

Recent Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis

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Received June 5, 2008

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1. Introduction

Compounds containing a chiral oxazoline ring have become one of the most successful, versatile, and commonly used classes of ligands for asymmetric catalysis due to their ready accessibility, modular nature, and applicability in a wide range of metal-catalyzed transformations.

The large majority of these ligands are derived from readily available chiral amino alcohols in short, high yielding synthetic sequences. 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, a diverse range of ligands with one, two, or more oxazoline rings incorporating

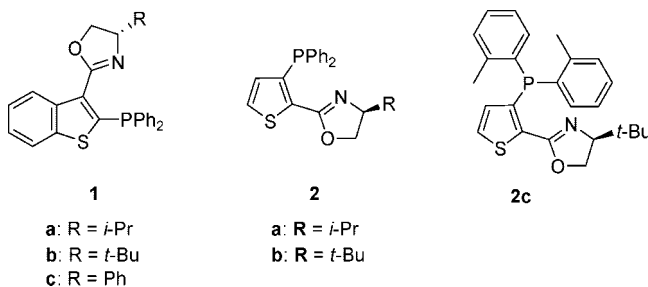
various heteroatoms, additional chiral elements, and specific structural features have been used with great success in a wide range of asymmetric reactions.

This review reports on the use of such ligands in homogeneous metal-catalyzed asymmetric synthesis since 2004, when the area was last reviewed.¹ We cover, to the best of our knowledge, all applications of oxazoline-containing ligands reported in the literature until the end of 2007. This review will be structured in the same manner as our 2004 review, as we classify ligands not by the reaction to which their metal complexes have been applied but by the nature of the denticity, chirality, and donor atoms involved. In this manner, the continued development of ligand architectural design can be more easily monitored.

2. Mono(oxazoline) Ligands

2.1. Phosphinooxazoline Ligands with Only a Stereocenter

Guiry has applied HETPHOX ligands **1** and **2** to a range of asymmetric intermolecular Heck reactions using 2,3-dihydrofuran (**3**) as the substrate (Schemes 1.1–1.2).²



The catalyst derived from **1c** gave good yields and enantioselectivities of **4** up to 66% and 77%, respectively (Table 1.1, entry 1). The *i*-Pr-substituted ligand **1a** was found to give a lower yield (23%) but a higher enantioselectivity of 89% (Table 1.1, entry 2). The optimum result of 33% yield and 87% ee was obtained using diisopropylamine as the base. Thiophene-containing ligand **2a** gave moderate yields but high enantioselectivities (Table 1.1, entries 4, 5). Ligand **2b** gave good to excellent yields of up to 97% and high enantioselectivities of up to 95%, regardless of the base employed (Table 1.1, entries 6–8). This ligand (**2b**) also gave excellent results in the cyclohexenylation of **3**, with yields of up to 97% and enantioselectivities of up to 97%.

More recently, ligand class **2** has been applied to the intramolecular asymmetric Heck reaction of aryl triflate **6** (Scheme 1.2, Table 1.2).³

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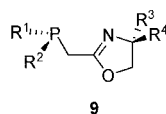
Gráinne Hargaden was born in Dublin, Ireland. She studied at University College Dublin and received a B.Sc. (Honours) degree in chemistry in 2003 and was awarded the Hugh Ryan Medal based on her final year results. Working in the group of Professor Pat Guiry, she has recently completed her Ph.D. studies, in which she researched the application of new oxazoline-containing ligands in the catalytic enantioselective Nozaki–Hiyama–Kishi reaction. During her Ph.D., she also worked in the laboratory of Professor P. G. Cozzi at the University of Bologna, applying oxazoline-containing ligands in new chromium-catalyzed asymmetric processes. She is currently a postdoctoral research associate in the group of Professor Tim Donohoe at the University of Oxford.

Ligand **2b** gave good to excellent regioselectivities of up to 99:1 (Table 1.2, entries 1–5), with the best result obtained using PMP as the base and toluene as the solvent (Table 1.2, entry 1). The enantioselectivities were found to vary greatly with the base and solvent, with toluene and proton sponge affording the best overall result of 59% conversion, 98:2 regioselectivity, and 76% ee.

Guiry has also reported the application of HETPHOX ligands **2** in the asymmetric Kinugasa reaction (Scheme 1.3)⁴ and the hydrosilylation reaction (Scheme 1.4).⁵

Naud has applied a ligand similar to **2a**, where the oxazoline and phosphine units have switched positions, in the enantioselective hydrogenation of acetophenone with an ee of 97% (Scheme 1.5).⁶

Imamoto has prepared chiral *P*-stereogenic phosphine/oxazoline ligands **9** and applied them to the palladium-catalyzed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate (Scheme 1.6, Table 1.3).⁷



	R ¹	R ²	R ³	R ⁴		R ¹	R ²	R ³	R ⁴
9a	<i>t</i> -Bu	Me	H	<i>i</i> -Pr	9e	<i>t</i> -Bu	Me	H	<i>t</i> -Bu
9b	<i>t</i> -Bu	Me	<i>i</i> -Pr	H	9f	1-Ad	Me	H	<i>t</i> -Bu
9c	Cy	Cy	H	<i>i</i> -Pr	9g	Ph	Me	H	<i>t</i> -Bu
9d	<i>t</i> -Bu	Me	Me	Me	9h	Fc	Me	H	<i>t</i> -Bu

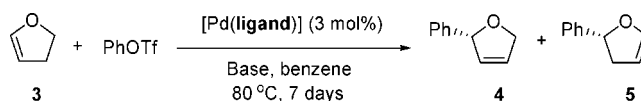
Ligand **9a** gave an excellent isolated yield of 99% with an enantiomeric excess of 86% (Table 1.3, entry 1). Its diastereomer **9b** gave a lower reactivity and an ee of 26%, most likely due to mismatched combination of the two stereogenic centers (Table 1.3, entry 2). Non-*P*-stereogenic ligand **9c** furnished an ee of 62% (Table 1.3, entry 3). Ligand



Pat Guiry graduated with an Honours B.Sc. degree in chemistry from University College Dublin (UCD) in 1986. He stayed at UCD for his Ph.D., working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his Ph.D., he also worked in Marseille in 1988 under the supervision of Dr. Jean-Pierre Finet (Cu-catalyzed *N*-arylation) and at Texas A&M in 1989 with Professor Sir Derek Barton (mechanistic studies of arylation/phenol arylation). He received his Ph.D. degree in 1990 and moved 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 UCD 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 a broad range of asymmetric catalytic transformations. He was a visiting researcher in the group of Professor Andreas Pfaltz at the MPI at Mülheim an-der-Ruhr in 1996. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from UCD. He was promoted to Senior Lecturer in 2002, to Associate Professor of Synthetic Organic Chemistry in 2003, and to Professor of Synthetic Organic Chemistry in 2006. He was the Merck Frost Visiting Professor at the University of Toronto in early 2004. He was appointed as the Chief Executive of the Conway Institute of Biomolecular and Biomedical Sciences at UCD in 2004–5 and Director of the Synthesis and Chemical Biology in 2006. A keen tennis player, he represented Ireland in the Home Nations International held in Bolton, U.K., in 2009.

9d without a stereogenic center at the oxazoline ring gave only 10% ee (Table 1.3, entry 4). The best enantioselectivity of 96% (*S*) was obtained using ligands **9e** and **9f** containing bulky *t*-Bu-substituted oxazolines (Table 1.3, entries 5, 6). Interestingly, increasing the Pd/L ratio from 1/1 to 1/2 for the reaction with **9e** led to a reversal of enantioselection to 88% ee (*R*).

Scheme 1.1



Scheme 1.2

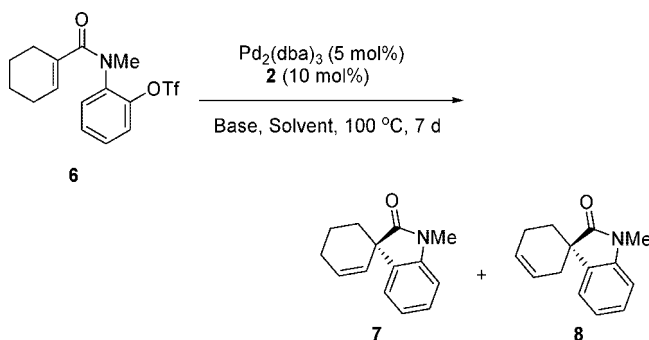


Table 1.1. Asymmetric Phenylation of 2,3-Dihydrofuran Using Ligands 1 and 2

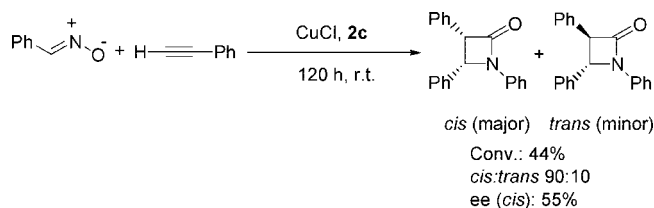
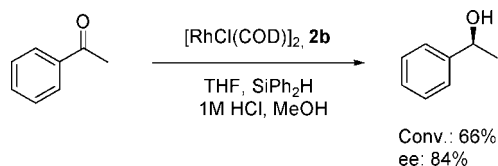
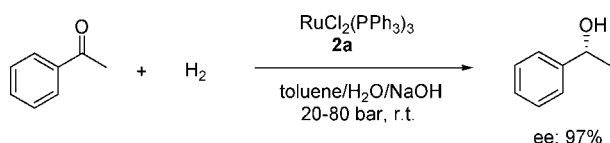
entry	ligand	base	yield (%) of 4 (5)	ee (%) of 4 (R)
1	1c	<i>i</i> -Pr ₂ NH	66 (8)	77
2	1a	Proton sponge	23 (6)	89
3	1a	<i>i</i> -Pr ₂ NH	33 (7)	87
4	2a	Et ₃ N	17 (1)	81
5	2a	Proton sponge	18 (2)	82
6	2b	Et ₃ N	90 (9)	95
7	2b	Proton sponge	72 (8)	91
8	2b	<i>i</i> -Pr ₂ NH	97 (2)	95

Table 1.2. Asymmetric Intermolecular Heck Reaction of Substrate 6 Using Ligand Class 2

entry	ligand	base	solvent	conv (%)	7:8	ee (%) of 7 (R)
1	2b	PMP ^b	toluene	67	99:1	68
2	2b	proton sponge	toluene	59	98:2	76
3	2b	DIPEA	toluene	9	94:6	60
4	2b	K ₂ CO ₃	toluene	3	65:35	62
5 ^a	2b	Cy ₂ NMe	toluene	60	98:2	72

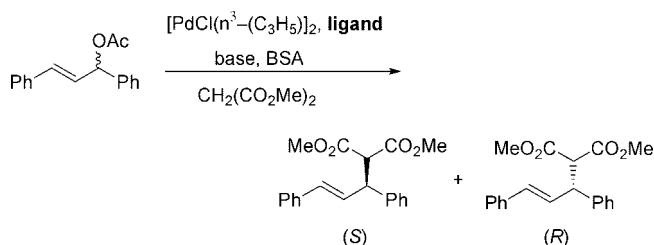
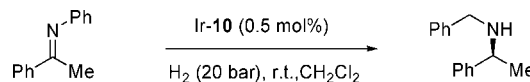
^a Reaction carried out at 140 °C. ^b 1,2,2,6,6-Pentamethylpiperidine.**Table 1.3. Asymmetric Pd-Catalyzed Allylic Alkylation Using Ligand Class 9**

entry	ligand	yield (%)	ee (%) (conf)
1	9a	99	86 (<i>S</i>)
2	9b	88	26 (<i>R</i>)
3	9c	99	62 (<i>S</i>)
4	9d	89	10 (<i>S</i>)
5	9e	99	96 (<i>S</i>)
6	9f	99	96 (<i>S</i>)
7	9g	54	57 (<i>S</i>)
8	9h	99	95 (<i>S</i>)

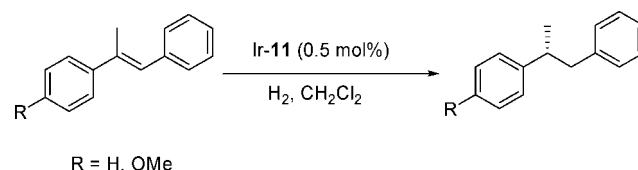
Scheme 1.3**Scheme 1.4****Scheme 1.5**

James has applied iridium complexes of new chiral *P,N* ligands **10** in the asymmetric hydrogenation of imines (Scheme 1.7, Table 1.4).⁸

Iridium catalysts bearing ligands **10a–c** led to excellent conversions of 66–100%. The enantioselectivities varied greatly, with the ethyl-substituted oxazoline ligand **10b** furnishing the highest ee of 63% even under mild conditions

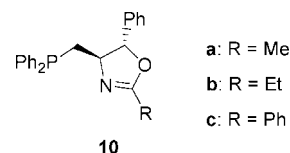
Scheme 1.6**Scheme 1.7****Table 1.4. Enantioselective Imine Hydrogenation Using Ligand Class 10**

entry	ligand (mol %)	H ₂ (atm)	temp (°C)	time (h)	conv (%)	ee (%) (<i>S</i>)
1	10a (0.1)	48	80	108	83	10
2	10b (0.1)	55	80	72	89	35
3	10b (4.0)	55	80	3	100	63
4	10b (0.1)	3	22	24	100	63
5	10b (4.0)	1	22	22	66	59
6	10c (4.0)	55	80	5	100	7

Scheme 1.8**Table 1.5. Asymmetric Hydrogenation of Methylstilbene Derivatives Using Ir Complexes of 11**

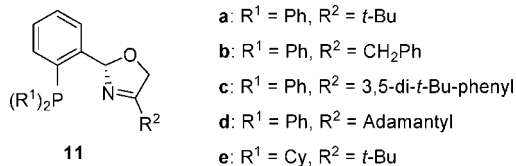
entry	ligand	R	H ₂ (bar)	temp (°C)	conv (%)	ee (%)
1	11a	H	10	rt	31	98
2	11a	H	50	rt	64	98
3	11a	H	90	rt	94	97
4	11a	H	50	50	98	98
5	11b	H	50	rt	77	83
6	11c	H	50	rt	68	97
7	11d	H	50	rt	98	97
8	11e	H	50	rt	>99	99
9	11e	OMe	100	rt	>99	98
10	11a	OMe	100	rt	>99	97
11	11d	OMe	100	rt	>99	97
12	11e	OMe	100	rt	>99	90

of room temperature, low catalyst loading, and low H₂ pressure (Table 1.4, entry 4). The methyl- and phenyl-substituted ligands **4a** and **4c** gave low selectivities of 10% and 7%, respectively.



