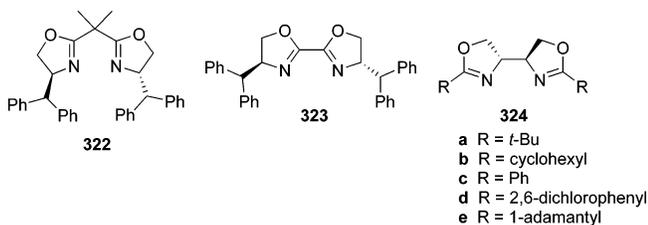
Gómez investigated the catalytic behavior of rhodium, iridium, and ruthenium complexes of a number of C<sub>2</sub>-symmetric bis(oxazoline) ligands **319**–**321**, containing aliphatic and aromatic backbones, in the asymmetric hydrogenation, transfer hydrogenation, and hydrosilylation of acetophenone **40**.<sup>146</sup> In all three reduction processes, the majority of the catalytic systems gave only low enantioselectivities (up to 38% ee), although moderate asymmetric induction [50% ee (*S*) and 89% conversion after 6 h at 50 °C with 2 mol % Ir] was afforded in the iridium-catalyzed hydrosilylation reaction with diphenylsilane using

20% yield of *trans*-cyclopropane products  
d.r. 75:25 (**313**:**314**)



ligand **319**. In general, ligands (**319** and **321**) with a two-carbon link between the two oxazoline rings afforded the best results in terms of catalytic activity and enantioselectivity.

Kanemasa has prepared the bis(oxazoline) ligand **322** and the bi(oxazoline) ligand **323** bearing bulky 4-diphenylmethyl substituents and has applied these ligands in the asymmetric Lewis acid-catalyzed Di-

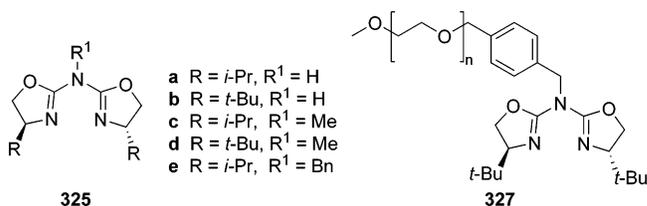


els–Alder reaction of cyclopentadiene **164** with 3-acryloyl-2-oxazolidinone **221**.<sup>147</sup> Of the various metal salts and ligands used, the nickel(II) aqua complex (10 mol %) generated from Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and ligand **322** proved to be optimum, affording a 93:7 mixture of *endo*-**222** and *exo*-**223** cycloadducts in 96% yield with 78% ee (*R*) for the *endo*-product at -40 °C in dichloromethane. The use of copper(II) triflate as the Lewis acid, which had previously given >98% ee in this reaction with the *tert*-butyl-substituted ligand (*S,S*)-**286b**, gave the enantiomeric *endo*-product in only 35% ee using ligand **322**.

The bi(oxazoline) ligands **324**, derived from *L*-tartaric acid, were applied in the Cu(I)-catalyzed asymmetric cyclopropanation of both 1,1-diphenylethylene and styrene **177** with ethyl diazoacetate **178a**.<sup>148</sup> In these reactions, the presence of molecular sieves was found to be essential for high catalytic activity. The Cu(I) complex (2 mol %), formed from the adamantyl-substituted ligand **324e** and copper(I) triflate, afforded the best results of 86% yield and 78% ee (*S*) for the cyclopropanation of 1,1-diphenylethylene and 41% yield with a *trans/cis* ratio of 67:

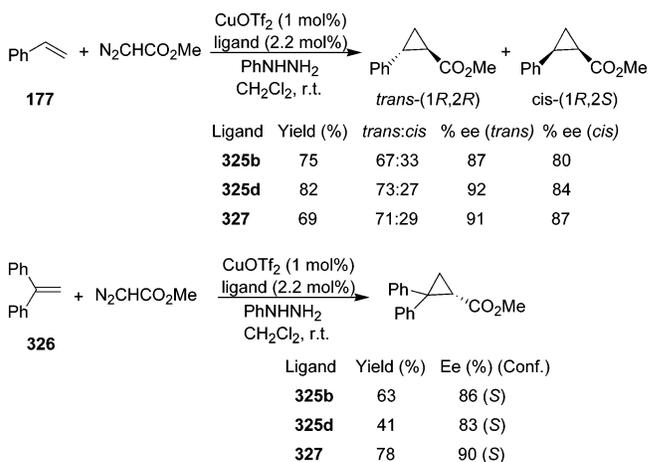
33 and enantioselectivities of 60% ee for the *trans*-isomer (*1S,2S*)-**179a** and 79% ee for the *cis*-isomer (*1S,2R*)-**180a** for the reaction with styrene **177**.

Reiser has reported the synthesis of aza-bis(oxazoline) ligands **325**, in which a single nitrogen atom connects the two oxazoline rings. These ligands were tested for their enantiocontrolling ability in palladium-catalyzed allylic alkylation and copper-catalyzed cyclopropanation.<sup>149</sup> Although no product was obtained using the secondary amine ligands **325a** and **325b** in the palladium-catalyzed alkylation of



1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**, high enantioselectivity [97% ee (*R*) with both **325c** and **325d**] was achieved, albeit with low catalytic activity (66 and 38% yield, respectively, after 165 h at room temperature with 5 mol % Pd), using the *N*-alkylated aza-bis(oxazoline) ligands **325c** and **325d**. The alkylated and nonalkylated *tert*-butyl-substituted bis(oxazoline) derivatives **325b** and **325d** were the most effective ligands for the copper(I)-catalyzed asymmetric cyclopropanation of both styrene **177** and 1,1-diphenylethylene **326** with methyl diazoacetate, affording good diastereo- and enantioselectivities (Scheme 66).

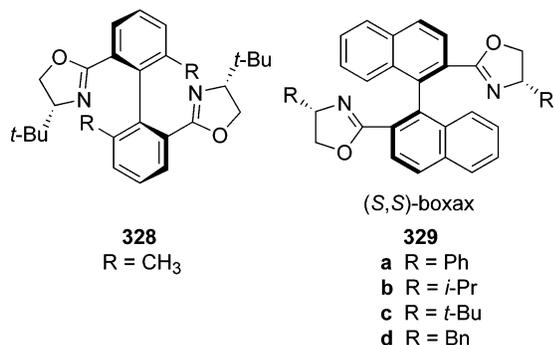
#### Scheme 66



Reiser also prepared a soluble polymer-supported ligand **327** by attaching the *tert*-butyl-substituted ligand **325b** to methoxypoly(ethylene glycol) (MeO-PEG). This ligand induced high enantiodiscrimination in the cyclopropanation of both **177** and **326** with methyl diazoacetate, giving similar results compared to the unbound ligand **325d** (Scheme 66). The Cu(I)-catalyst generated in situ from the polymeric ligand **327** was recycled a total of 13 times, maintaining a very high level of enantioselection [87–90% ee (*trans*) and 81–85% ee (*cis*)] for the cyclopropanation of styrene **177**.<sup>149</sup>

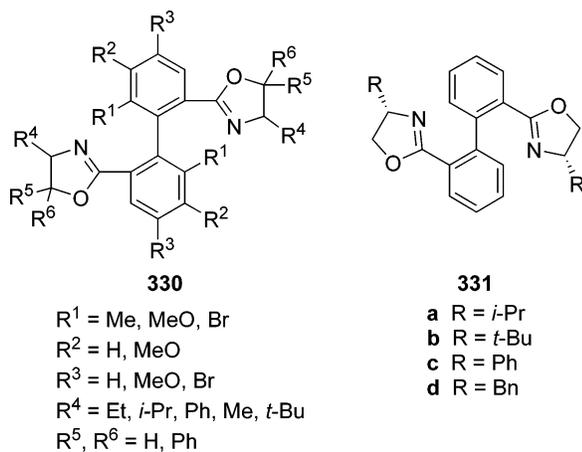
## 3.1.2. Bis(oxazoline) Ligands with a Stereoaxis

Ligands **328** and **329**, with a biphenyl and binaphthyl backbone, respectively, were the first stereoaxis-containing bis(oxazoline) ligands to be employed in



asymmetric catalysis, affording high enantioselectivities in a number of reactions.<sup>1,150,151</sup> In recent years, modification of these general ligand structures has led to the development of a number of novel chiral ligands with a stereoaxis.

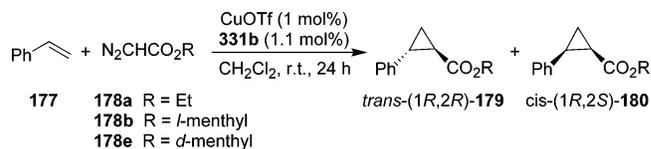
Rippert prepared a large array of bis(phenyl) analogues **330** with different substitution patterns on the oxazoline and phenyl rings and investigated the steric and electronic properties of these ligands on asymmetric induction in the copper(I)-catalyzed cyclopropanation of styrene **177** with ethyl diazoacetate **178a**.<sup>152</sup> In general, it was found that the enantioselectivity increased with the presence of sterically demanding groups at the 5-position of the oxazoline rings and with the introduction of electron-donating groups on the biphenyl backbone. The best



enantioselectivities were achieved with the matched diastereomer **330** (with R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = OMe, R<sup>4</sup> = (*S*)-*t*-Bu, and R<sup>5</sup>, R<sup>6</sup> = H) affording 88% ee for *trans*-**179a** and 89% ee for *cis*-**180a** with a *trans/cis* ratio of 67:33.

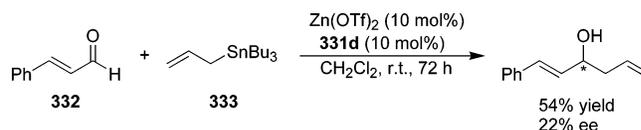
Ikeda reported the synthesis of ligands **331** bearing an axis-unfixed biphenyl backbone.<sup>153</sup> <sup>1</sup>H NMR studies revealed that these ligands exist as an equilibrium mixture of diastereomers in solution as a result of rotation around the internal bond of the biphenyl backbone. On complexation of ligands **331** with various metal salts, a single diastereomeric metal complex was obtained for all ligands with copper(I) salts (CuOTf, CuCl, and CuI), whereas only the bulky

## Scheme 67



Diazoacetate	Yield (%)	<i>trans</i> : <i>cis</i>	% ee ( <i>trans</i> )	% ee ( <i>cis</i> )
<b>178a</b>	69	68:32	74	84
<b>178b</b>	60	81:19	84	92
<b>178e</b>	58	87:13	89	82

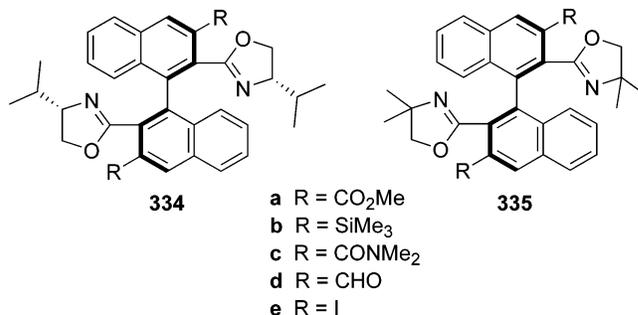
## Scheme 68



*tert*-butyl-substituted ligand **331b** afforded only one of the two possible diastereomeric complexes with palladium(II) chloride, silver(I) triflate, and zinc(II) salts [Zn(OTf)<sub>2</sub>, ZnCl<sub>2</sub>, ZnI<sub>2</sub>]. In the Cu(I)-catalyzed cyclopropanation of styrene **177** with different diazoacetates **178**, ligands **331** yielded the *trans*-cyclopropane **179** as the major product and afforded moderate to good enantioselectivities (21–92% ee), with the *cis*-product **180** being obtained in higher enantiomeric excess than the *trans*-product. The *tert*-butyl-substituted derivative **331b** was the ligand of choice, furnishing the highest level of asymmetric induction for all three diazoacetates (Scheme 67).