Zhang has developed new conformationally rigid phosphino-oxazolines of type **11**, architecturally related to the PHOX ligands.⁹

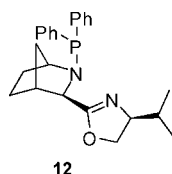
The ligands were successfully applied in the asymmetric hydrogenation of unfunctionalized methylstilbene derivatives (Scheme 1.8, Table 1.5).



All the catalysts gave excellent enantioselectivities (97–99% ee), with the exception of **11b**, which gave a lower ee of 83% (Table 1.5, entry 5). However, the conversions were disappointing using catalysts **11a–c** at 50 bar H₂, but in contrast, **11d** and **11e** gave near quantitative conversions (Table 1.5, entries 7, 8). Increasing the H₂ pressure to 100 bar gave complete conversion with catalyst **11a** (Table 1.5, entry 10) with the high level of enantioselectivity maintained. Ligand class **11** was also applied to the hydrogenation of a range of β -methylcinnamic esters with excellent conversions and enantioselectivities reported, with **11d** routinely furnishing enantiomeric excesses of 99%.

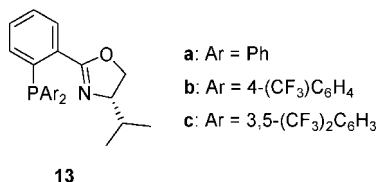
These ligands have also proven to be successful in the palladium-catalyzed allylic alkylation, with **11a** giving an ee of 98%, and in the intermolecular Heck reaction between 2,3-dihydrofuran and phenyl triflate, with **11a** giving the optimum ee of 94%.¹⁰

Andersson has applied a new chiral phosphino-oxazoline ligand **12** in the iridium-catalyzed asymmetric hydrogenation of acyclic aromatic *N*-arylamines (Scheme 1.9, Table 1.6).¹¹



Initial hydrogenation of the model substrate (R = R¹ = H) resulted in a 90% ee with 98% conversion in 2 h. Having *ortho*-methoxy substituents on the aromatic rings led to a decrease in reaction rate and a slight decrease in enantioselectivity (Table 1.6, entries 2, 3). The imines bearing electron-withdrawing and electron-donating groups at the *para*-positions also resulted in lower enantiomeric excesses (Table 1.6, entries 4–8) although full conversions were obtained within 3 h at room temperature. There was not reported to be any correlation between the electronic nature of the *para*-substituent and the ee of the product obtained.

The application of phosphino-oxazolines **13** in the iridium-catalyzed allylic alkylation (Scheme 1.10) of linear substrates of type **14** has been reported by Helmchen.¹²



The results obtained clearly show the importance of both electronic and steric effects during the reaction (Table 1.7). Thus, the CF₃-substituted ligands **13b** and **13c** were found to be superior to the parent ligand **13a**, with ligand **13b** giving enhanced yields and enantioselectivities (Table 1.7, entries 2, 5, 8). The degree of regioselectivity was significantly higher with the *para*-methoxy-substituted substrate **14b**, with the best overall result being obtained using this

Scheme 1.9

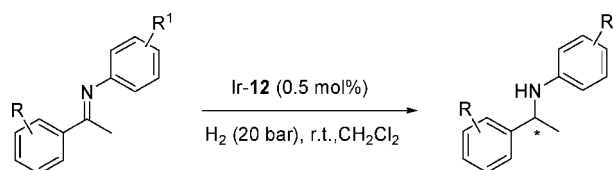


Table 1.6. Asymmetric Hydrogenation of Acyclic *N*-Arylamines Catalyzed by Ir Complexes of **12**

entry	R	R ¹	time (h)	conv (%)	ee (%) (conf)
1	H	H	2	98	90 (<i>R</i>)
2	2-Me	H	12	52	83 (–)
3	H	2-Me	3	99	80 (–)
4	4-F	H	2	99	89 (–)
5	4-OMe	H	3	99	86 (+)
6	H	4-OMe	1.5	99	89 (+)
7	4-OMe	4-OMe	2	99	86 (+)
8	4-Cl	4-OMe	1.5	99	89 (+)

Scheme 1.10

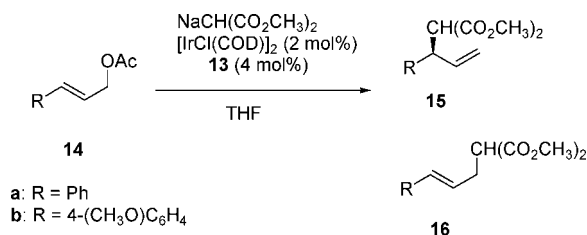
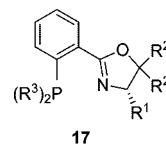


Table 1.7. Iridium-Catalyzed Enantioselective Allylic Alkylation of **14 Using Ligand Class **13****

entry	ligand	substrate	temp (°C)	yield (%)	15:16	ee of 15 (%)
1	13a	14a	rt	61	92:8	30
2	13b	14a	rt	85	87:13	92
3	13c	14a	rt	46	86:14	87
4	13a	14a	67	92	77:23	78
5	13b	14a	67	99	95:5	91
6	13c	14a	67	95	89:11	84
7	13a	14b	67	89	99:1	72
8	13b	14b	67	98	99:1	95
9	13c	14b	67	71	93:7	62

substrate (**14b**), which afforded a 98% yield, 99:1 regioselectivity, and 95% ee at 67 °C (Table 1.7, entry 8).

Pfaltz has reported the application of PHOX ligands **17** in the enantio- and diastereoselective [3 + 2] silver-catalyzed cycloadditions of azomethine ylides with α,β -unsaturated carboxylic esters (Scheme 1.11, Table 1.8).¹³



Ligand	R ¹	R ²	R ³	Ligand	R ¹	R ²	R ³
17a	<i>i</i> -Pr	H	Ph	17g	<i>i</i> -Pr	Ph	Cy
17b	<i>t</i> -Bu	H	Ph	17h	<i>i</i> -Pr	Me	<i>o</i> -Tol
17c	<i>i</i> -Pr	H	<i>o</i> -Tol	17i	<i>i</i> -Pr	Ph	<i>o</i> -Tol
17d	Ph	H	<i>o</i> -Tol	17j	<i>i</i> -Pr	Cy	<i>o</i> -Tol
17e	<i>i</i> -Pr	<i>n</i> -Pr	Ph	17k	<i>i</i> -Pr	<i>o</i> -Tol	<i>o</i> -Tol
17f	<i>i</i> -Pr	Ph	Ph				

Scheme 1.11

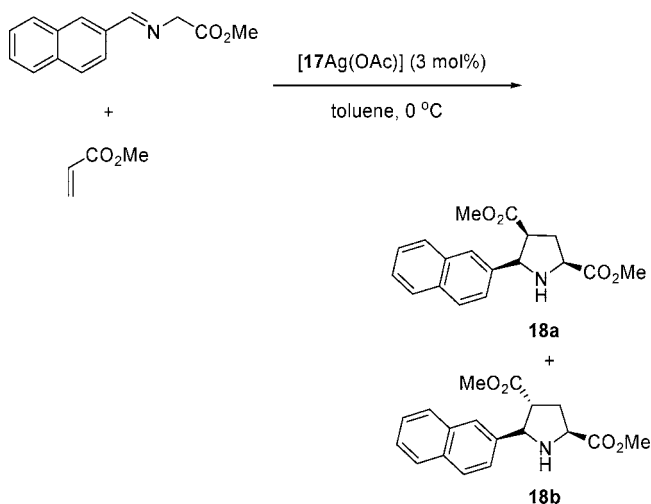
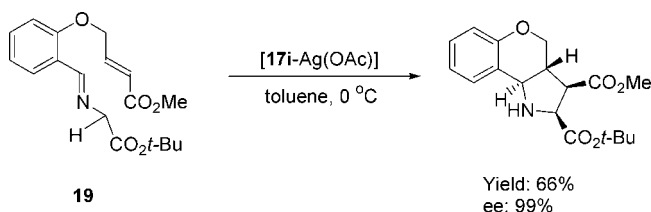


Table 1.8. Asymmetric Ag(I)-Catalyzed Intermolecular [3 + 2] Cycloaddition Using Ligand Class 17

entry	ligand	time (h)	yield (%)	18a:18b	ee of 18a (%)
1	17a	5	95	>40:1	29
2	17b	6	94	>40:1	27
3	17c	8	93	>40:1	45
4	17d	7	95	>40:1	15
5	17e	8	57	>24:1	43
6	17f	7	86	>24:1	49
7	17g	7	80	24:1	62
8	17h	8	49	24:1	62
9	17i	7	90	40:1	65
10	17j	9	40	9:1	62
11	17k	6	56	12:1	67

Scheme 1.12



The standard PHOX ligands **17a** and **17b** led to the formation of pyrrolidine **18a** in high yields and high diastereoselectivities but with low enantioselectivities (Table 1.8, entries 1, 2). Replacing the *P*-phenyl by *P*-*ortho*-tolyl groups (**17c**) resulted in a moderate increase in ee to 45% (Table 1.8, entry 3). The introduction of two geminal alkyl or aryl groups at C(5) of the oxazoline ring also had a beneficial effect on the ee (Table 1.8, entries 5–11). Ligand **17i** afforded the best overall result in terms of yield, regioselectivity, and enantioselectivity (Table 1.8, entry 9).

This ligand (**17i**) was subsequently applied in the asymmetric Ag(I)-catalyzed intramolecular [3 + 2] cycloaddition reaction of **19** (Scheme 1.12) and afforded an enantioselectivity of 99%.¹³

Moeborg has developed new phosphino-4-(1-hydroxyalkylo)oxazoline ligands **20** and **21** and applied them in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6, Table 1.9).¹⁴

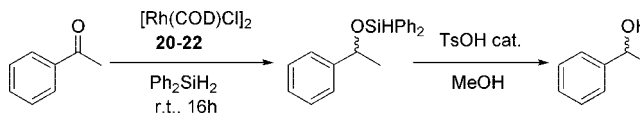
In all cases, the reactions proceeded with excellent conversions, and for ligands **20a–d** and **21a–b**, only minor differences in enantioselectivity were observed between reactions using hydroxyl- and alkoxy-containing ligands with

Table 1.9. Asymmetric Pd-Catalyzed Allylic Alkylation Using **20** and **21**

entry	ligand	conv (%)	ee (%) (conf)
1 ^a	20a	99	95 (<i>R</i>)
2 ^a	20b	100	95 (<i>R</i>)
3 ^a	20c	100	92 (<i>R</i>)
4 ^a	20d	100	88 (<i>R</i>)
5 ^a	21a	100	97 (<i>S</i>)
6 ^a	21b	100	98 (<i>S</i>)
7 ^a	21c	100	88 (<i>S</i>)
8 ^a	21d	100	99 (<i>S</i>)
10 ^b	20b	100	91 (<i>R</i>)
11 ^b	21c	100	76 (<i>S</i>)
12 ^b	21d	81	97 (<i>S</i>)

^a Reaction carried out at 0 °C. ^b Reaction carried out at 25 °C.

Scheme 1.13

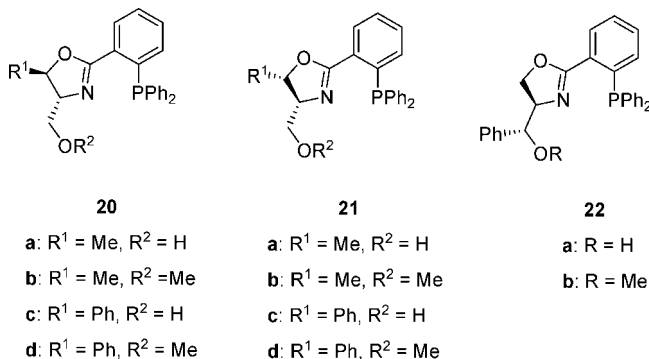
Table 1.10. Enantioselective Hydrosilylation of Acetophenone Using Ligands **20** and **22**

entry	ligand	conv (%)	ee (%) (conf)
1	20a	100	12 (<i>S</i>)
2 ^a	20a	100	63 (<i>S</i>)
3	20b	100	70 (<i>S</i>)
4 ^a	20b	100	60 (<i>S</i>)
5	22a	100	66 (<i>R</i>)
6 ^a	22a	97	91 (<i>R</i>)
7 ^{a,b}	22a	100	95 (<i>R</i>)
8	22b	100	56 (<i>R</i>)
9	22b	100	87 (<i>R</i>)

^a AgBF₄ added. ^b Reaction was carried out at 0 °C.

the same substitution pattern (Table 1.9, entries 1–6). In contrast, **21c** and **21d** exhibited a somewhat larger difference of 11% (Table 1.9, entries 7, 8). This was increased to 21% when the reaction was carried out at 25 °C (Table 1.9, entries 11, 12). Overall, ligand **21d** afforded the highest enantioselectivities of 99% and 97% at 0 and 25 °C, respectively.

This work has recently been extended to include ligands **22**, which have been applied in the enantioselective Rh-catalyzed hydrosilylation of acetophenone (Scheme 1.13).¹⁵ Employing both **20** and **22** gave excellent conversions and moderate to excellent enantioselectivities. The process was improved by the addition of AgBF₄ and carrying out the reaction at 0 °C, with ligand **22a**, giving the best result of 100% conversion and 95% ee (Table 1.10, entry 7).

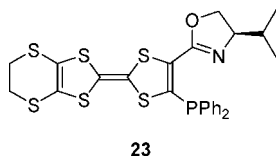


The development of a chiral tetrathiafulvene-based phosphino-oxazoline ligand **23** has been reported by Niedercorn

Scheme 1.14



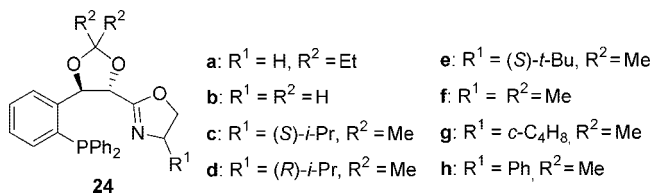
and Avarvari.^{16a} In the asymmetric palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6), an enantiomeric excess of 85% (*R*) was obtained after 18 h at room temperature.



23

In the asymmetric hydrogenation of *N*-(phenylethylidene)aniline, the iridium complex of ligand **23** gave complete conversion and an enantioselectivity of 68%, after 15 h at 20 °C.^{16b}

StepHOX **24**, a new family of optically active, tunable phosphinothioether ligands, has been described by Morken.¹⁷



24

The ligands were applied in the palladium-catalyzed allylic alkylation (Scheme 1.6) with very good yields reported in all cases. The optimum enantioselectivities were obtained using ligands **24d** and **24g**, which gave 97% ee and 95% ee, respectively. Ligand **24d** also gave the highest ee of 59% in the enantioselective Tsuji allylation (Scheme 1.14).

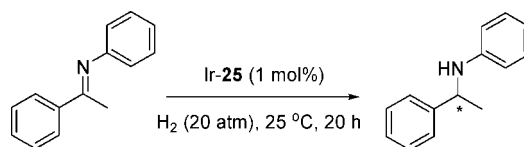
Zhou has synthesized new chiral phosphinothioether ligands **25** and reported their application in the iridium-catalyzed hydrogenation of imines (Scheme 1.15).¹⁸ Using the iridium complex of (*S,S*)-**25a**, *N*-(1-phenylethylidene)aniline was hydrogenated with 98% conversion and 76% ee (Table 1.11, entry 1). Ligand (*S,R*)-**25a** gave a racemic product with very low conversion (Table 1.11, entry 2). The

Table 1.11. Asymmetric Hydrogenation of *N*-(1-Phenylethylidene)aniline Using **25**

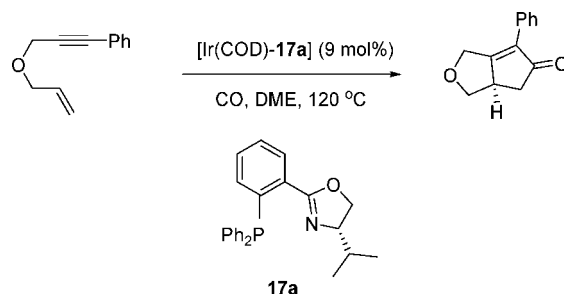
entry	ligand	solvent	conv (%)	ee (%)
1	(<i>S,S</i>)- 25a	CH ₂ Cl ₂	96	76
2	(<i>S,R</i>)- 25a	CH ₂ Cl ₂	7	0
3	(<i>S,S</i>)- 25b	CH ₂ Cl ₂	18	74
4	(<i>S,S</i>)- 25c	CH ₂ Cl ₂	98	81
5	(<i>S,S</i>)- 25c	THF	65	79
6	(<i>S,S</i>)- 25c	toluene	98	82
7	(<i>S,S</i>)- 25c	EtOAc	40	74
8	(<i>S,S</i>)- 25c	MeOH	8	nd
9	(<i>S,S</i>)- 25c	ether	99	87
10	(<i>S,S</i>)- 25d	ether	99	88
11	(<i>S,S</i>)- 25e	ether	>99	90
12 ^a	(<i>S,S</i>)- 25e	ether	>99	89
13 ^b	(<i>S,S</i>)- 25e	ether	70	90
14 ^c	(<i>S,S</i>)- 25e	ether	>99	93
15 ^{c,d}	(<i>S,S</i>)- 25e	<i>t</i> -BuOMe	>99	93

^a 0.5 mol% catalyst used. ^b 0.1 mol % catalyst used. ^c Reaction carried out at ambient H₂ pressure at 10 °C. ^d 4 Å MS used.

Scheme 1.15



Scheme 1.16



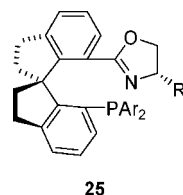
17a

Table 1.12. Enantioselective Pauson-Khand Reaction Using Ir-17a

entry	P _{CO} (bar)	yield (%)	ee (%)
1	1.4	51	97 (<i>R</i>)
2	1.6	61	96 (<i>R</i>)
3	1.8	71	94 (<i>R</i>)
4	2.0	81	92 (<i>R</i>)
5	2.2	85	91 (<i>R</i>)

catalyst bearing ligand **25c**, with a benzyl group on the oxazoline ring gave better results, with complete conversion and an enantiomeric excess of 87% (Table 1.11, entry 9). The introduction of two groups onto the *P*-phenyl ring (**25e**) led to a further augmentation in the enantioselectivity, with 93% ee reported (Table 1.11, entries 14, 15).

Ligand **25e** was also successfully applied to the enantioselective hydrogenation of a range of *N*-aryl ketimines, with enantioselectivities of 91–97% reported for all substrates tested.



25

- a:** Ar = Ph, R = *i*-Pr
b: Ar = Ph, R = Ph
c: Ar = Ph, R = Bn
d: Ar = 4-MeOC₆H₅, R = Bn
e: Ar = 3,5-Me₂C₆H₃, R = Bn

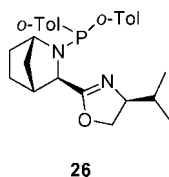
Pfaltz has applied iridium complexes of the PHOX ligand **17a** to the asymmetric catalytic intramolecular Pauson-Khand reaction (Scheme 1.16, Table 1.12).¹⁹

The enantioselectivities observed were excellent (91–97%), with the yields varying from moderate to very good. Increasing the CO pressure from 1.4 to 2.2 bar resulted in an increase in yield from 51–81%. This trend was coupled with a drop in enantiomeric excess from 97% to 91%. Replacing the ether linkage in the substrate by a C(CO₂Me)₂ group also resulted in enantiomeric excesses of 82–94% with generally lower yields of 48–80% reported.

Andersson has reported the application of *P,N* ligand **26** in the first asymmetric hydrogenation of enol phosphinates (Scheme 1.17, Table 1.13).²⁰

The hydrogenation of **27a** was successful with complete conversion after 30 min, with the corresponding alkylphosphinate obtained in 95% ee (Table 1.13, entry 1). Substrates bearing an electron-withdrawing group at the *para*-position

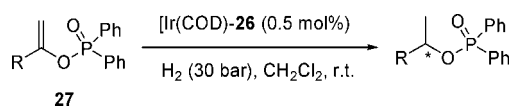
were more reactive (Table 1.13, entries 5–7), with full conversion within 1 h, compared to those substrates with electron-donating groups at the *para*-position (Table 1.13, entries 2–4), which took up to 4 h for full conversion. The electronics of the substrate are shown to have an effect on the reactivity but not the stereoselectivity of the process. Alkyl enol phosphinates **27i** and **27j** were both hydrogenated with excellent selectivity of 95% ee.²⁰



The synthesis and application of phosphino-oxazoline ligands **28** in the palladium-catalyzed Tsuji allylation has been reported by Stoltz (Scheme 1.18, Table 1.14).²¹

At 25 °C all three ligands tested gave excellent yields (96–99%) and very good enantioselectivities (87–89% ee), with the ligand bearing CF₃ being significantly more reactive (Table 1.14, entries 2, 3). This ligand gave an enhanced enantioselectivity of 92% at 0 °C, with a reasonable yield of 54% after 150 min (Table 1.14, entry 5).

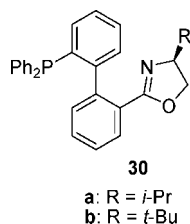
Scheme 1.17



2.2. Phosphino-oxazoline Ligands with a Stereoaxis

Pregosin has applied ligand **29** in the palladium-catalyzed ring opening alkylation of oxabenzonorbornadiene (Scheme 1.19) and achieved yields of up to 86% with enantioselectivities of 92% (**29a**) and 93% (**29b**).²²

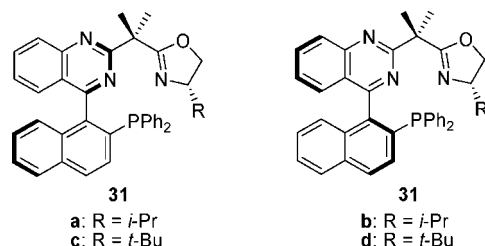
Zhang and co-workers have reported the synthesis of a novel chiral phosphine-oxazoline **30** with an axis-unfixed biphenyl backbone.²³



The ligands were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (Scheme 1.6, Table 1.15).

Both **30a** and **30b** resulted in high chemical yields and high enantiomeric excesses of the (*S*)-configured product. Particularly successful was the *t*-Bu-substituted ligand **30b**, which gave the highest ee of 90%. This is one of few examples of an axis-unfixed ligand giving a similar level of both reactivity and stereoselectivity to axis-fixed biaryl ligands.

Guiry has reported the synthesis and application of quinazoline-oxazoline containing ligands **31** and their application in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (Scheme 1.6, Table 1.16).²⁴



Ligand class **31** all led to excellent isolated yields after 24 h at room temperature. The results show that the axial chirality of the quinazolinap unit is the dominant stereogenic element (e.g., Table 1.16, entries 2, 4). The less sterically demanding substituent (*i*-Pr) on the oxazoline ring had a beneficial effect on the level of enantioselection (Table 1.16, entries 1, 3). Additionally, for ligands **31a** and **31b**, the match/mismatch of the stereoaxis and stereogenic center is

Table 1.13. Iridium-Catalyzed Hydrogenation of 27 Using Ir-26

Entry	Substrate	Conv. (%)	ee (%) (Conf.)
1		>99	95 (<i>R</i>)
2		>99	95 (<i>R</i>)
3		>99	95 (<i>R</i>)
4		>99	95 (<i>R</i>)
5		>99	95 (<i>R</i>)
6		>99	95 (<i>R</i>)
7		>99	95 (<i>R</i>)
8		>99	95 (<i>R</i>)
9		>99	95 (<i>R</i>)
10		>99	95 (<i>R</i>)

Scheme 1.18

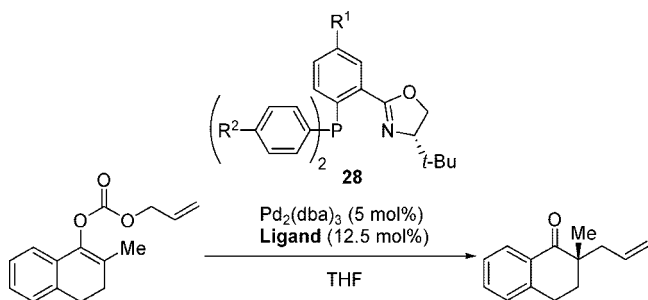


Table 1.14. Asymmetric Allylation Using Ligand 28

entry	ligand	temp (°C)	time (min)	yield (%)	ee (%)
1	R ¹ = R ² = H	25	120	96	88
2	R ¹ = R ² = CF ₃	25	10	99	87
3	R ¹ = H, R ² = CF ₃	25	10	99	89
4	R ¹ = R ² = H	0	150	0	
5	R ¹ = R ² = CF ₃	0	150	54	92

Scheme 1.19

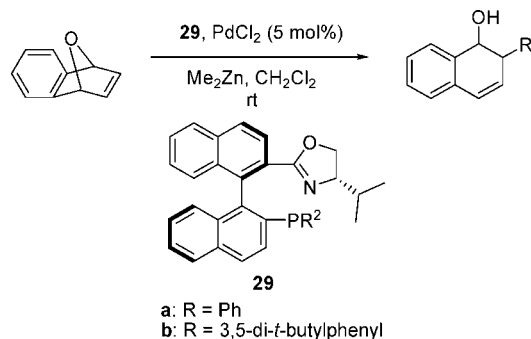


Table 1.15. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligand Class 30

entry	ligand	solvent	yield (%)	ee (%) (conf)
1	30a	THF	96	83 (<i>S</i>)
2	30a	CH ₂ Cl ₂	89	82 (<i>S</i>)
3	30b	THF	97	88 (<i>S</i>)
4	30b	CH ₂ Cl ₂	96	90 (<i>S</i>)

Table 1.16. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligand Class 31

entry	ligand	base	yield (%)	ee (%) (conf)
1	31a	LiOAc	>95	81 (<i>R</i>)
2	31a	KOAc	>95	55 (<i>R</i>)
3	31b	LiOAc	>95	58 (<i>S</i>)
4	31b	KOAc	>95	15 (<i>S</i>)
5	31c	LiOAc	>95	60 (<i>R</i>)
6	31c	KOAc	>95	7 (<i>S</i>)
7	31d	LiOAc	88	39 (<i>S</i>)
8	31d	KOAc	>95	55 (<i>R</i>)

well pronounced with **31a** resulting in higher enantioselectivity than **31b** (Table 1.16, entries 1, 3).