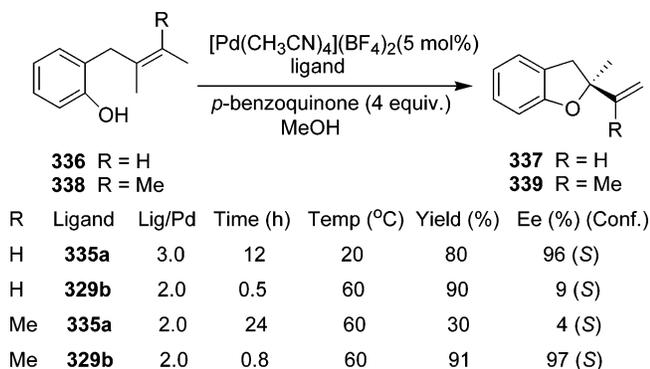
Ligands **331** were also tested in the zinc(II)-catalyzed allylation of *trans*-cinnamaldehyde **332** with allyltri-*n*-butyltin **333** (Scheme 68).<sup>153</sup> The reaction proceeded in moderate to high yields (35–69%), with the best enantioselectivity of 22% ee being obtained with ligand **331d** and zinc(II) triflate. Although the *tert*-butyl-substituted ligand **331b** formed only one diastereomeric complex with zinc(II), it afforded only racemic product in this reaction.

By way of modification of the (*S,S*)-boxax ligands **329**, which have induced high enantiocontrol in copper(I)-catalyzed cyclopropanation<sup>150a</sup> and in palladium(II)-catalyzed Wacker-type cyclizations,<sup>151</sup> Hayashi has prepared ligands **334** and **335** containing



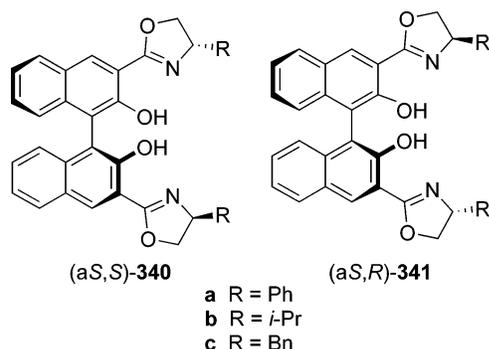
functional groups in the 3- and 3'-positions of the binaphthyl skeleton.<sup>154</sup> Ligands **334** and **335** were examined for asymmetric induction in the palladium(II)-catalyzed Wacker-type cyclization of the trisubstituted olefin (*E*)-2-(2-methyl-2-butenyl)phenol **336**, forming the 2,3-dihydrobenzofuran **337** (Scheme 69). Ligand **335a**, with *gem*-dimethyl groups at the oxazoline 4-positions and methoxycarbonyl groups at

## Scheme 69



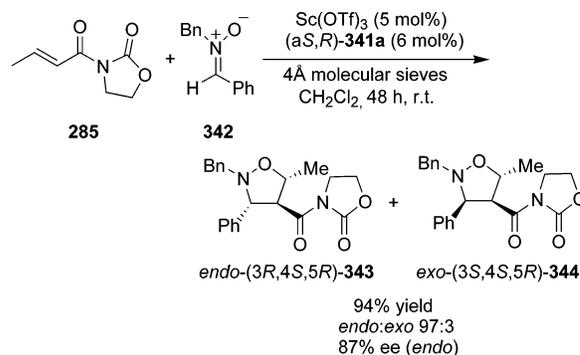
the C3- and C3'-positions of the binaphthyl skeleton, was optimal, affording product **337** in 90% yield and 67% ee (*S*) at 60 °C. The enantioselectivity was increased to 96% ee (*S*) on running the reaction at the reduced temperature of 20 °C with an increased ligand-to-palladium ratio of 3:1. Using ligand **335a**, the cyclization of the tetrasubstituted *o*-allylphenol **338** proceeded with both low catalytic activity and enantioselection [30% yield and 4% ee (*S*) at 60 °C after 24 h].<sup>154</sup> The results furnished by ligand **335a** were complementary to those obtained with the isopropyl-substituted (*S,S*)-boxax ligands **329b**, which gave a high enantioselectivity of 97% ee (*S*) for the reaction with the tetrasubstituted substrate **338** but a low enantiodiscrimination of 9% ee (*S*) for the cyclization of the trisubstituted *o*-allylphenol **336**.<sup>151b</sup>

The (*S*)-BINOL-derived bis(oxazoline) ligands **340** and **341**, with stereogenic oxazoline units at the 3- and 3'-positions of the binaphthyl skeleton, were



applied by Ohta in the lanthanide-catalyzed 1,3-dipolar cycloaddition of *N*-benzylidenebenzylamine *N*-oxide **342** to 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **285**.<sup>155</sup> Excellent diastereoselectivity and good enantioselectivity [*endo/exo* 97:3 and 87% ee (*endo*-(3*R*,4*S*,5*R*))] were obtained using scandium triflate (5 mol %) and the matched diastereomeric ligand (*a,S,R*)-**341a** in the presence of 4 Å molecular sieves (Scheme 70). The magnitude and sense of the asymmetric induction was highly dependent on the lanthanide triflate used, the nature of the oxazoline substituent, and the presence of an additive (4 Å molecular sieves, H<sub>2</sub>O, MgSO<sub>4</sub>, or alcohols). This dependence was attributed to different coordination modes of the ligand, through the two hydroxyl groups, in the lanthanide intermediate.

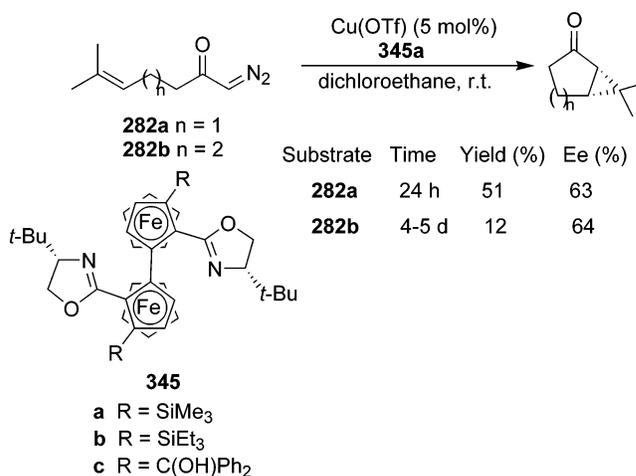
## Scheme 70



## 3.1.3. Bis(oxazoline) Ligands with a Stereoplane

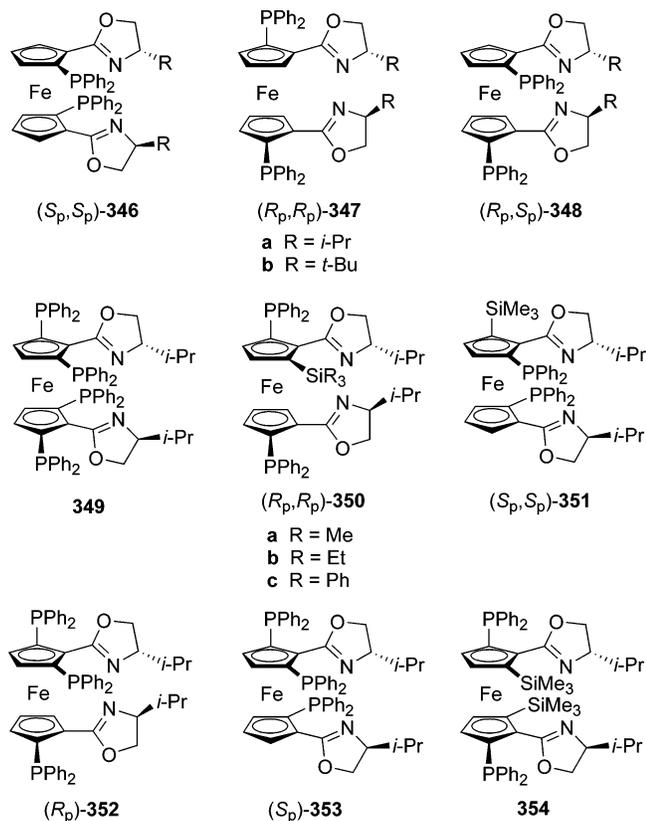
Copper(I) complexes of the bis(oxazolinyl)biferrocene ligands **345** have been utilized by Ahn in both inter- and intramolecular copper(I)-catalyzed asymmetric cyclopropanation.<sup>156,157</sup> Excellent enantioselectivities of 99% ee [*cis*-(1*R*,2*S*)-**180b**] and 90% ee [*trans*-(1*R*,2*R*)-**179b**] with a *cis/trans* selectivity of 23:77 were afforded by the silylated derivatives **345a** and **345b** for the reaction between styrene **177** and *l*-menthyl diazoacetate **178b**.<sup>156</sup> Copper(I)-catalyzed intramolecular cyclopropanation of ene-diazoacetates **282a** and **282b** using ligand **345a** proceeded with moderate levels of enantiodiscrimination (up to 64% ee) but with low reaction rates (Scheme 71). Only

## Scheme 71



12% yield was obtained for the cyclopropanation of 1-diazo-7-methyl-6-octen-2-one **282b** after a reaction time of 4–5 days. The enantioselectivity was dependent on the substrate used, with only 25% ee being obtained for the reaction with 1-diazo-5-hexen-2-one.<sup>157</sup>

1,1'-Bis(diphenylphosphino)-2,2'-bis(oxazolinyl)ferrocene ligands **346–348** were investigated by Park in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>158</sup> The palladium catalysts, generated in situ from ligands (*S<sub>p</sub>,S<sub>p</sub>*)-**346b** and (*R<sub>p</sub>,S<sub>p</sub>*)-**348a,b** and [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (1 mol %), were highly efficient, affording product [(*S*)-**9**] in almost quantitative yield (after 10 and 30 min at room temperature) with 94 and 99% ee, respectively. Ikeda has achieved an enantioselectivity of 99% ee (*S*) for this reaction using



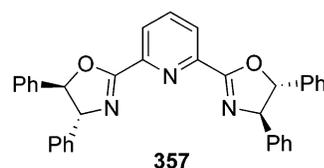
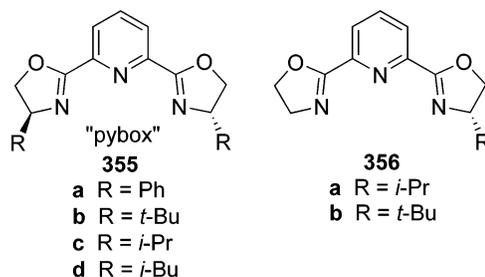
ligand ( $S_p, S_p$ )-**346b** and sodium dimethyl malonate as the nucleophile under slightly different reaction conditions.<sup>159</sup>

Ligands **349–354**, prepared by *ortho*-silylation and phosphorylation of compounds **346–348**, were also examined in the palladium-catalyzed alkylation of **7** with **26**.<sup>160</sup> In all cases, the allylic alkylation product was accessed in almost quantitative yield after 10 min at room temperature and, apart from the tetraphosphorylated derivative **349** and the disilylated derivative **354**, these ligands afforded very high enantioselectivities (88–96% ee). A reversal of enantioselection in favor of the (*R*)-allylic alkylation product was observed with ligands ( $R_p, R_p$ )-**350** and ( $R_p$ )-**352** [89–91 and 88% ee (*R*), respectively], compared to ligands ( $R_p, R_p$ )-**347a** and ( $R_p, S_p$ )-**348a**, which afforded the (*S*)-product in 38 and 99% ee, respectively. An X-ray crystal structure of the  $\pi$ -allylpalladium complex of ligand ( $S_p, S_p$ )-**346b** revealed that the ligand coordinated in a bidentate fashion through the two phosphorus atoms, whereas <sup>31</sup>P NMR studies suggested that *P,P*- and *P,N*-chelations were predominant in (1,3-diphenylallyl)palladium complexes of ligands ( $S_p, S_p$ )-**351** and ( $R_p, R_p$ )-**350**, respectively.<sup>160</sup>