2.3. Phosphino-oxazoline Ligands with a Stereoplane

Zhang has reported the application of *P,N* ligands **32** in the enantioselective [3 + 2] cycloaddition of azomethine ylides with acrolates (Scheme 1.20, Table 1.17).²⁵

Phosphino-oxazolines **32** were found to catalyze the [3 + 2] cycloaddition reaction in the presence of CuOAc with good *exo* selectivity and high enantiomeric excesses (Table

Scheme 1.20

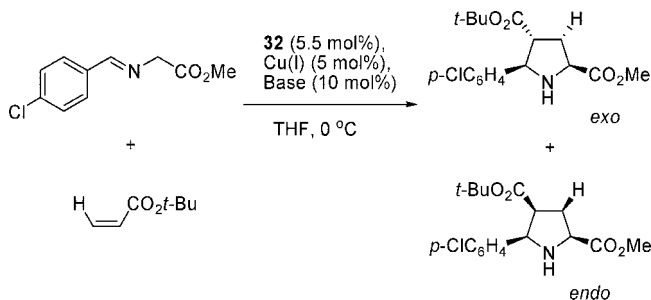
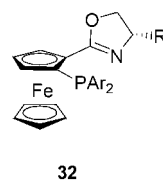


Table 1.17. Enantioselective Cu(I)-Catalyzed [3 + 2] Cycloaddition Using Ligand Class 32

entry	Cu(I)	ligand	yield of <i>exo</i> (%)	yield of <i>endo</i> (%)	ee of <i>exo</i> (%)
1	CuOAc	32a	62	20	70
2	CuOAc	32b	72	11	76
3	CuOAc	32c	67	16	86
4	CuOAc	32d	76	5	89
5	CuOAc	32e	64	12	77
6	CuOAc	32f	69	16	72
7	CuClO ₄	32d	92	6	89
8 ^a	CuClO ₄	32d	85	4	91

^a Reaction carried out at −25 °C.

1.17, entries 1–5). The highest *exo* selectivity and enantiomeric excess was obtained using the *t*-Bu-substituted ligand **32d** (Table 1.17, entry 4). The yield and enantiomeric excess obtained using this ligand was further improved to 91% ee by applying CuClO₄ and conducting the reaction at a lower temperature (Table 1.17, entry 8). Ligand **32d** was subsequently applied in the cycloaddition of a range of substrates with very good yields (60–85%) and excellent enantiomeric excesses (>90%) reported in all cases.



a: Ar = Ph, R = *i*-Pr

b: Ar = 3,5-(Me)₂C₆H₃, R = *i*-Pr

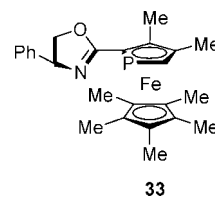
c: Ar = Ph, R = *t*-Bu

d: Ar = 3,5-(Me)₂C₆H₃, R = *t*-Bu

e: Ar = 3,5-(Me)₂C₆H₃, R = Ph

f: Ar = 3,5-(Me)₂C₆H₃, R = Bn

Fu has successfully applied ligand **33** in the kinetic resolution of azomethine imines via copper-catalyzed [3 + 2] cycloadditions (Scheme 1.21).²⁶



Ligand **33** furnished a good selectivity factor for a range of electron-poor alkynes, with ethylpropiolate and 4-(trifluoromethyl)phenylacetylene being the most effective reported to date (Table 1.18, entries 1, 3). The enantioselectivities were very high to excellent. It was also possible to effectively resolve a variety of C-5-substituted dipoles (Table 1.18, entries 4–8), including nonaryl entities (Table 1.18, entries 7, 8), again with excellent enantioselectivities reported.

Zhou has reported the application of a range of *P,N* ligands of type **34a–j** in the Ag-catalyzed asymmetric cycloaddition of azomethine ylides (Scheme 1.22, Table 1.19).²⁷

Scheme 1.21

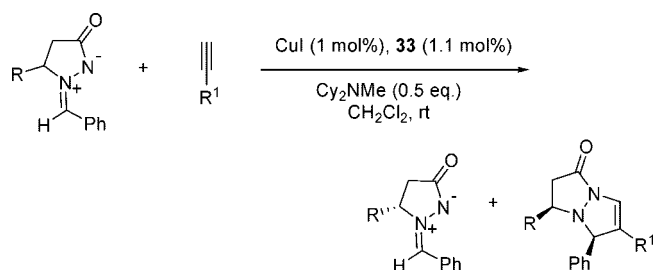


Table 1.18. Kinetic Resolution of Azomethine Imines Using Ligand 33

entry	R	R ¹	<i>s</i> ^a	yield (%) ^b	ee (%) ^b
1	Ph	CO ₂ Et	53	42	99
2	Ph	CON(Me)Ph	30	42	91
3	Ph	4-(trifluoromethyl)phenyl	53	39	99
4	Ph	CO ₂ Et	53	42	99
5	Ph	CON(Me)Ph	54	44	99
6	3-BrC ₆ H ₄	CO ₂ Et	15	31	98
7	<i>i</i> -Pr	CON(Me)Ph	76	40	97
8	<i>t</i> -Bu	CON(Me)Ph	51	48	93

^a Selectivity factor. ^b Yield and ee of the dipole.

Scheme 1.22

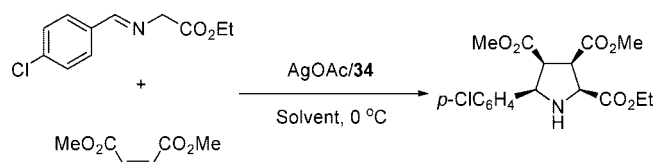
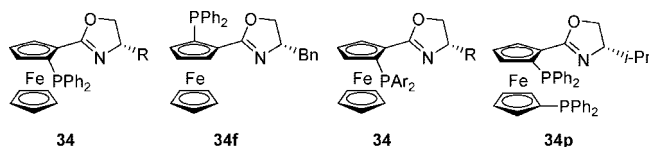


Table 1.19. AgOAc-Catalyzed Asymmetric Cyloaddition Using Ligand Class 34

entry	ligand	solvent	yield (%)	ee (%)
1	34a	toluene	89	68
2	34b	toluene	86	53
3	34c	toluene	88	69
4	34d	toluene	98	81
5	34d	THF	86	86
6	34d	Et ₂ O	93	88
7	34e	Et ₂ O	98	81
8	34f	Et ₂ O	96	78 ^a
9	34g	Et ₂ O	91	84
10	34h	Et ₂ O	88	89
11	34i	Et ₂ O	89	83
12	34j	Et ₂ O	94	94
13 ^b	34j	Et ₂ O	88	98
14 ^c	34j	Et ₂ O	98	98

^a (-) configuration obtained ^b Reaction carried out at -25 °C
^c Reaction carried out at -40 °C

Initial investigation showed that silver complexes of ligand **34a** efficiently catalyzed the cycloaddition in toluene with high activity and moderate enantioselectivity in the absence of base (Table 1.19, entry 1). Variation of the substituent on the oxazoline ring led to an increased ee for ligand **34d** (Table 1.19, entry 4). This enantioselectivity was further improved to 88% in the presence of Et₂O (Table 1.19, entry 6). The effect of the electronic properties of the phosphorus substituent was also studied (Table 1.19, entries 9–14). An improvement in enantiomeric excess to 94% was observed using ligand **34j**, bearing a strong electron-withdrawing group at the *para*-position (Table 1.19, entries 12–14). Ligand **34j** was subsequently applied in the cycloaddition of a range of

a: R = *i*-Prb: R = *t*-Bu

c: R = Ph

d: R = Bn

e: R = H

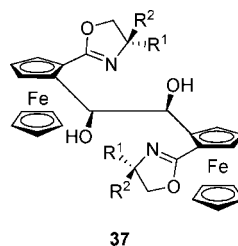
g: R = Bn, Ar = 4-MeOC₆H₄h: R = Bn, Ar = 3,5-Me₂C₆H₃i: R = Bn, Ar = 3,5-(CF₃)₂C₆H₃j: R = Bn, Ar = 4-CF₃C₆H₄k: R = *i*-Pr, Ar = Phl: R = *i*-Pr, Ar = 4-CF₃C₆H₄m: R = *i*-Pr, Ar = 4-MeOC₆H₄n: R = *i*-Pr, Ar = 3,5-Me₂C₆H₃o: R = *i*-Pr, Ar = 3,5-(CF₃)₂C₆H₃

azomethine ylides and afforded enantiomeric excesses of >88% in all cases.

This work was further extended by Hou, who reported the application of ligands **34k–p** in the reaction of imino ester **35** with nitroalkene **36** (Scheme 1.23, Table 1.20).²⁸

The reaction with ligand **34k** yielded only the *exo*-product with 97% ee (Table 1.20, entry 1). Varying the groups on the phosphorus led to dramatic variations in diastereoselectivity. Ligands **34m** and **34n** with electron-donating substituents gave exclusively *exo*-product, with excellent enantioselectivities (Table 1.20, entries 3, 4). Ligand **34l** with one CF₃ substituent gave a mixture of *exo:endo* isomers (73:27), whereas **34o** with two CF₃ substituents on each phenyl ring gave the *endo*-isomer with 97% ee.

Fukuzawa has synthesized a new chiral bisferrocenyl oxazoline ligand class **37** and reported their application in the asymmetric Diels–Alder reaction (Scheme 1.24, Table 1.21).²⁹

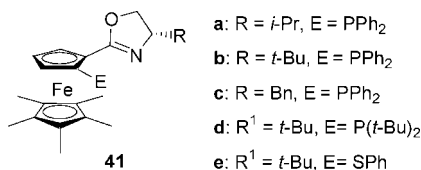
a: R¹ = *i*-Pr, R² = Hb: R¹ = *t*-Bu, R² = Hc: R¹ = Ph, R² = Hd: R¹ = Bn, R² = He: R¹ = R² = Me

Ligand **37a** resulted in very good to excellent conversions for the Diels–Alder reaction and excellent *endo/exo* ratios, with the *endo*-isomer being favored in all cases. The results also showed the dramatic effect which the Lewis acid had on enantioselectivity, with Yb(OTf)₃ providing the best overall result, with the *endo* isomer being formed in 80:20 ratio, with an enantiomeric excess of 70% reported (Table 1.21, entry 4).

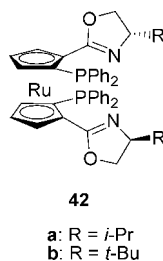
The enantioselective hydrogenation of an α-alkoxy-substituted ketone **39** (Scheme 1.25, Table 1.22) with chiral ruthenium (phosphinoferrocenyl)oxazoline complexes **38** has been reported by Tellers.³⁰

Each of the ligands showed good enantioselectivities and reactivities in 2-propanol (75–86% ee, 100% conversion), with the complex bearing ligand **38b** giving the highest enantiomeric excess of 86% (Table 1.22, entry 2). This ee was improved to 93% by changing the solvent to toluene and the base to NaOH (Table 1.22, entry 7).

These ligands have also been used in the hydrogenation of a range of ketones by Naud.⁶ They were subsequently shown to be effective, industrially viable catalysts and were

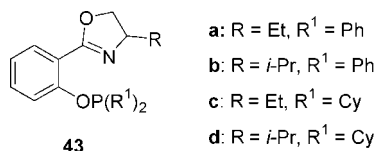


been reported by Zhang.³⁴ The ligands all resulted in excellent enantiomeric excess (>82%), with the best ee of 92% being obtained using **42a**.



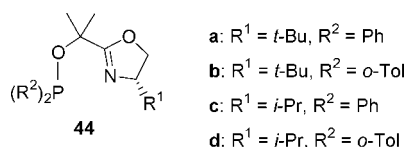
2.4. Oxazoline-Phosphonite Ligands

The development of a new range of bidentate chiral *P,N* ligands **43** was reported by Gómez.³⁵



The ligands were applied in the palladium-catalyzed asymmetric allylic alkylation of 1,2-diphenylpropenyl acetate (Scheme 1.6, Table 1.24).

Oxazolynyl phosphinites **43a** and **43b** provided the highest enantiomeric excesses of 78% and 82%, respectively (Table 1.24, entries 1, 2). The analogous ligands **43c** and **43d** containing PCy₂ groups were more active but less selective (Table 1.24, entries 3, 4).



In 2004, Pfaltz reported the synthesis of SimplePHOX ligands **44**, a readily available class of chiral ligands for the iridium-catalyzed asymmetric hydrogenation of unfunctionalized olefins (Scheme 1.28, Table 1.25).³⁶

Full conversion was achieved for the hydrogenation of (*E*)-1,2-diphenyl-1-propene after 2 h at 50 bar H₂ using SimplePHOX ligands **44a–d**. The enantioselectivities were also excellent, with the *t*-Bu-substituted oxazoline/*o*-tolyl-substituted phosphorus ligand system **44b** giving the best ee of 98%. The ligands were also successful in the hydrogenation of a range of other substrates, with complete conversion and excellent enantioselectivities (66–95% ee) reported.

Pfaltz has applied iridium complexes of **45a** and **45b** to the enantioselective hydrogenation of terminal alkenes **46** (Table 1.26a and b).³⁷

The iridium complex of **45a** with a dicyclohexylphosphinite unit was the most selective catalyst in the hydrogenation of substrates **46a–g**, with complete conversion in all cases. The highest enantioselectivity of 94% was obtained in the hydrogenation of electron-rich alkene **46a** and **46g**

Table 1.24. Enantioselective Allylic Alkylation Using Ligands 43a–d

entry	ligand	time (h)	ee (%) (conf)
1	43a	1	78 (<i>R</i>)
2	43b	1.5	82 (<i>S</i>)
3	43c	0.5	44 (<i>R</i>)
4	43d	0.5	69 (<i>S</i>)

Scheme 1.28

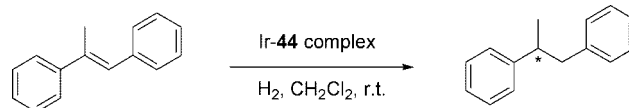


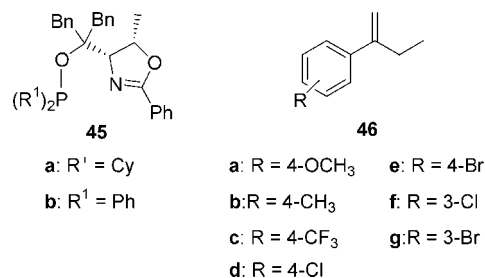
Table 1.25. Enantioselective Hydrogenation of Trisubstituted, Unfunctionalized Olefins with Ir Catalysts Derived from Ligand Class 44

entry	ligand	conv (%)	ee (%)
1	44a	>99	96 (<i>R</i>)
2	44b	>99	98 (<i>R</i>)
3	44c	>99	85 (<i>R</i>)
4	44d	>99	90 (<i>R</i>)

Table 1.26. Enantioselective Hydrogenation of Substrates 46a–g (1 bar H₂)

entry	substrate	temp (°C)	time (min)	conv (%)	ee (%)
(a) Using Ligand 45a					
1	46a	25	30	>99	94
2	46b	25	30	>99	91
3	46c	25	30	>99	88
4	46d	25	30	>99	89
5	46e	0	30	>99	90
6	46f	25	30	>99	92
7	46g	25	30	>99	94
(b) Using Ligand 45b					
1	45a	25	30	>99	90
2	45b	25	30	>99	88
3	45c	0	30	>99	64
4	45d	25	30	>99	73
5	45e	25	30	>99	71
6	45f	25	0	>99	76
7	45g	25	30	>99	76

and electron-poor alkene **46g** (Table 1.26a, entries 1, 7). The iridium complex of ligand **45b** with a diphenylphosphinite unit again resulted in excellent conversions, but the enantioselectivities were significantly lower (Table 1.26b), with the exception of substrate **46a**, which gave an ee of 90% (Table 1.26b, entry 1).



2.5. Oxazoline Ligands with Phosphorus Bonded to One N Atom

Niedercorn has previously reported the synthesis of a range of new aminophosphine oxazoline ligands **47–49**. The preparation of cationic iridium(I) complexes of **47–49** and their use in the asymmetric hydrogenation of imines (Scheme 1.29, Table 1.27) was more recently reported.³⁸

Scheme 1.29

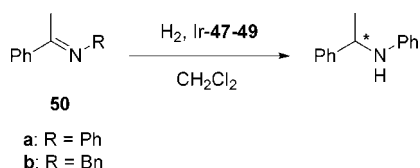
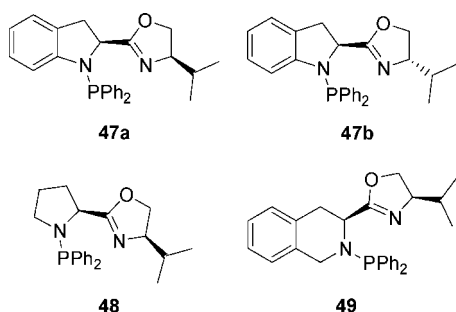


Table 1.27. Asymmetric Hydrogenation of 50 Using Ligands 47–49

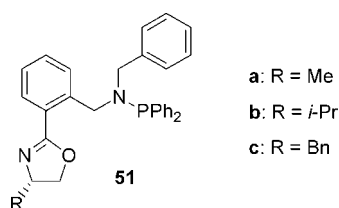
entry	ligand	substrate	P_{H_2} (bar)	temp (°C)	S/Ir	conv (%)	ee (%) (conf)
1	47a	50a	50	25	50	98	80 (S)
2	47b	50a	50	25	80	83	14 (R)
3	48	50a	50	25	50	100	72 (S)
4	49	50a	50	25	50	94	68 (S)
5 ^a	47a	50a	50	0	50	100	84 (S)
6	48	50a	50	0	30	82	85 (S)
7	47a	50a	20	25	50	100	86 (S)
8	47a	50a	5	25	50	100	81 (S)
9	48	50a	20	25	50	100	73 (S)
10	49	50a	30	25	30	91	72 (S)
11	47a	50a	50	25	50	91	83 (S)
12 ^a	47a	50a	1	25	50	39	87 (S)
13	47a	50a	50	0	50	100	89 (S)
14	47a	50a	20	25	50	100	90 (S)
15	47a	50b	50	25	50	100	81 (S)

^a Reaction time of 4 h.

Generally, high conversions and moderate to high enantiomeric excesses (over 68%) were obtained under 50 bar H_2 at room temperature for 12 h. Using the complex bearing ligand **47a** with (*R*)-configuration on the oxazoline ring and (*S*)-configuration on the aminophosphine residue induced an enantiomeric excess of 80% (Table 1.27, entry 1), significantly higher than that of its diastereomer **47b** (Table 1.27, entry 2). The complex bearing ligand **47a** was subjected to a range of conditions with a decrease in the temperature (Table 1.27, entry 5) and a decrease in the H_2 pressure (Table 1.27, entries 7, 12), leading to enhanced enantioselectivities. The highest ee of 90% was obtained using 20 bar H_2 at 25 °C with a substrate/Ir ratio of 50 (Table 1.27, entry 14).



Guiry has developed a novel series of aminophosphine-oxazoline ligands **51** and applied them in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6).³⁹



Scheme 1.30

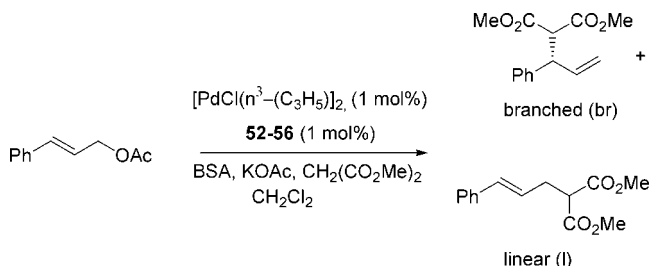


Table 1.28. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligands 52–56

entry	ligand	conv (%)	ee (%) (conf)	br/l
1	52a	100	94 (S)	84:16
2	53a	100	93 (S)	53:47
3	52b	100	89 (S)	38:62
4	52d	100	94 (S)	33:67
5 ^a	52e	100	94 (S)	67:33
6	52f	100	94 (S)	84:16
7	55a	100	95 (S)	60:40
8	53b	100	88 (S)	30:70
9	55b	100	90 (S)	65:35
10	55c	100	96 (S)	62:38
11	54a	100	91 (S)	82:18
12	54b	100	96 (S)	77:23
13	56a	100	87 (S)	26:74
14	56d	100	97 (S)	21:79

Scheme 1.31

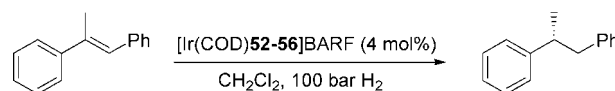


Table 1.29. Enantioselective Ir-Catalyzed Hydrogenation Using Ligands 52–56

entry	ligand	conv (%)	ee (%) (conf)
1	52a	16	86 (R)
2	53a	49	87 (R)
3	55a	15	94 (R)
4	53b	11	72 (R)
5	55c	73	91 (R)
6	54a	71	68 (R)
7	53c	59	92 (R)
8	56a	100	75 (R)
10	56d	69	84 (R)

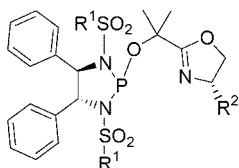
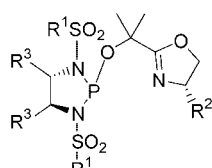
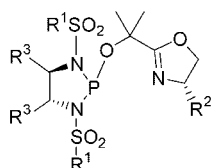
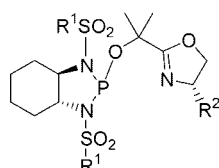
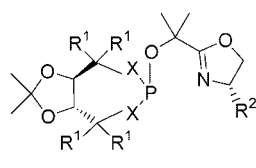
The best enantioselectivity of 38% (*R*) was obtained using *i*-Pr-substituted oxazoline ligand **51b**, with the conversions varying greatly with the base. For example, ligand **51b** led to a conversion of 11% using KOAc, but changing to CS_2CO_3 resulted in an increase in conversion to 64%.

2.6. Oxazoline-Phosphoramidate Ligands

Pfaltz reported a series of *P,N* ligands **52–56** containing a chiral oxazoline ring and a bis(*N*-sulfonylamino)phosphine group embedded in a diazaphospholidine ring or a cyclic phosphite group derived from TADDOL. The ligands were applied in the palladium-catalyzed allylic alkylation (Scheme 1.30, Table 1.28) and iridium-catalyzed hydrogenation of methylstilbene (Scheme 1.31, Table 1.29).⁴⁰

In all reactions, complete conversions were observed after 20 h at room temperature. In general, ligands derived from (*R,R*)-diamines and (*S*)-oxazolines were superior to the corresponding diastereomers (Table 1.28, entries 1, 2, 7, 8). Ligand **52a** was the most effective for regio- and enantio-control, with an enantiomeric excess of 94% and a branched/

linear ratio of 84:16 (Table 1.28, entry 1). Variations of the substituents on both the oxazoline ring or the tosyl group resulted in lower regioselectivity and enantiomeric excesses (Table 1.28, entries 3–6). Ligands **55a** and **55c** afforded higher enantiomeric excesses of 95% and 96%, respectively, but lower regioselectivities (Table 1.28, entries 7, 10). The TADDOL-derived ligand **56d** showed the highest ee of 97%, but as observed for all other TADDOL-derived ligands, the regioselectivity was significantly lower (Table 1.28, entry 14). The Pd-catalyzed allylic alkylation of more complex substrates was also carried out, with similar trends being observed.

**52**a: R¹ = 4-tolyl, R² = *t*-Bub: R¹ = 4-tolyl, R² = Phc: R¹ = CF₃, R² = *t*-Bud: R¹ = mesityl, R² = *t*-Bue: R¹ = 1-naphthyl, R² = *t*-Buf: R¹ = 2-naphthyl, R² = *t*-Bu**53**a: R¹ = 4-tolyl, R² = *t*-Bu, R³ = Phb: R¹ = 4-tolyl, R² = *t*-Bu, R³ = (CH₂)₄c: R¹ = 4-tolyl, R² = *t*-Bu, R³ = Cy**54**a: R¹ = 4-tolyl, R² = *t*-Bu, R³ = Cyb: R¹ = 4-tolyl, R² = *t*-Bu, R³ = (CH₂)₄c: R¹ = 4-tolyl, R² = *t*-Bu, R³ = 3,5-xylyl**55**a: R¹ = 4-tolyl, R² = *t*-Bub: R¹ = 1-naphthyl, R² = *t*-Buc: R¹ = 2-naphthyl, R² = *t*-Bu**56**a: R¹ = Ph, R² = *t*-Bu, X = Ob: R¹ = Ph, R² = Ph, X = Oc: R¹ = 2-naphthyl, R² = *t*-Bu, X = Od: R¹ = Ph, R² = *t*-Bu, X = NMe

Application of ligands **52–56** in the hydrogenation of (*E*)-1,2-diphenylpropene (Scheme 1.31) resulted in moderate to high enantioselectivities, but mostly with low conversions after 2 h at room temperature. Interestingly, ligands **52a** and **53c** containing 1,2-diphenyl and 1,2-dicyclohexyldiamine backbones were more efficient than their corresponding diastereomers **52a** and **54a**, in contrast to the allylic alkylation results, where **52a** and **54a** gave better results (Table 1.29, entries 1, 2, 6, 7). The TADDAMIN-derived ligand **56d** afforded a higher ee than the TADDOL-derived ligand **56a** (Table 1.29, entries 8, 9). Similar trends were observed for the hydrogenation of (*E*)-2-(4-methoxyphenyl)propene and a range of other substrates.

Table 1.30. Enantioselective Palladium-Catalyzed Allylic Alkylation Using Ligand Class 57

entry	ligand	conv (%)	ee (%) (conf)
1	57a	100	92 (<i>S</i>)
2	57b	89	84 (<i>S</i>)
3	57c	57	86 (<i>S</i>)
4	57d	95	86 (<i>S</i>)
5	57e	91	86 (<i>S</i>)
6	57f	67	45 (<i>S</i>)
7	57g	100	85 (<i>S</i>)
8 ^a	57a	54	95 (<i>S</i>)
9 ^{a,b}	57a	100	99 (<i>S</i>)

^a Reaction carried out at 0 °C. ^b Toluene used as solvent.**Table 1.31. Pd-Catalyzed Enantioselective Phenylation Using Ligands 57a–f**

entry	ligand	solvent	conv (%) (4/5)	ee of 4 (%)	ee of 5 (%)
1	57a	toluene	80 (85:15)	96 (<i>R</i>)	90 (<i>R</i>)
2	57a	benzene	77 (84:16)	95 (<i>R</i>)	60 (<i>R</i>)
3	57a	DMF	15 (71:29)	87 (<i>R</i>)	nd
4	57a	THF	98 (87:13)	97 (<i>R</i>)	88 (<i>R</i>)
5 ^a	57a	THF	100 (80:20)	93 (<i>R</i>)	87 (<i>R</i>)
6 ^b	57a	THF	28 (88:12)	98 (<i>R</i>)	88 (<i>R</i>)
7	57b	THF	86 (85:15)	97 (<i>R</i>)	89 (<i>R</i>)
8	57c	THF	45 (60:40)	80 (<i>R</i>)	69 (<i>R</i>)
9	57d	THF	100 (97:3)	99 (<i>R</i>)	nd
10	57e	THF	80 (71:29)	84 (<i>R</i>)	90 (<i>R</i>)
11	57f	THF	12 (65:35)	83 (<i>R</i>)	23 (<i>R</i>)

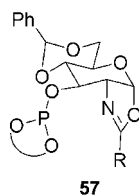
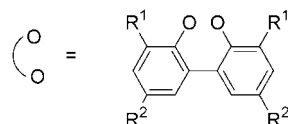
^a Reaction carried out at 75 °C. ^b Reaction carried out at 25 °C.