## 3.2. Tridentate Bis(oxazoline) Ligands

### 3.2.1. Bis(oxazoline) *N,N,N*-Ligands

The introduction of a donor atom into the link between two stereogenic oxazoline rings has led to the development of tridentate bis(oxazoline) ligands. Nishiyama's "pybox" derivatives **355**, which have been used successfully in various asymmetric reactions, represent the best-known examples of this class of ligands. They induce high enantiocontrol in copper-



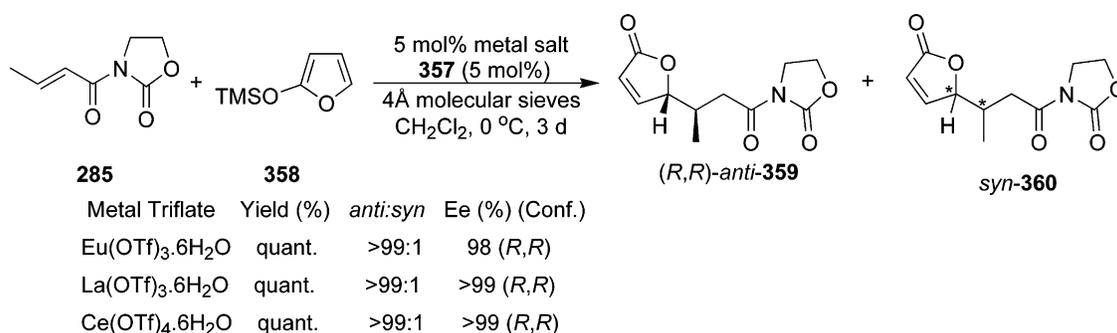
(II)-catalyzed Diels–Alder reactions, ruthenium(II)-catalyzed cyclopropanation of olefins, and rhodium(III)-catalyzed hydrosilylation of ketones.<sup>1</sup> In recent years, "pybox ligands" have also been applied in copper(I)-catalyzed oxidations of allylic and benzylic compounds,<sup>161</sup> copper(II)-catalyzed 1,3-dipolar cycloaddition reactions of nitrones with electron-rich alkenes,<sup>162</sup> palladium(II)-catalyzed resolution of racemic tosylaziridines,<sup>163</sup> copper(I)-catalyzed [2,3]-sigmatropic rearrangement of sulfur ylides,<sup>164</sup> tin(II)- and copper(II)-catalyzed aldol reactions,<sup>165,166</sup> copper(I)-catalyzed addition of terminal alkynes to imines,<sup>167</sup> lanthanide(III)-catalyzed glyoxylate-ene reactions,<sup>168</sup> scandium(III)-catalyzed Diels–Alder reactions,<sup>169</sup> and scandium triflate-catalyzed addition and annulation reactions of allenylsilanes with ethyl glyoxylate.<sup>170</sup>

In 1998 Nishiyama showed that the unsymmetrical ligands **356**, containing a single stereocenter, could facilitate high enantiodiscrimination in the ruthenium(II)-catalyzed asymmetric cyclopropanation of styrene **177** with various diazoacetates.<sup>171</sup> The best results were afforded by the *tert*-butyl-substituted ligand **356b** for the reaction with *l*-menthyl diazoacetate **178b**, providing 94% ee for the *trans*-product [(1*R*,2*R*)-**179b**] and 64% ee for the *cis*-product [(1*R*,2*S*)-**180b**] with 84% yield and a *trans/cis* ratio of 99:1. A lower enantioselectivity of 62% ee was obtained for the reaction of 1,1-diphenylethylene with *d*-menthyl diazoacetate **178e**, whereas 1,2-disubstituted olefins such as *trans*-1,2-diphenylethylene, *trans*-1,2-diethylethylene, and dihydronaphthalene gave no cyclopropanation products.

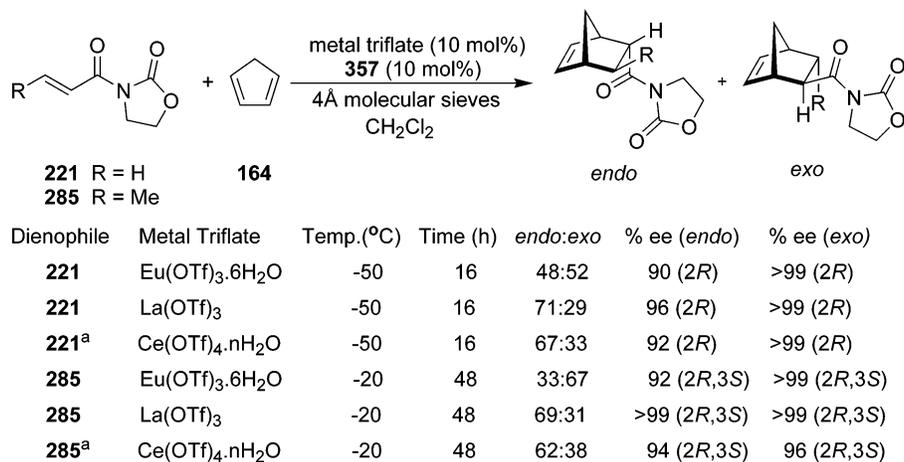
The tridentate bis(oxazoline) pybox ligand **357**, with *trans*-4,5-diphenyl substitution of the oxazoline rings, was prepared by Desimoni and utilized in the lanthanide-catalyzed Mukaiyama–Michael and Diels–Alder reactions.<sup>172,173</sup> For the Mukaiyama–Michael reaction between 2-(trimethylsilyloxy)furan **358** and 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **285**, catalysts derived from ligand **357** and lanthanide triflates [Eu(III), La(III), and Ce(IV)] gave the *anti*-product (*R,R*)-**359** in quantitative yield with excellent enantioselectivity (>98% ee) (Scheme 72).<sup>172</sup>

With the aim of achieving an *exo*-selective asymmetric Diels–Alder reaction, Desimoni used ligand **357**, together with different inorganic salts, in the reaction of acryloyl-1,3-oxazolidin-2-one **221** and cyclopentadiene **164** (Scheme 73). Although Mg(II), Co-

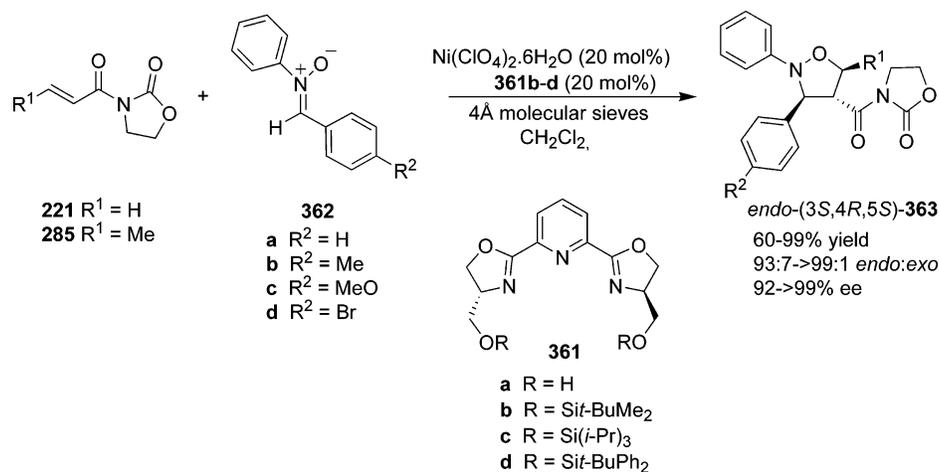
## Scheme 72



## Scheme 73

<sup>a</sup> 4Å molecular sieves not added

## Scheme 74



(II), Zn(II), Yb(III), and Sc(III) cations generated catalysts that afforded the *endo*-product with high diastereo- and enantioselectivity (up to 98:2 *endo/exo* and 84% ee), La(III), Eu(III), and Ce(IV) triflates gave up to 50% yield of the desired *exo*-product as a single enantiomer (>99% ee). For the reaction with 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **285**, significant amounts of the *exo*-product [up to 67% yield with Eu(III)] and high levels of asymmetric induction (up to >99% ee for both *exo*- and *endo*-products) were also furnished by the catalysts derived from ligand **357** and La(III), Eu(III), and Ce(IV) triflates.<sup>173</sup>

Nishiyama has reported the synthesis of various trialkylsiloxymethyl pybox ligands **361b-d** by ether-

ification of the hydroxymethyl-substituted ligand **361a**. These ligands were applied in nickel(II)-catalyzed 1,3-dipolar cycloaddition reactions of acryloyl-1,3-oxazolidin-2-one **221** and 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **285** with different nitrones **362a-d** (Scheme 74).<sup>174</sup> In all cases, the *endo*-cycloaddition products were afforded in high yields (60–99%) with excellent levels of diastereoselectivity (93:7–>99:1 *endo/exo*) and enantiodiscrimination (92–>99% ee). Nickel complexes of the triisopropylsilyloxymethyl ligand **361c** and the *tert*-butyldiphenylsilyloxymethyl ligand **361d** were highly active for the reaction of **221** with nitron **362a**, providing the *endo*-product in quantitative yield and >99% ee at 0

**Table 37. Asymmetric Ruthenium(II)-Catalyzed Transfer Hydrogenation of Aromatic Ketones Using Ligand **364**<sup>a</sup>**

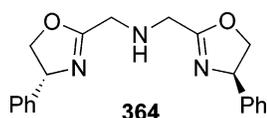
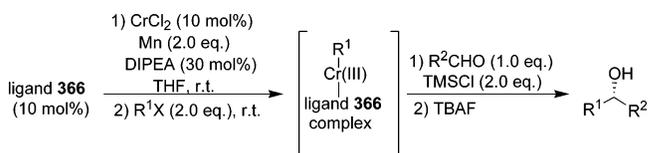
Entry	Ketone		Time (min)	Conversion (%)	Ee (%) (Conf.)
1		R = Me	5 (10)	80 (91)	98 (97) (S)
2		R = Et	10 (20)	77 (92)	95 (92) (S)
3		R = <i>i</i> -Pr	10	15	78 (S)
4		R = Me	40	96	98 (S)
5		R = Cl	5	>99	97 (S)
6		R = MeO	240	3	19 (S)
7		R = Me	5 (7)	75 (90)	96 (94) (S)
8		R = Cl	10	5	92 (S)
9		R = MeO	7 (10)	91 (94)	95 (93) (S)
10		R = Me	4	68	95 (S)
11		R = Cl	10	97	90 (S)
12		R = MeO	10	41	98 (S)
13			10	42	95 (S)
14			2 (5)	72 (98)	96 (94) (S)
15			2 (7)	55 (91)	96 (92) (S)

<sup>a</sup> RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (1 mol %), **364** (1.1 mol %), NaO-*i*-Pr (1 equiv), 2-PrOH, 82 °C.

°C after 4 and 1.5 h, respectively. These cycloadditions also proceeded efficiently at low catalyst loading (1 mol %) with no decrease in enantioselectivity, albeit with prolonged reaction times.

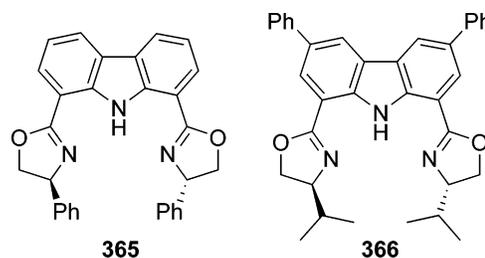
Zhang has applied the bis(oxazolinylmethyl)amine [(*R*)-Ph-ambox<sup>+</sup>] **364**, a ligand with a secondary amine link, in the asymmetric Ru(II)-catalyzed transfer hydrogenation of aromatic ketones.<sup>175</sup> The catalyst generated in situ from ligand **364** and RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> was highly active, affording, in general, excellent enantioselectivities (78–98% ee) and very high conversions (after 10 min at 82 °C, 1 mol % Ru) for the reduction of a range of arylalkyl ketones (Table 37). The poor result obtained with *o*-methoxyacetophenone (Table 37, entry 6) was attributed to chelation of the substrate to the ruthenium catalytic center. The importance of the NH group of this ligand in the catalytic cycle was evident by the significantly inferior results afforded by the corresponding *N*-methylated ligand (17% conversion, 10% ee after 30 min for acetophenone).