2.7. Oxazoline-Phosphite Ligands

Claver has reported the synthesis of new carbohydrate-based phosphite-oxazoline ligands **57** and their application in a range of catalytic asymmetric transformations.⁴¹

The ligands were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6, Table 1.30).

The effect of the phosphite moieties was initially examined (Table 1.30, entries 1–4). It was found that the substituents at the *ortho* positions of the biphenyl unit affected activity, with enantioselectivities mainly being affected by the substituents at the *para*-positions of the biphenyl unit. A high enantiomeric excess of 92% was thus obtained using ligand **57a** (Table 1.30, entry 1), and this was further enhanced to an ee of 99% by carrying out the reaction in toluene at 0 °C (Table 1.30, entry 9).

**57**a: R = Ph, R¹ = R² = *t*-Bub: R = Ph, R¹ = *t*-Bu, R² = OMec: R = Ph, R¹ = R² = Hd: R = Ph, R¹ = SiMe₃, R² = He: R = *i*-Pr, R¹ = R² = *t*-Buf: R = *t*-Bu, R¹ = R² = *t*-Bug: R = Me, R¹ = R² = *t*-Bu

This ligand class (**57**) was also applied to the asymmetric phenylation of 2,3-dihydrofuran **3** (Scheme 1.1, Table 1.31).⁴²

In all cases, the formation of the expected product **4** was favored. Screening a range of reaction conditions using ligand **57a** showed THF to give the best enantioselectivity of 88% with excellent conversion and regioselectivity (Table 1.31,

Table 1.32. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligands **58 and **59a****

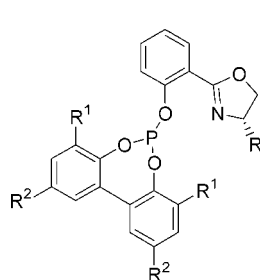
entry	ligand	conv (%)	ee (%)
1	58a	71	>99 (<i>S</i>)
2	58b	100	>99 (<i>S</i>)
3	58c	84	>99 (<i>S</i>)
4	58d	95	>99 (<i>S</i>)
5	58e	100	42 (<i>S</i>)
6	58f	100	95 (<i>S</i>)
7	58g	100	99 (<i>S</i>)
8	59a	100	99 (<i>R</i>)

entry 4). The phosphite moiety had an important effect on the activity and stereoselectivity of the reaction (Table 1.31, entries 6–9), with **57d** giving complete conversion with the highest enantioselectivity of 99% ee. Ligands **57e** and **57f**, whose substituents in the oxazoline moiety differ from those of **57a**, showed longer activities and lower regio- and stereoselectivities than **57a** (Table 1.31, entries 10, 11), illustrating that as the size of the group on the oxazoline increases, the activity and regio- and enantioselectivity decrease.

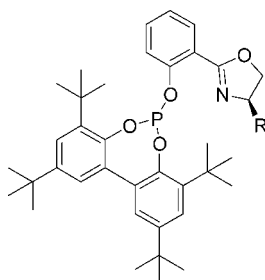
The microwave-assisted palladium-catalyzed enantioselective arylation and alkenylation of 2,3-dihydrofuran using ligand **57d** were also examined, with typical conversions of 82–100%, regioselectivities of up to 98:2, and enantioselectivities of 91–99%.⁴³

Ligand **57d** was applied in the copper-catalyzed 1,4-addition of 2-cyclohexenone and gave an enantiomeric excess of 64% and yield of 50% after 2 h at –30 °C. Changing the copper precursor from Cu(OAc)₂ to [Cu(MeCN)₄]BF₄ led to an increase in ee to 78% with no improvement in yield after 2 h at –30 °C.⁴⁴

Claver has also reported the development of new phosphite-oxazoline ligands **58** and **59** and their application in palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6, Table 1.32).⁴⁵

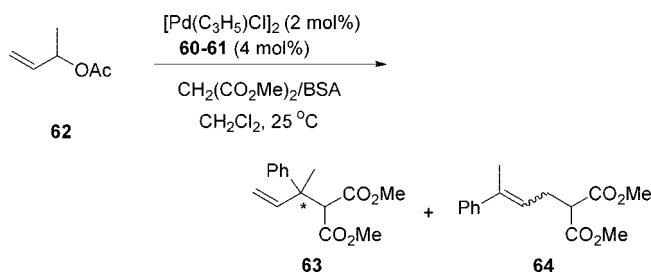
**58**

- a:** R = *t*-Bu, R¹ = R² = *t*-Bu
b: R = Ph, R¹ = R² = *t*-Bu
c: R = *i*-Pr, R¹ = R² = *t*-Bu
d: R = Et, R¹ = R² = *t*-Bu
e: R = Et, R¹ = R² = H
f: R = Et, R¹ = *t*-Bu, R² = OMe
g: R = *i*-Pr, R¹ = *t*-Bu, R² = OMe

**59**

- a:** R = Ph
b: R = *i*-Pr
c: R = *t*-Bu
d: R = Ph
e: R = Et

The effect of the oxazoline substituent was studied with ligands **58a–d**, with excellent conversions and enantioselectivities (>99% ee) being obtained in all cases (Table 1.32, entries 1–4), an uncommon example of varying the oxazoline substituent resulting in no effect on enantioselection. The effect of the phosphite moieties was then examined using ligands **58c–g**, with bulky substituents in the *ortho* positions

Scheme 1.32**Table 1.33. Pd-Catalyzed Regio- and Enantioselective Allylic Alkylation of **62** Using Ligands **60** and **61****

entry	ligand	time (h)	yield (%)	63 /(<i>E</i>)- 64 /(<i>Z</i>)- 64	ee 63 (%)
1	(<i>S,S,P,R</i>)- 60a	6	89	90/5/5	49
2	(<i>S,S,P,R</i>)- 60b	72	76	92/8/0	39
3	(<i>S,S,P,R</i>)- 60c	20	96	74/22/4	38
4	(<i>S,S,P,R</i>)- 60d	2.5	96	79/5/16	35
5	(<i>S,P,R</i>)- 61a	1	92	59/16/25	24
6	(<i>S,P,R</i>)- 61b	19	66	96/4/0	73
7	(<i>R,P,R</i>)- 61b	19	56	96/4/0	49
8	(<i>S,S,P,R</i>)- 61c	16	77	90/10/0	63

of the biphenyl phosphite unit shown to be necessary for high enantioselection (Table 1.32, entries 4, 6).

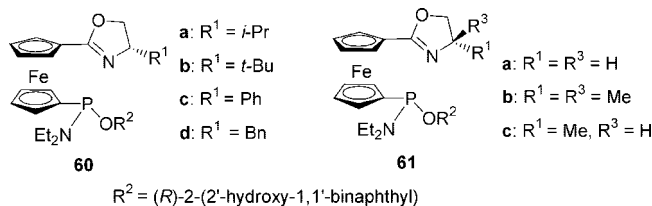
The application of ligands **58e–g** and **59a–e** in the hydrosilylation of acetophenone (Scheme 1.4) was subsequently reported. The ligands gave moderate to good conversions (48–85%), with the highest enantioselectivity of 45% being obtained using rhodium complexes of **58c**. Other ketones were also investigated, with rhodium complexes of **59a** giving an enantioselectivity of 62% for the hydrosilylation of *p*-methoxyacetophenone.⁴⁶

2.8. Miscellaneous *P,N*-Oxazoline-Containing Ligands

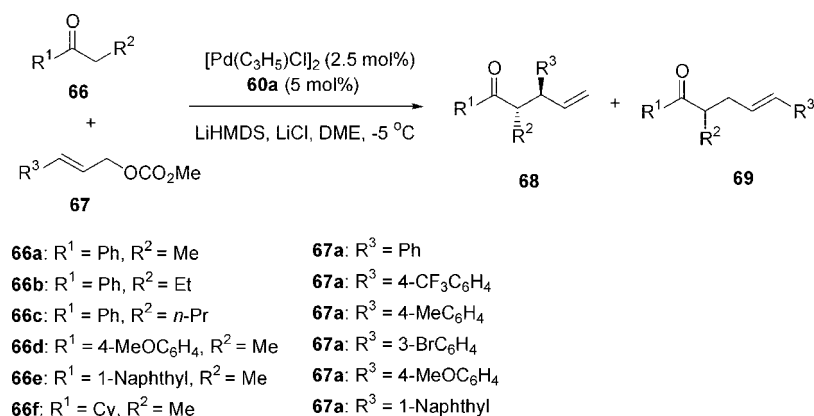
Hou has developed a range of *P,N*-ferrocene/oxazoline containing ligands **60** and **61**.⁴⁷

The ligands were applied in the palladium-catalyzed regio- and enantioselective allylic alkylation of allylic acetate **62** (Scheme 1.32, Table 1.33).

Among the four diastereomers, (*S,S,P,R*)-**60a** gave the best regioselectivity (90/10) and enantioselectivity (49% ee), most likely due to a match of the different chiralities. The results also showed the profound steric effect which the group on the oxazoline had on the enantioselectivity. Changing from *i*-Pr to *t*-Bu resulted in a decrease in ee from 49% to 39% (Table 1.33, entries 1, 2). Lower regio- and enantioselectivities were reported when the oxazoline was phenyl- or benzyl-containing (Table 1.33, entries 3, 4). Structurally modified ligands **61a–c** were also applied in this reaction, with a significant increase in enantioselectivity to 63% reported, when the oxazoline unit had a methyl substituent (Table 1.33, entry 8).

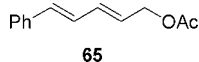


Scheme 1.33

Table 1.34. Application of Ligand **61a** in the Enantioselective Allylic Alkylation of **67**

entry	ketone	olefin	yield (%)	68:69	anti/syn 68	ee of anti-68 (%)
1	66a	67a	83	98:2	9:1	98
2	66a	67b	90	>98:2	8:1	98
3	66a	67c	80	>98:2	9:1	96
4	66a	67d	85	>98:2	10:1	99
5	66a	67e	73	>98:2	7:1	92
6	66a	67f	83	>98:2	20:1	99
7	66b	67a	88	>98:2	7:1	92
8	66c	67a	85	>98:2	8:1	98
9	66d	67a	82	>98:2	7:1	97
10	66e	67a	89	>98:2	21:1	93
11	66f	66e	72	>98:2	5:1	99

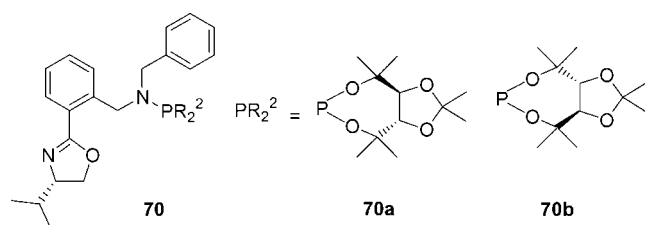
Ligand class **60** was also applied in the palladium-catalyzed allylic alkylation of **65**, with ligand **60d** affording the highest enantiomeric excess of 92%.⁴⁸



Ligand **61a** has recently been applied in the allylic alkylation of a range of acyclic ketone enolates (Scheme 1.33, Table 1.34).⁴⁹

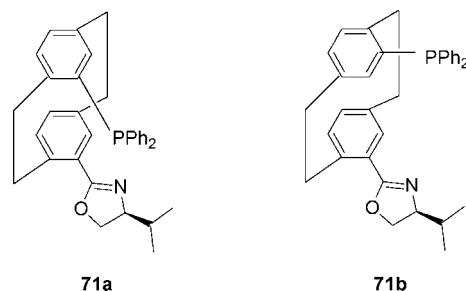
In general, the reaction proceeded smoothly to afford allylation products in high yields. Excellent regio- and enantioselectivities were obtained for all substrates, with the ratio of **68**:**69** being >98:2, while the ee values varied between 92 and 99%. Excellent diastereoselectivities were also observed, with a ratio for product **69** between 5 and 21:1. Substrates bearing an electron-rich aromatic ring led to slightly lower diastereo- and enantiomeric excesses (Table 1.34, entries 5, 9). The nonaromatic ketone **66f** was also successfully allylated, with an ee of 99% (Table 1.34, entry 11).

Guiry has reported the synthesis and application of novel phosphoramidite-oxazoline ligand **70** in the palladium-catalyzed enantioselective Suzuki coupling, an asymmetric transformation which has received limited attention to date (Scheme 1.34, Table 1.35).³⁹



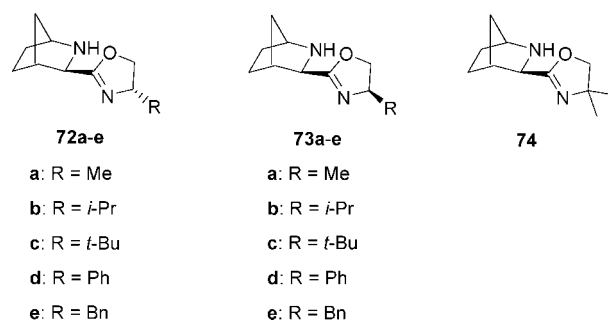
Moderate conversions and enantioselectivities were observed for both ligands **70a** and **70b**. The nature of the base was found to have a large impact both on conversion and enantioselection, with Cs₂CO₃ giving the best results of 46% ee with 43% yield for **70a** (Table 1.35, entry 5). In contrast, this base led to racemic product when **70b** was used as the ligand (Table 1.35, entry 10), with CsOH providing the most promising results (Table 1.35, entry 9).

Bolm has developed new aromatic-substituted phosphinyl-oxazoliny[2.2]paracyclophanes of type **71** and applied them in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6), with **71a** resulting in an ee of 56%, and **71b** resulting in 82% ee.⁵⁰



3. Mono(oxazoline) N,N-Ligands

Andersson has reported the synthesis of new 2-azanorbornane ligands of type **72–74** and their application in the asymmetric transfer hydrogenation of acetophenone.⁵¹



The best result was obtained using ligand **72b**, which resulted in a 79% ee and a conversion of 32% using [IrCl(COD)]₂. It was found that a further increase in the size of the oxazoline substituent led to a decrease in both conversion and enantioselectivity to 10% and 18%, respectively.