Ligand **364** was also used in the palladium(II)-catalyzed aza-Claisen rearrangement of allylic imidates (Scheme 47), providing at best 76% yield and

**Scheme 75**

81% ee (*R*) for the reaction of 2-hexenyl-*N*-(4-trifluoromethylphenyl)benzimidate **266**. Significantly decreased yields (1–47%) and lower enantioselectivities (13–76% ee) were obtained for the rearrangement of other allylic imidates, the low yields being a consequence of competing *anti*-Claisen rearrangement and C–O cleavage side reactions.<sup>176</sup>

Bis(oxazoline) ligands **365** and **366**, with a carbazole backbone, were utilized by Nakada in the asymmetric Nozaki–Hiyama–Kishi reaction (Scheme 75).<sup>177,178</sup> Of the two ligands, chromium(II) complexes of the 3,6-diphenyl-substituted carbazole ligand **366**



afforded superior results for the allylation of benzaldehyde **197** with allyl bromide [90% ee (*S*) with **366** vs 68% ee (*S*) with **365**]. Using ligand **366**, excellent enantioselectivities (86–96% ee) were achieved for the allylation and methallylation of various aromatic and aliphatic aldehydes (Table 38). The chromium-

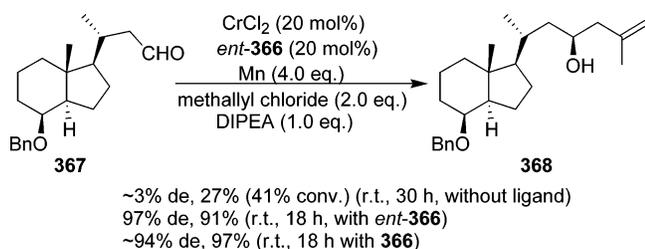
**Table 38. Catalytic Asymmetric Nozaki–Hiyama–Kishi Allylation and Methallylation of Aldehydes Using Chromium(II) Complexes of Ligand **366** (Scheme 75)**

entry	time (h)	R <sup>1</sup>	X	R <sup>2</sup>	yield (%)	ee (%) (conf)
1	12	allyl	Br	Ph	93	90 (S)
2 <sup>a</sup>	12	allyl	Br	Ph	89	93 (S)
3	16	allyl	Cl	Ph	95	89 (S)
4	12	allyl	I	Ph	52	64 (S)
5	12	allyl	Br	<i>p</i> -BrPh	87	92 (S)
6	12	allyl	Br	PhCH=CH	87	95 (S)
7 <sup>a</sup>	12	allyl	Br	PhCH <sub>2</sub> CH <sub>2</sub>	91	86 ( <i>R</i> )
8	12	allyl	Br	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	95	94 (S)
9	12	allyl	Cl	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	88	93 (S)
10	12	allyl	Br	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	83	92 ( <i>R</i> )
11	16	methallyl	Br	Ph	77	46 (S)
12	16	methallyl	Cl	Ph	96	95 (S)
13	16	methallyl	Cl	PhCH=CH	50	90 (S)
14	16	methallyl	Br	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	96	96 (S)
15	16	methallyl	Cl	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	98	95 (S)
16	16	methallyl	Br	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	65	79 ( <i>R</i> )
17	16	methallyl	Cl	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	83	96 ( <i>R</i> )

<sup>a</sup> Reaction carried out at 0 °C.

(II)/**366** complex was water-tolerant and was successfully recycled twice, maintaining high enantioselectivity, in the allylation of two aldehyde substrates. Crotylation of benzaldehyde **197** using ligand **366** and crotyl bromide was *anti*-selective (73:27 *anti*/*syn*), providing 75% ee (1*S*,2*S*) for the *anti*-product and

## Scheme 76



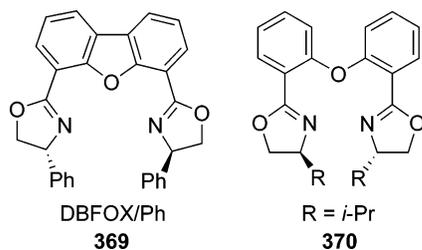
21% ee (*1R,2S*) for the *syn*-product in a low combined yield of 38%.

In addition, using ligand *ent*-**366**, a key intermediate, **368**, in the synthesis of calcitriol lactone was accessed in 97% de by the methallylation of the chiral aldehyde **367** (Scheme 76).

3.2.2. Bis(oxazoline) *N,O,N*-Ligands

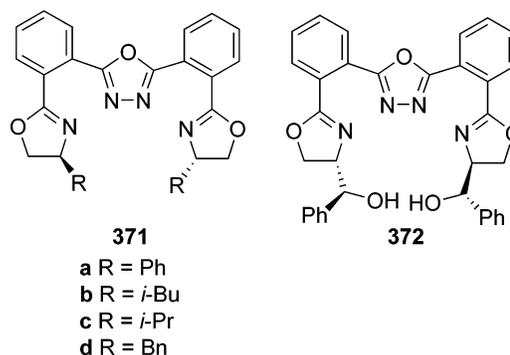
Chiral Lewis acid complexes of (*R,R*)-4,6-dibenzo-furandiyl-2,2'-bis(4-phenyloxazoline) (DBFOX/Ph) **369** have been used with some success in asymmetric conjugate additions,<sup>179</sup> 1,3-dipolar cycloadditions,<sup>180</sup> and Diels–Alder reactions.<sup>181</sup>

Palladium allyl complexes ( $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{ligand}]\text{PF}_6$ ) of the (*S,S*)-DBFOX/Ph ligand *ent*-**369** and the bis(oxazoline) ligand **370**, which contains a diphenyl ether backbone, were applied by Gómez in the pal-

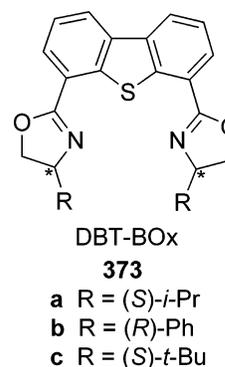


ladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>182</sup> The palladium complex (2 mol %) derived from ligand **370** afforded high enantioselectivity, giving 89% ee (*S*) and complete conversion after 2.5 days at room temperature. In contrast, the palladium allyl complex of ligand *ent*-**369** was inactive, affording no product after 7 days. This result was in agreement with the inability of this ligand to form stable palladium complexes with 1,3-diphenylallyl. The X-ray crystal structure of the palladium allyl complex of ligand **370** showed a distorted square-planar complex with coordination through the two nitrogen atoms of the oxazoline rings and the existence of *exo*- and *endo*-isomers in a ratio of 0.63:0.37, respectively.

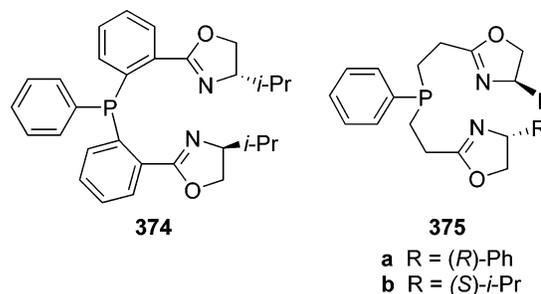
Bis(oxazoline) ligands **371** and **372**, with a 2,5-diaryl-1,3,4-oxadiazole backbone, were prepared by Du and tested in the copper(I)-catalyzed asymmetric cyclopropanation of styrene **177** with ethyl diazoacetate **178a**.<sup>183</sup> Copper(I) complexes of these ligands catalyzed the reaction with *trans*-selectivity and provided the *cis*-product in higher enantioselectivities than the *trans*-product. The benzyl-substituted derivative **371d** was the ligand of choice, affording cyclopropane products *trans*-**179a** and *cis*-**180a** in low



yield (25%) with a 74:26 *trans/cis* ratio with 20% ee (*1R,2R*) for *trans*-**179a** and 87% ee (*1R,2S*) for *cis*-**180a**.

3.2.3. Bis(oxazoline) *N,S,N*-Ligands

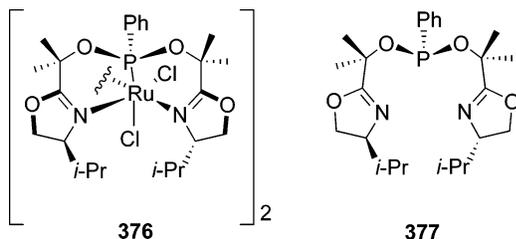
Schulz has applied the dibenzothiophene-bis(oxazoline) ligands **373** in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>184</sup> The (*S*)-isopropyl-substituted ligand **373** afforded the best result, giving 77% ee (*R*) and complete conversion after 70 h at 40 °C in dichloromethane using 2.5 mol % of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  and employing the BSA/KOAc methodology.

3.2.4. Bis(oxazoline) *N,P,N*-Ligands

Ligands **374** and **375**, with phosphine linking groups, have been prepared and applied by Zhang in the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of arylalkyl and dialkyl ketones, using 2-propanol as the hydrogen source.<sup>185</sup> Ligand **374** gave 94% conversion and 31% ee (*S*) after 48 h at room temperature for the reduction of acetophenone **40**. This low enantioselectivity was attributed to two different propeller orientations of the phenyl groups on the phosphine, which confer conformational am-

biguity on the ligand. Of the *N,P,N*-ligands **375**, the ruthenium(II) complex generated in situ from the phenyl-substituted ligand **375a** and  $[\text{RuCl}_2(\text{C}_6\text{H}_5)]_2$  (0.5 mol %) was the catalyst of choice, affording good conversions and variable enantioselectivities for the transfer hydrogenation of arylalkyl (14–79% ee) and dialkyl (63–92% ee) ketones.

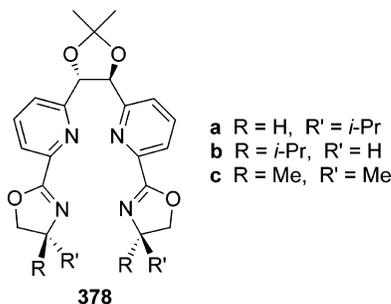
Braunstein has reported the preparation of a dimeric ruthenium complex **376** ( $[\text{Ru}(\mu\text{-Cl})\text{Cl}(\mathbf{377})]_2$ ) from the phosphonite-linked *N,P,N*-bis(oxazoline) ligand **377**.<sup>186</sup> For the cyclopropanation of styrene **177**



with ethyl diazoacetate **178a**, complex **376** (1 mol %) gave products in low yield (15%) with a *trans/cis* selectivity of 70:30 and without significant asymmetric induction. The ruthenium complex **376** was also investigated in the asymmetric transfer hydrogenation of acetophenone **40** furnishing, as the best result, 98% conversion and 26% ee after 1 h in refluxing 2-propanol. The enantioselectivity increased to 45% ee when the reaction was performed at room temperature but with decreased conversion (16%).