Guiry has reported the application of pyrrolidine-oxazoline containing ligands **75** in the asymmetric transfer hydrogenation of acetophenone (Scheme 1.35, Table 1.36).⁵²

Scheme 1.34



Table 1.35. Pd-Catalyzed Enantioselective Suzuki Coupling Using Ligand 70

entry	ligand	base	yield (%)	ee (%) (conf)
1	70a	KOH	30	38 (<i>R</i>)
2	70a	NaOH	25	36 (<i>R</i>)
3	70a	CsOH	16	37 (<i>R</i>)
4	70a	CsF	19	40 (<i>R</i>)
5	70a	Cs ₂ CO ₃	54	46 (<i>R</i>)
6	70a	Ba(OH) ₂	31	43 (<i>R</i>)
7	70b	KOH	45	35 (<i>R</i>)
8	70b	NaOH	43	34 (<i>R</i>)
9	70b	CsOH	61	33 (<i>R</i>)
10	70b	Cs ₂ CO ₃	49	0 (<i>R</i>)
11	70b	Ba(OH) ₂	25	18 (<i>R</i>)

Scheme 1.35

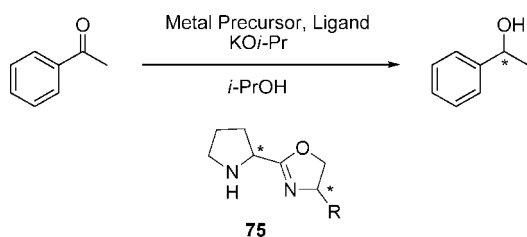


Table 1.36. Asymmetric Transfer Hydrogenation of Acetophenone Using Ruthenium Complexes of Ligands 75

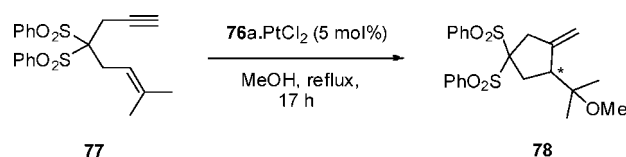
entry	ligand	R	conv (%)		ee (%)		conf
			1 h	15 h	1 h	15 h	
1	75a	H	6	8	7	4	<i>R</i>
2	75b	<i>i</i> -Pr	8	76	52	51	<i>R</i>
3	75c	<i>i</i> -Pr	8	73	63	61	<i>S</i>
4	75d	Ph	3	30	14	15	<i>R</i>
5	75e	Ph	1	24	10	14	<i>S</i>
6	75f	<i>t</i> -Bu	5	43	25	20	<i>R</i>
7	75g	<i>t</i> -Bu	5	37	34	25	<i>R</i>
8	75h	Me	2	51	14	16	<i>R</i>
9	75i	Bn	5	40	18	17	<i>R</i>

Using [IrCl(COD)]₂ as the metal precursor resulted in excellent conversions (up to 96% at room temperature after 1 h) but gave only modest enantioselectivities (up to 38% ee). [Ru(*p*-cymene)Cl₂]₂ was then used as the metal precursor, and the best results were obtained using the *i*-Pr-substituted ligands **75b** and **75c**, which gave enantiomeric excesses of 51% and 61%, respectively (Table 1.36, entries 2, 3). These ligands were also the most active with conversions of up to 76% after 15 h at room temperature. The other ligands afforded poor to moderate conversions (8–51%) and enantiomeric excesses (4–25%). A comparison of the results obtained with the diastereomeric ligand pairs (Table 1.36, entries 2–7) shows that the sense of asymmetric induction is controlled by the oxazoline stereocenter.

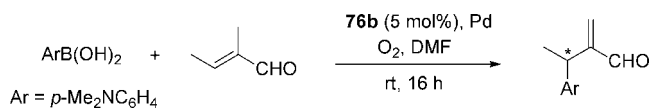
Echavarren has applied the platinum complex of *i*-Pr-pyrox **76a** in the alkoxy cyclization of enyne **77** to **78** (Scheme 1.36), and although this afforded the cyclized product **78** in 97% yield, the enantiomeric excess obtained was only 10%.⁵³

Jung has applied the palladium acetate complex of *t*-Bu-pyrox **76b** in the asymmetric oxidative Heck reaction

Scheme 1.36



Scheme 1.37



Scheme 1.38

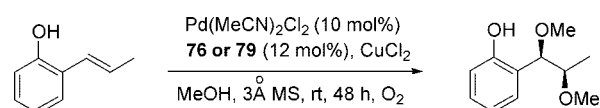
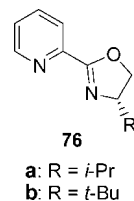


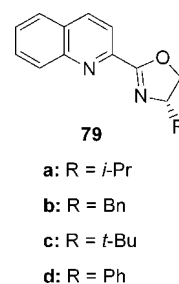
Table 1.37. Enantioselective Aerobic Dialkoxylation of 2-Propenyl Phenols Using Palladium Complexes of 76 and 79

entry	ligand	CuCl ₂ (mol %)	yield (%)	ee (%)
1	76	0	10	60
2	79a	0	67	82
3	79b	0	85	84
4	79c	0	10	83
5	79d	0	14	37
6	79a	2.5	80	72
7	79a	5	78	59
8	79a	10	81	26
9	79a	20	88	10

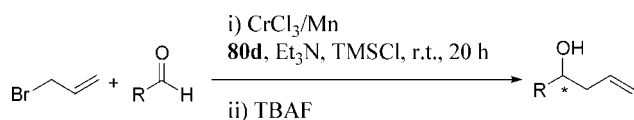
(Scheme 1.37). Yields of 67–79% and enantiomeric excesses of 68–75% were reported for the reaction of *trans*-2-methyl-2-butanal with a range of boronic acids.⁵⁴



Sigman has recently applied ligand **76** and its quinoline analogue **79** in the palladium-catalyzed enantioselective aerobic dialkoxylation of 2-propenyl phenols (Scheme 1.38, Table 1.37).⁵⁵



Scheme 1.39

Table 1.38. Nozaki-Hiyama-Kishi Allylation of a Range of Aldehydes Using **80d**

entry	R	yield (%)	ee (%)
1	C ₆ H ₅	89	94
2	4-BrC ₆ H ₄	73	90
3	4-MeOC ₆ H ₄	98	89
4	2-Furyl	61	92
5	PhCH ₂ CH ₂	98	48
6	C ₆ H ₁₁	64	87

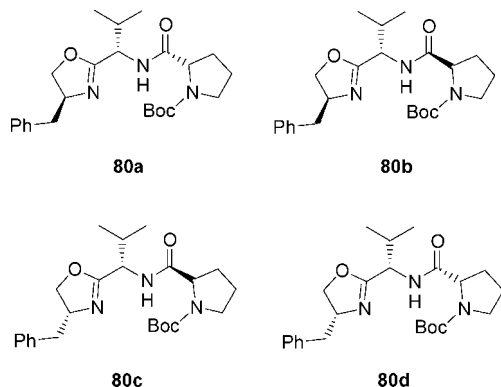
Good enantioselectivities were observed using quinoline-derived oxazoline ligands **79a–c** (Table 1.37, entries 2–4). Ligand **79b** gave a yield of 85% and an enantiomeric excess of 84% (Table 1.37, entry 2). Interestingly, increasing the amount of copper led to a significant decrease in enantioselectivity (Table 1.37, entries 6–9), consistent with a ligand exchange process.

Sigman has developed a range of modular proline-oxazoline ligands **80a–d**, synthesized from simple amino acids.

These ligands were applied in the Nozaki-Hiyama-Kishi allylation of benzaldehyde (Scheme 1.39),⁵⁶ with ligand **80d** affording the highest enantiomeric excess of 92% (*R*). This ligand was then applied in the allylation of a range of aldehydes (Table 1.38), with excellent yields and enantioselectivities reported.⁵⁷

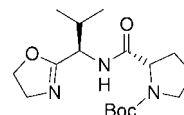
Aryl aldehydes proved to be excellent substrates, highlighted by a 94% ee for benzaldehyde (Table 1.38, entry 1) and a 92% ee for furaldehyde (Table 1.38, entry 4). A poorer ee of 48% was observed for aliphatic aldehydes (Table 1.38, entry 5). However, cyclohexaldehyde was an excellent substrate, with an ee of 87% obtained, although it was less reactive (Table 1.38, entry 6).

To further explore substrate scope, methallyl bromide and *trans*-crotyl bromide were used as reagent reactions with benzaldehyde. Crotylation yielded an *anti/syn* ratio of 2.3:1, with both *anti*- and *syn*-diastereomers having a high enantiomeric excess of 91% and 95%, respectively. Methallylation proceeded with an excellent ee of 91%. These results highlight the insensitivity of ligand **80d** to the nature of the allylic bromide.

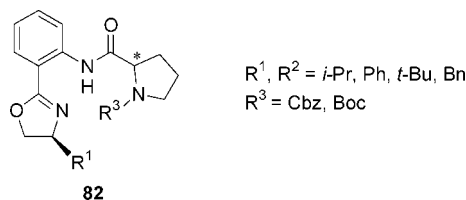


More recently, Sigman has reported the application of the structurally related ligand **81** in the first enantioselective allylation of ketones (Scheme 1.40, Table 1.39).⁵⁸

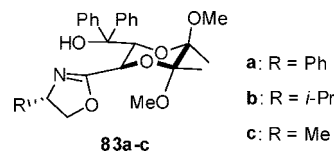
Aryl ketones were found to be excellent substrates for this transformation, with naphthone giving the highest enantioselectivity of 92% (Table 1.39, entry 6). The nature and position of the substituent on the aromatic ring had little effect on the enantioselective outcome of the reaction (Table 1.39, entries 1–6). Methallyl and crotylbromide were successfully added to acetophenone with very good enantioselectivities reported, although the addition of crotylbromide resulted in a modest diastereoselection (Table 1.39, entries 8, 9).

**81**

Guiry has reported the preparation of ligand class **82** and its application in the NHK allylation of benzaldehyde (Scheme 1.39). The highest enantioselectivity of 57% was obtained with complete conversion and high isolated yield using the ligand derived from proline- and the phenyl-substituted oxazoline.⁵⁹

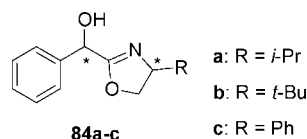
**82**4. Mono(oxazoline) *N,O*-Ligands

The synthesis of novel monooxazoline carbinols **83** from (+)-tartaric acid has been described by Barros.⁶⁰



The ligands were applied in the enantioselective addition of diethylzinc to benzaldehyde (Scheme 1.41), with very good conversions (up to 79%) and moderate enantioselectivities of up to 54% being observed using ligand **83a**.

Bolm has prepared a range of α -hydroxy-2-oxazolines **84** from enantiopure and (*S*)-mandelic acid.

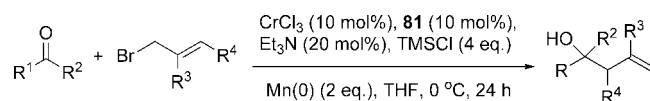


The ligands were applied in the asymmetric phenyl transfer reaction (Scheme 1.42) with moderate yields (up to 74%) and poor enantioselectivities reported, with (*S,S*)-**84b** affording the highest ee of 35% (*S*).⁶¹

The application of a chiral *N,O*-ferrocene ligand **85** in the enantioselective addition of phenylacetylene to aldehydes has been described by Hou.⁶²

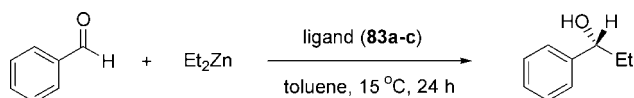
Screening of the ligands showed that ligand **85d** afforded the highest enantioselectivities and was subsequently applied in the alkynylation of a range of aldehydes (Scheme 1.43, Table 1.40, Scheme 1.43). The yields and enantioselectivities

Scheme 1.40

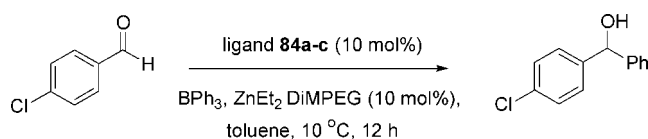
Table 1.39. NHK Allylation of a Range of Ketones Using **81**

Entry	Product	Yield (%)	ee (%)
1		82	92
2		73	90
3		94	86
4		83	87
5		63	91
6		95	92
7		77	93
8		73	91
9		69	88 (<i>anti</i>) 70 (<i>syn</i>)

Scheme 1.41

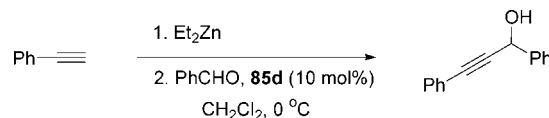


Scheme 1.42



were very good, with the best enantiomeric excesses of 90% and 93% being obtained for the reaction with *p*-anisaldehyde and 1-naphthaldehyde, respectively (entries 5, 6). Diminished enantioselectivities were reported using alkenyl-aldehydes as substrates (entries 13, 14).