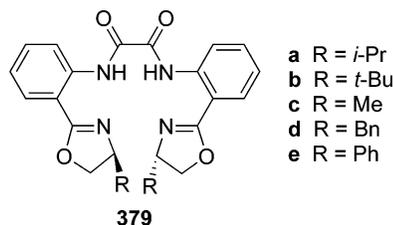
### 3.3. Tetradentate Bis(oxazoline) Ligands

Chelucci investigated the ability of  $C_2$ -symmetric bis(oxazolinyldiopyridinyl)dioxolane ligands **378** to in-



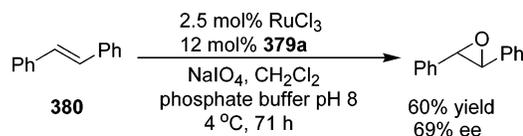
duce asymmetry in the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**.<sup>187</sup> Significantly different enantioselectivities of 67% ee (*S*) and >98% ee (*S*) were afforded by the diastereomeric ligands **378a** and **378b**, derived from (*R*) and (*S*)-valinol, respectively. This result, together with the high enantiodiscrimination (>98% ee) obtained using ligand **378c**, with achiral oxazoline rings, indicated that the stereochemical outcome of the reaction was determined mainly by the stereogenic unit of the dioxolane backbone.

Pfaltz showed that the chiral oxalamide ligands **379** can act as tetradentate anionic ligands forming stable nickel(II) and copper(II) complexes. Ruthenium complexes, prepared in situ from  $\text{RuCl}_3$  and the bis-amide ligands **379**, were used in the asymmetric



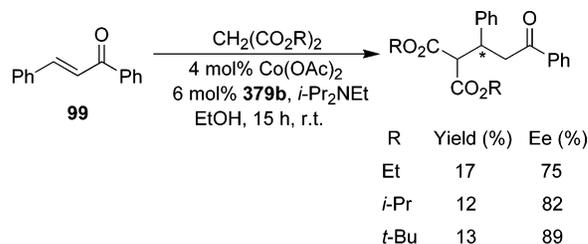
epoxidation of stilbene **380** (Scheme 77). The catalyst formed from the isopropyl-substituted ligand **379a** afforded the best result of 60% yield and 69% ee with only small amounts (~10%) of a benzaldehyde side-product being detected.<sup>188</sup>

#### Scheme 77



The oxalamide ligands **379** were also applied in the cobalt-catalyzed Michael addition of dialkyl malonates to chalcone **99** (Scheme 78). Good enantiose-

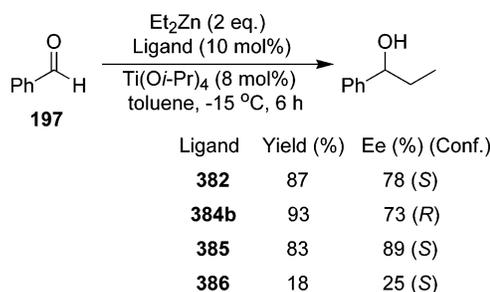
#### Scheme 78



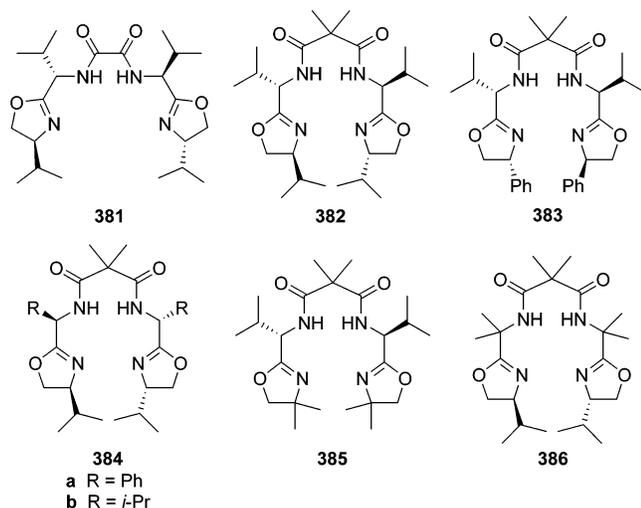
lectivities (75–89% ee) were provided by the ligand of choice, the *tert*-butyl-substituted derivative **379b**, with the highest enantiodiscrimination being achieved using the dialkyl malonates with the bulkier ester groups. In all cases the reactions proceeded with low yields (12–30%) after 15 h at room temperature.<sup>188</sup>

Tetradentate  $C_2$ -symmetric bis(oxazoline) ligands **381–386**, derived from a 1,2- or 1,3-diacid, a chiral  $\alpha$ -amino acid and a chiral 1,2-amino alcohol, have been investigated by Adolffson in the titanium-catalyzed addition of diethylzinc to benzaldehyde **197** (Scheme 79).<sup>189</sup> The malonic acid derivatives **382–**

#### Scheme 79



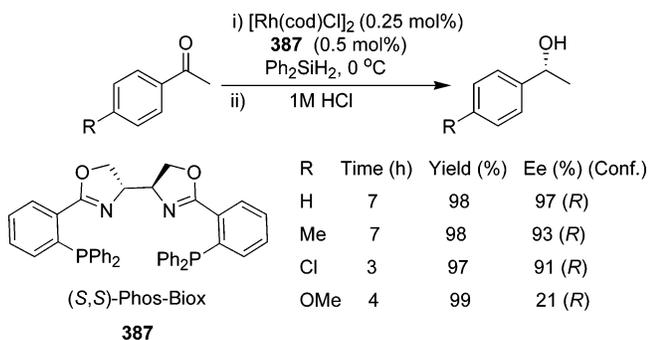
**386** afforded the highest enantioselectivities, with the best result of 83% yield and 89% ee (*S*) being achieved using ligand **385** with achiral oxazoline rings. This result, together with the good enantioselectivities but opposite sense of asymmetric induction obtained with



the diastereomeric ligands **382** and **384b** [78% ee (*S*) and 73% ee (*R*)] and the low level of enantioselection afforded by the achiral backbone-containing ligand **386**, suggested that the bis-amide part of the ligand controls the enantioinduction.

The chiral bisphosphinobioxazoline ligand **387** [(*S,S*)-phos-Biox] was utilized by Lee in asymmetric rhodium(I)-catalyzed hydrosilylation and in palladium-catalyzed asymmetric allylic alkylation.<sup>190,191</sup> In general, rhodium complexes, generated in situ from [Rh(cod)Cl]<sub>2</sub> and ligand **387**, afforded excellent enantioselectivities (91–97% ee) and almost complete conversions for the hydrosilylation of aromatic ketones (Scheme 80). However, the reduction of *p*-

#### Scheme 80

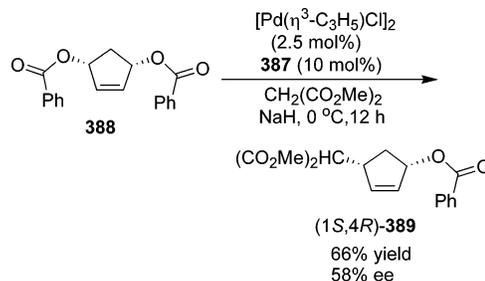


methoxyacetophenone proceeded with a much reduced enantioselectivity of 21% ee.<sup>190</sup>

The (*S,S*)-Phos-Biox ligand **387** also induced excellent enantiocontrol and catalytic activity in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with sodium dimethyl malonate **8** (prepared in situ from dimethyl malonate **26** and sodium hydride), affording 97% ee (*S*) and >99% yield under optimized conditions of [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (1 mol %) in THF for 40 min at 20 °C. This ligand was also investigated in the palladium-catalyzed desymmetrization of the *meso*-dibenzoate of *cis*-2-cyclopentene-1,4-diol **388** (Scheme 81). The best result was obtained using sodium dimethyl malonate **8** as the nucleophile, affording (1*S*,4*R*)-**389** in 66% yield and 58% ee.<sup>191</sup>

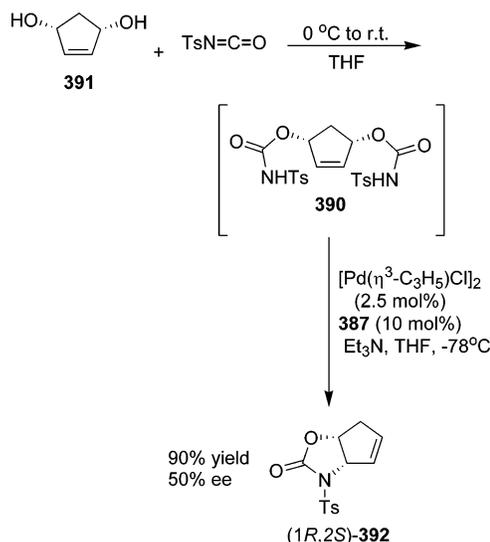
Asymmetric intramolecular cyclization of the bis-carbamate **390** (formed in situ from diol **391**) to form

#### Scheme 81



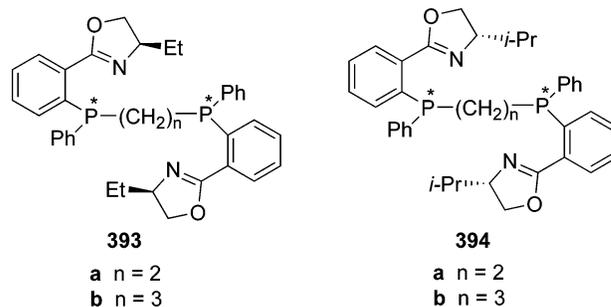
oxazolidin-2-one **392** was also achieved by palladium-catalyzed asymmetric desymmetrization using ligand **387** (Scheme 82). The reaction proceeded in 90% yield

#### Scheme 82



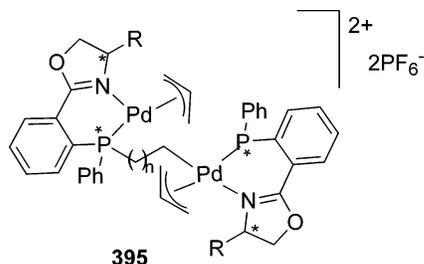
providing (1*R*,2*S*)-**392** in 90% yield and 50% ee. It was shown by X-ray crystallography that ligand **387** coordinates to palladium in a tetradentate fashion in complexes derived from both PdCl<sub>2</sub> and [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>. It was suggested that the active catalyst in the allylic alkylations arises from the dissociation of two of the four donor atoms.<sup>191</sup>

Bis(oxazolinyolphosphine) ligands **393** and **394**, which possess four stereocenters, were prepared by Gómez as a mixture of three diastereomers due to an unfixed configuration of the phosphorus atoms.



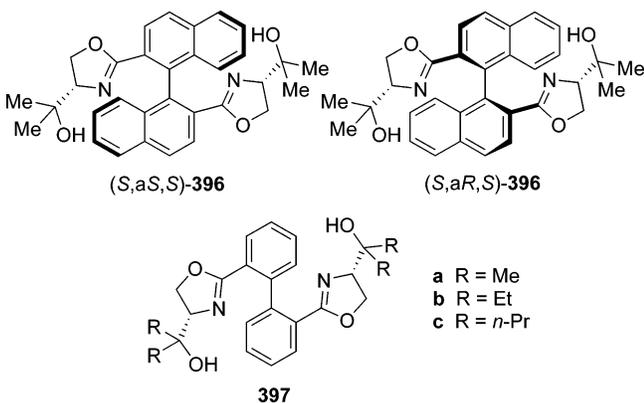
Only (*R*<sub>ox</sub>, *R*<sub>phos</sub>, *S*<sub>phos</sub>, *R*<sub>ox</sub>)-**393a** and (*S*<sub>ox</sub>, *S*<sub>phos</sub>, *R*<sub>phos</sub>, *S*<sub>ox</sub>)-**394b** diastereomers could be isolated, whereas 9:1 mixtures of [(*R*<sub>ox</sub>, *R*<sub>phos</sub>, *R*<sub>phos</sub>, *R*<sub>ox</sub>)-**393a** and (*R*<sub>ox</sub>, *S*<sub>phos</sub>, *S*<sub>phos</sub>, *R*<sub>ox</sub>)-**393a**] and [(*S*<sub>ox</sub>, *R*<sub>phos</sub>, *R*<sub>phos</sub>, *S*<sub>ox</sub>)-**394b** and (*S*<sub>ox</sub>, *S*<sub>phos</sub>, *S*<sub>phos</sub>, *S*<sub>ox</sub>)-**394b**] were obtained.

*N,P*-Bimetallic palladium allyl complexes **395**, derived from  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (2.0 equiv) and ligands **393** and **394** (1.0 equiv), were investigated in the asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**. A comparison of the results afforded by the palladium complexes **395** derived from a single diastereomer and from



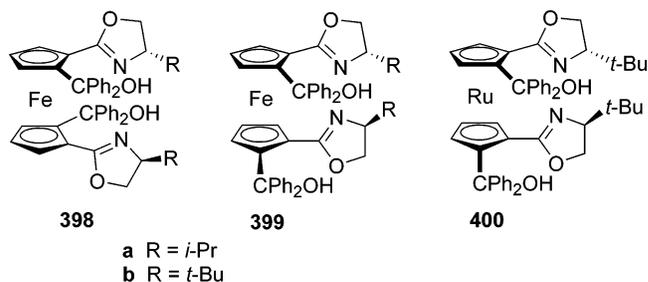
diastereomeric mixtures indicated that the phosphorus stereocenters had no significant effect on the enantioinduction. Palladium complexes (2 mol %) of the isopropyl-substituted ligands **394a** and **394b** gave the best enantioselectivities of 81 and 90% ee (*S*), respectively, but only moderate catalytic activity (100 and 70% conversion after 4 days at room temperature). Palladium/ligand (1:1) complexes gave significantly lower levels of enantioselection [48% ee (*S*) with **394b**], and this was attributed to the formation of *P,P*-monometallic palladium allyl complexes.<sup>192</sup>

In 2000 Ikeda reported the synthesis of the  $C_2$ -symmetric bis(oxazoline) ligands **396** and **397** containing a hydroxyalkyl group as the oxazoline 4-substituent and an axis-fixed and unfixed biaryl backbone, respectively.<sup>193</sup> These ligands were examined for their



enantiocontrolling ability in the asymmetric addition of diethylzinc to benzaldehyde **197**. The best result of 92% yield and 88% ee (*R*) was obtained using the axis-fixed ligand (*S*,*aS*,*S*)-**396**. The stereoaxis of the backbone had a significant effect on the enantioinduction, with the diastereomeric ligand (*S*,*aR*,*S*)-**396** affording only 37% ee (*R*). Of the axis-unfixed ligands **397**, the methyl-substituted ligand **397a** was optimal, giving 93% yield and 78% ee (*R*).

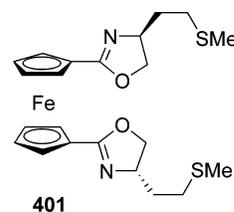
Diastereomeric 1,1'-bis(oxazoliny)ferrocene ligands **398** and **399**, with hydroxy(diphenyl)methyl substituents, have been prepared by Ikeda and tested in the asymmetric addition of diethylzinc to benzaldehyde **197**.<sup>194</sup> The *tert*-butyl-substituted derivatives **398b** and **399b** (10 mol %) afforded the best results, providing similar levels of enantioselection [91 and



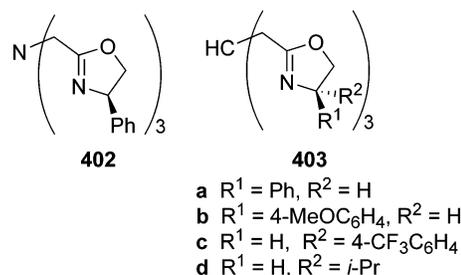
93% ee (*R*), respectively] but greatly different catalytic activities [63% yield (after 24 h) vs 97% yield (after 8 h), respectively], possibly due to the larger steric repulsion between the two oxazoline substituents in the zinc complex of **398b**.

In addition, ligand **399b** and its ruthenocene analogue **400** also catalyzed the asymmetric phenyl transfer from organozincs to different aldehydes with similar levels of enantiodiscrimination (71–96% ee).<sup>195</sup>

Bryce prepared the redox active bis(oxazoliny)ferrocene ligand **401**, which was tested in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate **26**, affording 93% yield and 91% ee (*R*).<sup>120</sup>



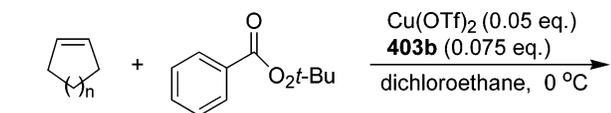
#### 4. Tris(oxazoline) Ligands



$C_3$ -Symmetric tris(oxazoline) ligands **402** and **403** were examined by Katsuki in the copper(II)-catalyzed asymmetric allylic oxidation of cycloalkenes **185–188** (Kharash–Sosnovsky reaction) (Scheme 83).<sup>196,197</sup> The copper(II) complex, derived from  $\text{Cu}(\text{OTf})_2$  and the tetradentate ligand **402**, afforded high enantioselectivities for the oxidation of cyclopentene **185** with *tert*-butyl peroxybenzoate **189** [93% ee (*S*) (30% yield) at  $-20^\circ\text{C}$  and 76% ee (*S*) (83% yield) at room temperature] and moderate enantioselectivities for the reaction with other cycloalkenes.<sup>196</sup> Of the ligands **403**, the (*R*)-*p*-methoxyphenyl-substituted derivative **403b** was optimal, giving high enantioinduction [82–88% ee (*R*)], opposite product configuration (compared to ligand **402**), and moderate yields for the allylic oxidation of cycloalkenes **185–188**, under optimized reaction conditions (Scheme 83).<sup>197</sup>

Ligands **402** and **403** were also applied in the copper(II)-catalyzed oxidative desymmetrization of

## Scheme 83

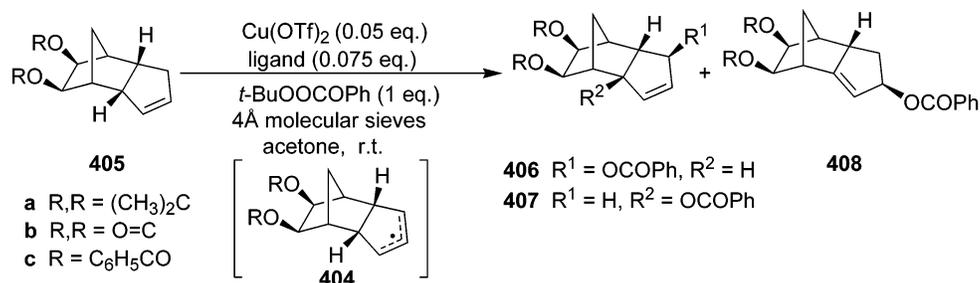


**185**  $n = 1$   
**186**  $n = 2$   
**187**  $n = 3$   
**188**  $n = 4$

Substrate	Yield (%)	Ee (%) (Conf.)
<b>185</b>	73	85 ( <i>R</i> )
<b>186</b>	80	82 ( <i>R</i> )
<b>187</b>	64	88 ( <i>R</i> )
<b>188</b>	25	85 ( <i>R</i> )

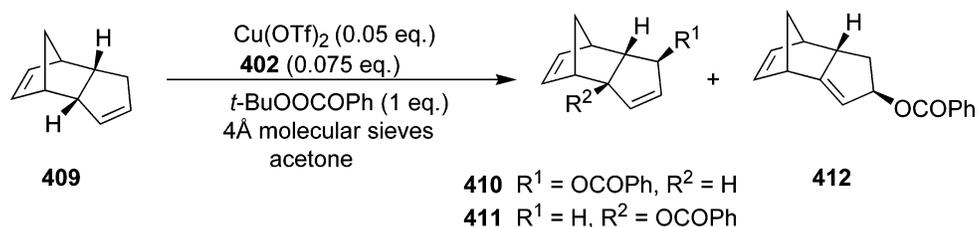
racemic dicyclopentadiene derivatives, which proceeds via the desymmetrization of a *meso*-allyl radical intermediate **404** (Schemes 84 and 85).<sup>197,198</sup> For the reaction of racemic dioxxygenated dicyclopentadienes **405**, with various diol protecting groups, the allylic oxidation product **406** was obtained in moderate to high enantioselectivity (59–87% ee) using copper(II) complexes of ligand **402** (Scheme 84). Poor to moderate enantioselectivities (5–69% ee) were afforded by this ligand for the side-products **407** and **408**, which

## Scheme 84



Ligand	Olefin	Time (h)	Yield (%)	Regioselectivity ( <b>406</b> : <b>407</b> : <b>408</b> )	Ee (%) ( <b>406</b> , <b>407</b> , <b>408</b> )
<b>403b</b>	<b>405a</b>	200 (-20 °C)	38	2.9:1.2:1.0	81,58,85
<b>402</b>	<b>405a</b>	69	78	6.0:5.9:1.0	80,12,42
<b>402</b>	<b>405b</b>	144	57	3.8:3.6:1.0	87,22,69
<b>402</b>	<b>405c</b>	132	69	3.2:3.2:1.0	59,7,17

## Scheme 85



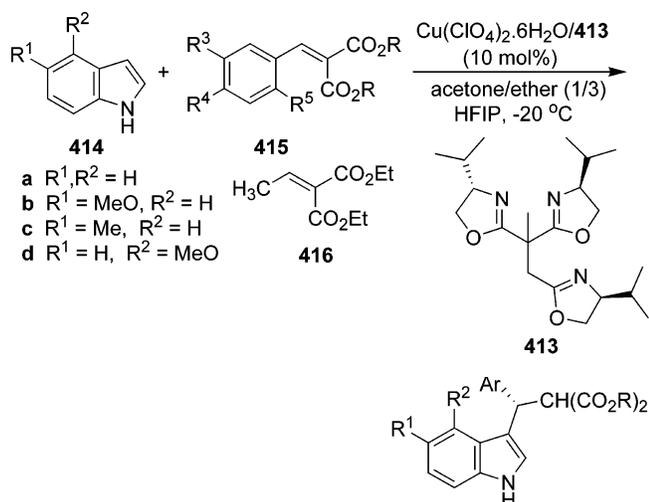
Temp. (°C)	Time (h)	Yield (%)	Regioselectivity ( <b>410</b> : <b>411</b> : <b>412</b> )	Ee (%) ( <b>410</b> , <b>411</b> )
r.t.	69	69	1.1:1.0:0	72,0
0	200	25	1.0:1.0:0	85,0

were obtained as a consequence of low regioselectivity in the formation of the allylic radical intermediate. This regioselectivity was dependent on the solvent used with a ratio of 1:1 [for **406**:(**407**+**408**)] in acetone and 2:1 in acetonitrile.<sup>198</sup> Ligand **403b** was also effective in the desymmetrization of olefin **405a**, giving 81% ee for the desired product **406a** and 58 and 85% ee for side-products **407a** and **408a**, respectively.<sup>197</sup> Oxidative desymmetrization of dicyclopentadiene **409** mediated by the copper(II) complex of ligand **402** afforded at best a 1.1:1.0 mixture of the desired product **410** (with up to 85% ee) and the racemic side-product **411** (Scheme 85).<sup>198</sup>

Tang has reported the synthesis of the (*S*)-valinol-derived pseudo- $C_3$ -symmetric tris(oxazoline) ligand **413**.<sup>199</sup> This ligand formed an air- and water-stable Lewis acid complex,  $[\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}(\mathbf{413})]$  (10 mol %), which catalyzed the Michael addition of structurally different indole derivatives **414** to a range of arylidene malonates **415** with excellent yields (73–99%) and high enantioselectivities (88–93% ee) in the presence of hexafluoro-2-propanol (HFIP) at –20 °C (Scheme 86 and Table 39). The reaction of diethyl ethylidene malonate **416** with indole **414a** also proceeded with high yield (84%) but with a lower level of enantiodiscrimination of 60% ee (Table 39, entry 9).

In 2002 Gade reported the modular synthesis of the  $C_1$ - and  $C_3$ -symmetric tripodal tris(oxazoline) ligands **417**. The enantiodiscriminating ability of

## Scheme 86

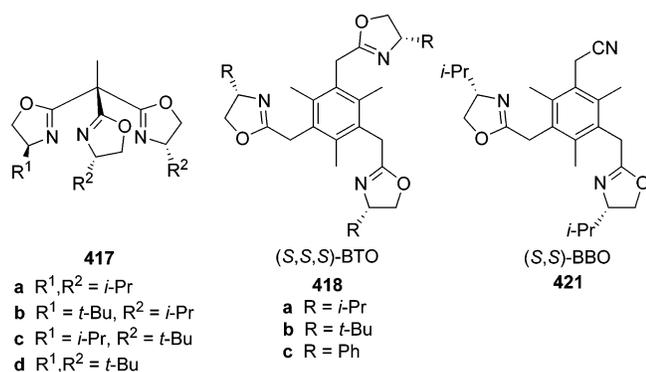


**Table 39. Asymmetric Addition of Indole Derivatives 414 to Malonates 415 and 416 Using  $[Cu(ClO_4)_2 \cdot 6H_2O]$  (413) (Scheme 86)**

entry	indole	malonate (415)	yield (%)	ee (%)
1	<b>414a</b>	R = Et, $R^3, R^4, R^5 = H$	84	89
2	<b>414a</b>	R = Me, $R^3, R^4, R^5 = H$	98	88
3	<b>414a</b>	R = Me, $R^4 = NO_2, R^3, R^5 = H$	99	91
4	<b>414a</b>	R = Et, $R^4 = NO_2, R^3, R^5 = H$	99	91
5	<b>414a</b>	R = Et, $R^3 = NO_2, R^4, R^5 = H$	99	91
6	<b>414a</b>	R = Et, $R^4 = Br, R^3, R^5 = H$	95	90
7	<b>414a</b>	R = Et, $R^5 = Cl, R^3, R^4 = H$	99	92
8	<b>414a</b>	R = Et, $R^4 = Cl, R^3, R^5 = H$	84	90
9 <sup>a</sup>	<b>414a</b>	<b>416</b>	84	60
10	<b>414b</b>	R = Et, $R^3, R^4, R^5 = H$	73	91
11	<b>414c</b>	R = Et, $R^3, R^4, R^5 = H$	92	93
12	<b>414d</b>	R = Et, $R^3, R^4, R^5 = H$	97	91
13	<b>414a</b>	R = Et, $R^5 = Cl, R^3, R^4 = H$	95	91

<sup>a</sup> Reaction run at  $-35$  °C.

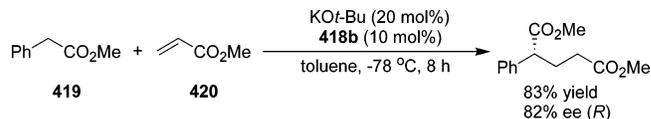
these ligands was investigated in the copper(I)-catalyzed asymmetric cyclopropanation of styrene **177**.<sup>200</sup> The unsymmetrical derivative **417c** was the



ligand of choice, providing good diastereo- and enantioselectivity for the reaction with both ethyl diazoacetate **178a** [*trans/cis* ratio 69:31, 86% ee (*trans*-(1*R*,2*R*)-**179a**), 81% ee (*cis*-(1*R*,2*S*)-**180a**)] and *tert*-butyl diazoacetate **178d** [*trans/cis* ratio 77:23, 81% ee (*trans*-(1*R*,2*R*)-**179d**), 85% ee (*cis*-(1*R*,2*S*)-**180d**)].

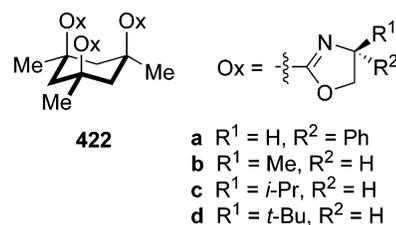
Because of their high affinity for potassium ions, the benzene-based tripodal oxazoline ligands [(*S,S,S*)-BTO] **418** were utilized by Ahn in the enantioselective Michael reaction between methyl phenylacetate **419** and methyl acrylate **420** mediated by catalytic

## Scheme 87



amounts of potassium *tert*-butoxide (Scheme 87).<sup>201</sup> The best result of 83% yield and 82% ee (*R*) was afforded by 20 mol % of potassium *tert*-butoxide and 10 mol % of ligand **418b** in toluene at  $-78$  °C. By comparison with the ineffective bis(oxazoline) ligand **421** [(*S,S*)-BBO], which gave no product, and the unsuccessful result obtained using sodium *tert*-butoxide, the authors suggested that ligands **418** coordinate to the potassium enolate in a tripodal fashion via the oxazoline nitrogen atoms.

*C*<sub>3</sub>-Symmetric tris(oxazoline) ligands **422**, with a rigid cyclohexane backbone, were prepared from Kemp's triacid and tested by Fang in asymmetric diethylzinc addition and in copper(II)-catalyzed asymmetric allylic oxidation.<sup>202</sup> For both reactions, only



moderate enantioselectivities were obtained, with ligand **422c** affording the optimum result of 46% yield and 43% ee (*R*) for diethylzinc addition to benzaldehyde **197** and ligand **422a** giving the best result of 94% yield and 45% ee (*S*) for the allylic oxidation of cyclopentene **185** with *tert*-butyl perbenzoate **189**.

## 5. Conclusion

This review reports on recent developments in the design of oxazoline-based ligands for asymmetric catalysis. In particular, new mono(oxazoline), bis(oxazoline) and tris(oxazoline) ligands, which were reported in the literature between 1998 and 2003, are discussed. The broad utility of this class of ligands in catalytic asymmetric synthesis is demonstrated by the high enantiocontrol induced in a diverse array of metal-catalyzed transformations ranging from oxidations and reductions to cycloadditions and carbon-carbon bond-forming reactions.

The enantiocontrolling ability of the chiral oxazoline ligand in a metal-catalyzed reaction is determined mainly by the type of donor atoms present and by the overall ligand structure. From this review, it is evident that certain structural features are preferable for oxazoline-containing ligands to induce high levels of asymmetry in particular transformations. Palladium-catalyzed asymmetric allylic alkylation and amination, iridium-catalyzed enantioselective hydrogenation of unfunctionalized alkenes, and the asymmetric intermolecular Heck reaction all proceed with good levels of enantioselection in the presence of mono(oxazoline) ligands possessing phosphine

groups. Mono(oxazoline) *P,N*-ligands with phosphorus–heteroatom (*O* or *N*) bonds are also effective ligands for palladium-catalyzed allylic alkylation and amination and iridium-catalyzed hydrogenation, whereas sulfur-containing mono(oxazoline) (*N,S*) or bis(oxazoline) (*N,S,N* or *N,S,S,N*) ligands and bis(oxazoline) ligands with additional phosphorus donor groups are also commonly applied in palladium-catalyzed allylic alkylation.

In contrast to the reactions mentioned above, copper(I)-catalyzed asymmetric cyclopropanations, rhodium(I)-catalyzed asymmetric hydrosilylations, Cu(I)-catalyzed asymmetric oxidation of cyclic olefins, asymmetric Diels–Alder reactions, asymmetric Mukaiyama–Michael and aldol reactions, and asymmetric 1,3-dipolar cycloadditions proceed with good enantiodiscrimination in the presence of metal complexes of mainly bidentate mono(oxazoline) *N,N*-ligands, bidentate bis(oxazoline) *N,N*-ligands, and tridentate bis(oxazoline) *N,N,N*- and *N,O,N*-ligands.

For the asymmetric addition of diethylzinc and diphenylzinc to aldehyde mono(oxazoline) *N,O*-ligands and oxazoline-containing ligands with secondary chelating hydroxy groups are preferred.

Although this review shows comprehensive research in the design, synthesis, and application of oxazoline-containing ligands, this area is far from being exhausted, and it is hoped that this review will stimulate the development of new ligands and their subsequent application in newly developed asymmetric reactions.

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## 7. References

- Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
- Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
- Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297.
- Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1.
- Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467.
- (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.
- Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841.
- Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435.
- Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083.
- Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833.
- Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2897.
- Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synlett* **2004**, 106.
- Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240.
- Gilbertson, S. R.; Xie, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2750.
- Gilbertson, S. R.; Xie, D.; Fu, Z. *Tetrahedron Lett.* **2001**, *42*, 368.
- Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
- Ma, S.-M.; Duan, D.-H. *Chinese J. Chem.* **2002**, *20*, 1363.
- Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424.
- Braunstein, P.; Graiff, C.; Naud, F.; Pfaltz, A.; Tiripicchio, A. *Inorg. Chem.* **2000**, *39*, 4468.
- Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.
- (a) Hou, D.-R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745. (b) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206.
- Burgess, K.; Porte, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2465.
- Hou, D.-R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem. Eur. J.* **2001**, *7*, 5391.
- Patti, A.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **2001**, *12*, 3375.
- Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62.
- Gläser, B.; Kunz, H. *Synlett* **1998**, 53.
- Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508.
- Sudo, A.; Yoshida, H.; Saigo, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3205.
- Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205.
- Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885.
- Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 943.
- Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343.
- Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1779.
- Selvakumar, K.; Valentini, M.; Würle, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 1207.
- Ogasawara, M.; Yoshida, K.; Hayashi, T. *Heterocycles*, **2000**, *52*, 195.
- Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A.; Eisenträger, F. *Organometallics* **2000**, *19*, 1299.
- Dotta, P.; Magistrato, A.; Rothlisberger, U.; Pregosin, P. S.; Albinati, A. *Organometallics*, **2002**, *21*, 3033.
- Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713.
- Hatano, M.; Yamanaka, M.; Mikami, K. *Eur. J. Org. Chem.* **2003**, 2552.
- Hatano, M.; Mikami, K. *J. Mol. Catal. A—Chem.* **2003**, *196*, 165.
- Zhang, W.; Yoneda, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1998**, *9*, 3371.
- Park, J.; Quan, Z.; Lee, S.; Ahn, K. H.; Cho, C.-W. *J. Organomet. Chem.* **1999**, *584*, 140.
- Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483.
- Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285.
- Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659.
- Tu, T.; Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C. *Chem. Eur. J.* **2003**, *9*, 3073.
- Tu, T.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2003**, *5*, 3651.
- Bolm, C.; Xiao, L.; Kesselgruber, M. *Org. Biomol. Chem.* **2003**, *1*, 145.
- Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695.
- Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699.
- Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778.
- Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4082.
- Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374.
- Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K.-G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40.
- Hashizume, T.; Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2000**, *65*, 5197.
- Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 5553.
- Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4445.
- Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811.
- Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *44*, 953.
- Blanc, C.; Hannedouche, J.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2003**, *44*, 6469.
- You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Huo, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.
- Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.
- Gavrilov, K. N.; Bondarev, O. G.; Tsarev, V. N.; Shiryaev, A. A.; Lyubimov, S. E.; Kucherenko, A. S.; Davankov, V. A. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 122.
- (a) Prétôt, R.; Lloyd-Jones, G. C.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035. (b) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323. (c) Kawatsura, M.; Uozumi, Y.; Hayashi, T. *Chem. Commun.* **1998**, 217.
- Heldmann, D. K.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1096.
- (a) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett*, **1997**, 1429. (b) Escher, I. H.; Pfaltz, A. *Tetrahedron*, **2000**, *56*, 2879.
- Gladioli, S.; Loriga, G.; Medici, S.; Taras, R. *J. Mol. Catal. A—Chem.* **2003**, *196*, 27.
- (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (b) Brunner, H.; Brandl, P. *Tetrahedron: Asymmetry* **1991**, *2*, 919.

- (69) (a) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (b) Perch, N. S.; Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2000**, *65*, 3836.
- (70) Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 7639.
- (71) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Lad, L.; Russell, D. R. *Chem. Commun.* **1997**, 2347.
- (72) (a) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *J. Chem. Soc., Dalton Trans.* **2000**, 4432. (b) Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *Chem. Commun.* **1997**, 1351.
- (73) Fryzuk, M. D.; Jafarpour, L.; Rettig, S. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3191.
- (74) Brunner, H.; Störiko, R.; Nuber, B. *Tetrahedron: Asymmetry* **1998**, *9*, 407.
- (75) Brunner, H.; Brandl, P. *J. Organomet. Chem.* **1990**, *390*, C81.
- (76) Brunner, H.; Störiko, R.; Rominger, F. *Eur. J. Inorg. Chem.* **1998**, 771.
- (77) Brunner, H.; Störiko, R. *Eur. J. Inorg. Chem.* **1998**, 783.
- (78) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543.
- (79) Chelucci, G.; Deriu, S. P.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457.
- (80) Chelucci, G.; Deriu, S.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3803.
- (81) Chelucci, G.; Sanna, M. G.; Gladiali, S. *Tetrahedron* **2000**, 2889.
- (82) (a) Wu, X.-Y.; Li, X.-H.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **1998**, *9*, 4143. (b) Li, X.-G.; Wang, L.-X.; Zhou, Q.-L. *Chin. J. Chem.* **2002**, *20*, 1445.
- (83) Wu, X.-Y.; Shen, Y.-Y.; Ma, B.; Zhou, Q.-L.; Chan, A. S. C. *J. Mol. Catal. A-Chem.* **2000**, *157*, 59.
- (84) (a) Wu, X.-Y.; Xu, H.-D.; Tang, F.-Y.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2001**, *12*, 2565. (b) Wu, X.-Y.; Xu, H.-D.; Zhou, Q.-L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 1255.
- (85) (a) Li, X.-G.; Cheng, X.; Ma, J.-A.; Zhou, Q.-L. *J. Organomet. Chem.* **2001**, *640*, 65. (b) Chelucci, G.; Gladiali, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1393. (c) Chelucci, G.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **2000**, *11*, 4027.
- (86) Canal, J. M.; Gómez, M.; Jiménez, F.; Rocamora, M.; Muller, G.; Duñach, E.; Franco, D.; Jiménez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966.
- (87) Li, Z.-P.; Wu, X.-Y.; Zhou, Q.-L.; Chan, W.-L. *Chin. J. Chem.* **2001**, *19*, 40.
- (88) Zhou, Y.-B.; Tang, F.-Y.; Xu, H.-D.; Wu, X.-Y.; Ma, J.-A.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 469.
- (89) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580. (c) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998.
- (90) Ma, J.-A.; Wan, J.-H.; Zhou, Y.-B.; Wang, L.-X.; Zhang, W.; Zhou, Q.-L. *J. Mol. Catal. A-Chem.* **2003**, *196*, 109.
- (91) Andrus, M. B.; Soma Sekhar, B. B. V. *J. Heterocyclic Chem.* **2001**, *38*, 1265.
- (92) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 6565.
- (93) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197.
- (94) Wipf, P.; Pierce, J. G.; Wang, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3605.
- (95) (a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848. (b) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, *34*, 3405. (c) Bolm, C.; Schlingloff, G. *Chem. Commun.* **1995**, 1247.
- (96) Brunner, H.; Berghofer, J. *J. Organomet. Chem.* **1995**, *501*, 161.
- (97) Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, *12*, 3485.
- (98) Cozzi, P. G.; Floriani, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2357.
- (99) Peng, Y.; Feng, X.; Cui, X.; Jiang, Y.; Chang, A. S. C. *Synth. Commun.* **2001**, *31*, 2287.
- (100) Peng, Y.; Feng, X.; Yu, K.; Li, Z.; Jiang, Y.; Yeung, C.-H. *J. Organomet. Chem.* **2001**, *619*, 204.
- (101) (a) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1535. (b) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322.
- (102) Bertilsson, S. K.; Tedenborg, L.; Alonso, D. A.; Andersson, P. G. *Organometallics* **1999**, *18*, 1281.
- (103) (a) Bolm, C.; Muñoz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860. (b) Bolm, C.; Muñoz-Fernández, K.; Seger, A.; Raabe, G. *Synlett* **1997**, 1051. (c) Bolm, C.; Muñoz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491.
- (104) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñoz, K. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3465.
- (105) Bolm, C.; Hermanns, N.; Classen, A.; Muñoz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795.
- (106) Deng, W.-P.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 4689.
- (107) Jones, G.; Butler, D. C. D.; Richards, C. J. *Tetrahedron Lett.* **2000**, *41*, 9351.
- (108) (a) Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 649. (b) Allen, J. V.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 277.
- (109) Braga, A. L.; Rubim, R. M.; Schrekker, H. S.; Wessjohann, L. A.; de Bolster, M. W. G.; Zeni, G.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291.
- (110) Hiroi, K.; Watanabe, K.; Abe, I.; Koseki, M. *Tetrahedron Lett.* **2001**, *42*, 7617.
- (111) Watanabe, K.; Hirasawa, T.; Hiroi, K. *Chem. Pharm. Bull.* **2002**, *50*, 372.
- (112) (a) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065. (b) Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 7793. (c) Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015.
- (113) (a) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254.
- (114) Voituriez, A.; Schulz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 339.
- (115) Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377.
- (116) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **1999**, 1319.
- (117) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684.
- (118) Park, J.; Quan, Z.; Lee, S.; Ahn, K. H.; Cho, C.-W. *J. Organomet. Chem.* **1999**, *584*, 140.
- (119) Manoury, E.; Fossey, J. S.; Ait-Haddou, H.; Daran, J.-C.; Balavoine, G. G. A. *Organometallics* **2000**, *19*, 3736.
- (120) Chesney, A.; Bryce, M. R.; Chubb, R. W. J.; Batsanov, A. S.; Howard, J. A. K. *Tetrahedron: Asymmetry* **1997**, *8*, 2337.
- (121) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923.
- (122) You, S.-L.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2000**, *11*, 1495.
- (123) Bolm, C.; Kesselgruber, M.; Grenz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, 25, 13.
- (124) Braga, A. L.; Silva, S. J. N.; Lütke, D. S.; Drekenner, R. L.; Silveira, C. C.; Rocha, J. B. T.; Wessjohann, L. A. *Tetrahedron Lett.* **2002**, *43*, 7329.
- (125) Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* **2002**, 2422.
- (126) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712.
- (127) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.
- (128) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809.
- (129) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412.
- (130) (a) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878. (b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.
- (131) Park, S.-W.; Son, J.-H.; Kim, S.-G.; Ahn, K. H. *Tetrahedron: Asymmetry* **1999**, *10*, 1903.
- (132) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721.
- (133) van Lingen, H. L.; van de Mortel, J. K. W.; Hekking, K. F. W.; van Delft, F. L.; Sonke, T.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 317.
- (134) Thorhaug, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888.
- (135) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953.
- (136) Clariana, J.; Comelles, J.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1551.
- (137) Alexander, K.; Cook, S.; Gibson, C. L. *Tetrahedron Lett.* **2000**, *41*, 7135.
- (138) Hoarau, O.; Ait-Haddou, H.; Daran, J.-C.; Cramailère, D.; Balavoine, G. G. A. *Organometallics* **1999**, *18*, 4718.
- (139) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164.
- (140) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259.
- (141) Schinnerl, M.; Böhm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.
- (142) Du, D.-M.; Fu, B.; Hua, W.-T. *Tetrahedron* **2003**, *59*, 1933.
- (143) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045.
- (144) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A. *Eur. J. Org. Chem.* **2003**, 1428.
- (145) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pozzi, G. *Eur. J. Org. Chem.* **2003**, 1191.
- (146) Gómez, M.; Jansat, S.; Muller, G.; Bonnet, M. C.; Breuzard, J. A. J.; Lemaire, M. *J. Organomet. Chem.* **2002**, *659*, 186.
- (147) Kanemasa, S.; Adachi, K.; Yamamoto, H.; Wada, E. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 681.

- (148) Boulch, R.; Scheurer, A.; Mosset, P.; Saalfrank, R. W. *Tetrahedron Lett.* **2000**, *41*, 1023.
- (149) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045.
- (150) (a) Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603. (b) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745. (c) Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365.
- (151) (a) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.
- (152) Rippert, A. J. *Helv. Chim. Acta* **1998**, *81*, 676.
- (153) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *J. Org. Chem.* **2000**, *65*, 3326.
- (154) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620.
- (155) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2000**, *603*, 6.
- (156) Kim, S.-G.; Cho, C.-W.; Ahn, K. H. *Tetrahedron: Asymmetry* **1997**, *8*, 1023.
- (157) Kim, S.-G.; Cho, C.-W.; Ahn, K. H. *Tetrahedron* **1999**, *55*, 10079.
- (158) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.
- (159) Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545.
- (160) Lee, S.; Koh, J. H.; Park, J. *J. Organomet. Chem.* **2001**, *637–639*, 99.
- (161) Schulz, M.; Kluge, R.; Gelalcha, F. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4341.
- (162) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.
- (163) Leung, W.-H.; Mak, W.-L.; Chan, E. Y. Y.; Lam, T. C. H.; Lee, W.-S.; Kwong, H.-L.; Yeung, L.-L. *Synlett* **2002**, 1688.
- (164) Zhang, X.; Qu, Z.; Ma, Z.; Shi, W.; Jin, X.; Wang, J. *J. Org. Chem.* **2002**, *67*, 5621.
- (165) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.
- (166) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.
- (167) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.
- (168) Qian, C.; Wang, L. *Tetrahedron: Asymmetry* **2000**, *11*, 2347.
- (169) Fukuzawa, S.; Matsuzawa, H.; Metoki, K. *Synlett* **2001**, 709.
- (170) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095.
- (171) Nishiyama, H.; Soeda, N.; Naito, T.; Motoyama, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2865.
- (172) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203.
- (173) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron* **2002**, *58*, 2929.
- (174) (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227. (b) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715.
- (175) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817.
- (176) Jiang, Y.; Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 1449.
- (177) Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570.
- (178) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140.
- (179) (a) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (b) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2002**, *43*, 829. (c) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675.
- (180) (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (b) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.
- (181) (a) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074. (b) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E. *J. Org. Chem.* **1997**, *62*, 6454. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 7521.
- (182) Gómez, M.; Jansat, S.; Muller, G.; Maestro, M. A.; Mahía, J. *Organometallics* **2002**, *21*, 1077.
- (183) Du, D.-M.; Wang, Z.-Y.; Xu, D.-C.; Hua, W.-T. *Synthesis* **2002**, 2347.
- (184) Voituriez, A.; Fiaud, J.-C.; Schulz, E. *Tetrahedron Lett.* **2002**, *43*, 4907.
- (185) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215.
- (186) Braunstein, P.; Naud, F.; Pfaltz, A.; Rettig, S. J. *Organometallics* **2000**, *19*, 2676.
- (187) Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667.
- (188) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818.
- (189) Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743.
- (190) Lee, S.; Lim, C. W.; Song, C. E.; Kim, I. O. *Tetrahedron: Asymmetry* **1997**, *8*, 4027.
- (191) Lee, S.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445.
- (192) Gómez, M.; Jansat, S.; Muller, G.; Panyella, D.; van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J. *Organometallics* **1999**, *18*, 4970.
- (193) Imai, Y.; Matsuo, S.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 239.
- (194) Zhang, W.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 1512.
- (195) Bolm, C.; Hermanns, N.; Kesselgruber, M.; Hildebrand, J. P. *J. Organomet. Chem.* **2001**, *624*, 157.
- (196) (a) Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* **1995**, 1245. (b) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.
- (197) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.
- (198) Kohmura, Y.; Katsuki, T. *Synlett* **1999**, 1231.
- (199) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030.
- (200) Bellemín-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3473.
- (201) Kim, S.-G.; Ahn, K. H. *Tetrahedron Lett.* **2001**, *42*, 4175.
- (202) Chuang, T.-H.; Fang, J.-M.; Bolm, C. *Synth. Commun.* **2000**, *30*, 1627.

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