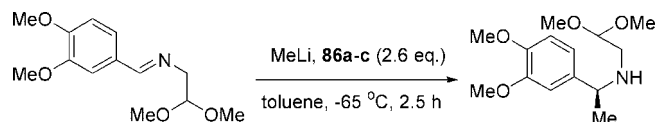
Scheme 1.43

Table 1.40. Application of Ligand **85d** in the Enantioselective Alkynylation of Aldehydes

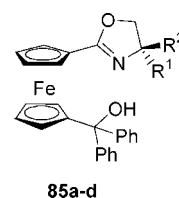
entry	aldehyde	yield (%)	ee (%)	conf
1	4-BrC ₆ H ₄ CHO	86	86	(-)
2	2-ClC ₆ H ₄ CHO	72	67	(-)
3 ^a	2-ClC ₆ H ₄ CHO	82	89	(-)
4	3-NO ₂ C ₆ H ₄ CHO	87	82	(-)
5	4-MeOC ₆ H ₄ CHO	82	90	(-)
6	1-naphthaldehyde	84	88	(-)
7 ^a	1-naphthaldehyde	86	93	(-)
8 ^a	α -furan-CHO	85	82	(-)
9 ^a	C ₆ H ₁₁ CHO	74	81	(-)-(R)
10 ^a	PhCH ₂ CHO	72	65	(-)
11 ^a	Me ₂ CHCHO	88	83	(-)
12 ^a	Me ₃ CCHO	88	75	(-)
13	PhCH=CHCHO	88	54	(-)
14 ^a	MeCH=CHCHO	82	59	(-)

^a 20 mol % of **85d** used.

Scheme 1.44

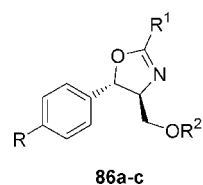


Rozwadowska has synthesized a range of ligands of type **86** and applied them in the enantioselective addition of methyllithium to a prochiral imine (Scheme 1.44).⁶³



- a** (S): R¹ = *i*-Pr, R² = H
b (S): R¹ = *t*-Bu, R² = H
c (S): R¹ = Bn, R² = H
d (R): R¹ = H, R² = Ph

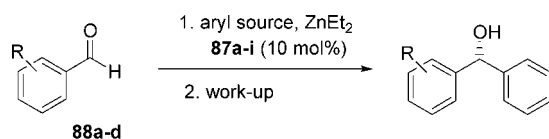
Ligands **86a–c** gave yields of up to 92%, with **86a** and **86c** both resulting in an enantioselectivity of 76%. A small change in ligand structure led to a decrease in ee to 52% for **86b**. Interestingly, decreasing the amount of ligand to 0.5 equiv led to decreases in enantioselectivities of up to 10% in all three cases.



- a**: R = SCH₃, R¹ = Me, R² = OMe
b: R = SCH₃, R¹ = Et, R² = OMe
c: R = H, R¹ = CH₃, R² = CH₃

Bolm has reported the synthesis of ferrocene-based organosilanol **87** and their application in asymmetric aryl transfer reactions (Scheme 1.45, Table 1.41).⁶⁴

Scheme 1.45



- a: R = 4-Cl
 b: R = 4-MeO
 c: R = 2-Br
 d: R = 4-Me

Table 1.41. Asymmetric Phenyl Transfer Reaction to Substituted Benzaldehydes **88** Using Ligands **87a–d**

entry	substrate	ligand	method	yield (%)	ee (%)
1	88a	87a	A	40	30
2	88a	87b	A	82	91
3	88a	87c	A	84	89
4	88a	87d	A	82	87
5	88a	87e	A	76	85
6	88a	87f	A	87	78
7 ^a	88a	87g	A	73	76
8	88a	87h	A	85	63
9	88a	87i	A	nd	58
10	88a	87c	B	73	88
11	88a	87c	C	67	83
12	88b	87c	A	81	87
13	88c	87c	A	70	84
14	88d	87c	A	84	83

^a

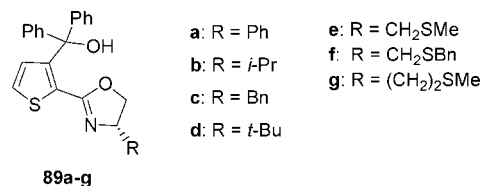
^a Method A: Ph₂Zn (0.65 equiv) and Et₂Zn (1.3 equiv) in toluene at 10 °C for 12 h. Method B: BPh₃ (1.0 equiv) and Et₂Zn (3.0 equiv) at 10 °C for 12 h. Method C: PhB(OH)₂ (2.4 equiv), Et₂Zn (7.2 equiv) and DiMPEG (10 mol %) in toluene at 60 °C for 12 h, and then 10 °C for 12 h.

Initially mixtures of diphenyl- and diethylzinc (Method A) were used as the phenyl source with *p*-chlorobenzaldehyde (**88a**) as substrate. The majority of ligands showed good enantioselectivities (up to 91% ee) with respectable yields (up to 87%). The best result was obtained with **87b** (Table 1.41, entry 2). Ligands with methyl or phenyl substituents on silicon led to products with lower enantioselectivities (Table 1.41, entries 1, 3). Replacing the *t*-Bu group on the oxazoline with a phenyl, *i*-Pr, or benzyl resulted in a decrease in enantioselectivity (Table 1.41, entries 4–9). Using triphenylborane (Method B) as the aryl source had a minor effect on the ee of the reaction (Table 1.41, entry 10), with phenylboronic acid (Method C) leading to a lowering of both yield and enantioselectivity (Table 1.41, entry 11).

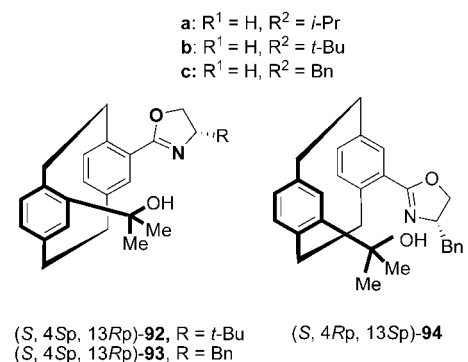
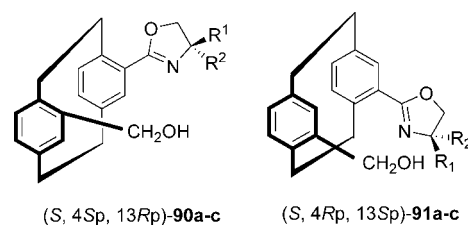
Ligand	R	R ¹
87a	Me	<i>t</i> -Bu
87b	<i>i</i> -Pr	<i>t</i> -Bu
87c	Ph	<i>t</i> -Bu
87d	<i>i</i> -Pr	Ph
87e	Ph	Ph
87f	<i>i</i> -Pr	<i>i</i> -Pr
87g	Ph	<i>i</i> -Pr
87h	<i>i</i> -Pr	Bn
87i	Ph	Bn

The application of a series of thiophene mono(oxazoline) *N,O*-ligands **89** in the asymmetric phenyl transfer reaction to aldehydes has been described by Zhao.⁶⁵

Screening ligands **89a–g** in the phenylation of *p*-chlorobenzaldehyde using (PhBO)₃ as the phenyl source resulted in excellent yields of 86–98% and varying enantioselectivities of 4–77%. The optimal results were obtained using ligands **89d** and **88e**, which provided enantioselectivities of 77% and 68%, respectively. Optimization of the reaction conditions led to ligand **89e**, giving up to 82% ee at –15 °C, and this ligand was therefore applied in the phenylation of a range of aromatic aldehydes. Changing the aldehyde did not lead to an improvement in the enantioselectivity, with the next best aldehyde substrate being *E*-cinnamaldehyde, affording an ee of 74%.



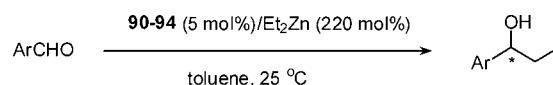
activities of 4–77%. The optimal results were obtained using ligands **89d** and **88e**, which provided enantioselectivities of 77% and 68%, respectively. Optimization of the reaction conditions led to ligand **89e**, giving up to 82% ee at –15 °C, and this ligand was therefore applied in the phenylation of a range of aromatic aldehydes. Changing the aldehyde did not lead to an improvement in the enantioselectivity, with the next best aldehyde substrate being *E*-cinnamaldehyde, affording an ee of 74%.



A range of oxazoline-containing paracyclophane ligands have been applied in a variety of asymmetric transformations to date.

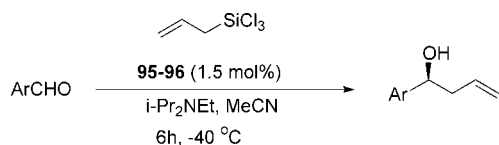
Hou has applied planar chiral *N,O* ligands **90–94** in the enantioselective addition of diethylzinc to aldehydes (Scheme 1.46, Table 1.42).⁶⁶

Scheme 1.46

Table 1.42. Enantioselective Addition of Diethylzinc to Aldehydes Using Ligands **90–94**

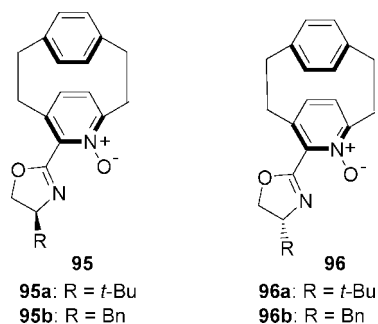
entry	Ar	ligand	time (h)	yield (%)	ee (%) (conf)
1	Ph	90a	5	94	91 (R)
2	Ph	91a	24	49	25 (S)
3	Ph	90b	7	93	94 (R)
4	Ph	91b	24	46	36 (S)
5	Ph	90c	5	94	91 (R)
6	Ph	91c	24	51	45 (S)
7	Ph	92	3.5	93	97 (R)
8	Ph	93	1.5	95	98 (R)
9	Ph	94	48	<5	
10	4-ClC ₆ H ₄	93	2	96	97 (R)
11	4-BrC ₆ H ₄	93	2	95	96 (R)
12	4-MeOC ₆ H ₄	93	3.5	94	96 (R)
13	2-MeOC ₆ H ₄	93	1	96	96 (R)

Scheme 1.47



Ligands **90a–c** with a hydroxymethyl moiety gave excellent enantiomeric excesses of up to 94% (Table 1.42, entries 1, 3, 5). Ligands **92** and **93** with a dimethylhydroxymethyl group showed higher reactivity and provided better enantiomeric excesses of 97% and 98%, respectively (Table 1.42, entries 7, 8). The effectiveness of ligand **93** was further demonstrated by reaction with a series of aryl aldehydes, with a minimum ee of 96% being achieved regardless of the nature of the aldehyde (Table 1.42, entries 10–13).

Ma and Andrus have synthesized novel aza-paracyclophane-oxazoline ligands **95** and **96**.



The ligands were applied in the allylation of aldehydes (Scheme 1.47), with excellent yields reported in all cases. Ligand **95a** provided the highest enantiomeric excess of 96% for the reaction of 4-FC₆H₄CHO.⁶⁷

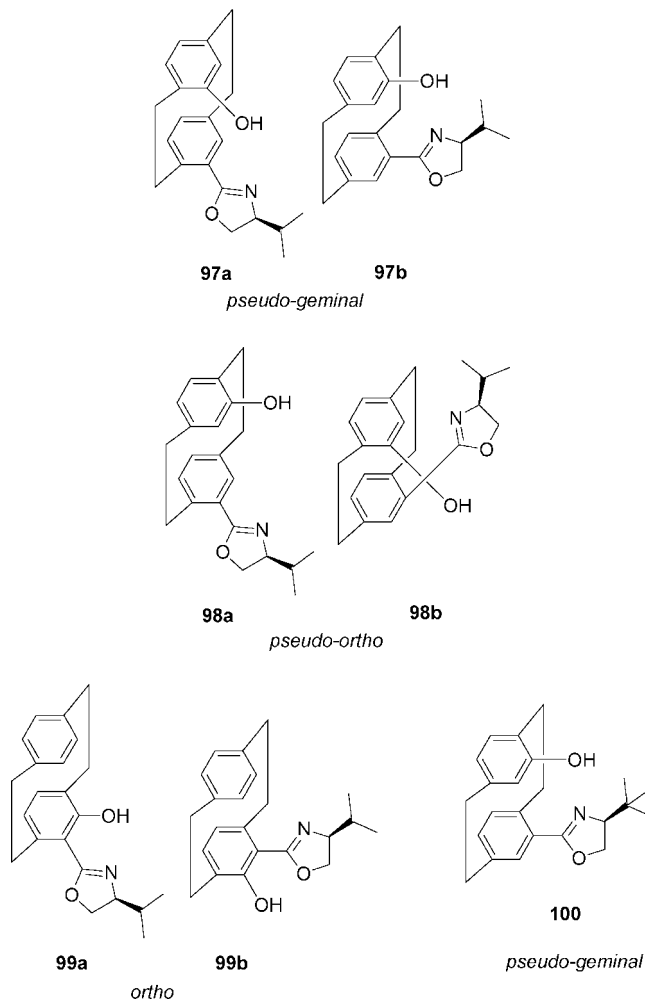
Bolm has reported the synthesis and application of hydroxyoxazoliny paracyclophanes **97–100** in the asymmetric addition of diethylzinc to benzaldehyde (Scheme 1.41, Table 1.43).⁶⁸

Both the highest reaction rate and enantiomeric excess were realized by pseudogeminal ligand **97b** (Table 1.43, entry 2). The importance of the position of both the oxazoline and hydroxyl groups on the [2.2]paracyclophane was highlighted by **97a**, which gave the lowest ee of 11% (Table 1.43, entry 1). The effect of the position of the bulk of the [2.2]paracyclophane was also of importance to the selectivity of the *ortho* ligands **99a** and **98b**, with opposite enantioselectivities of alcohol product being obtained (Table 1.43, entries 5, 6). Overall, the best ligand was the pseudogeminal *t*-Bu-substituted ligand **100**, which provided a yield of 93% and ee of 87% (Table 1.43, entry 7).

Wu and Zhang have reported the synthesis of ligand class **101** and their application in the enantioselective diethylzinc

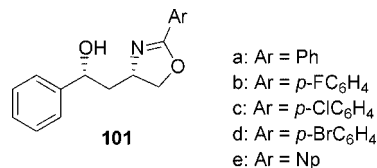
Table 1.43. Asymmetric Addition of Diethylzinc to Benzaldehyde Using Ligands 97–100

entry	substitution pattern	ligand	time (h)	yield (%)	ee (%) (conf)
1	<i>pseudo-geminal</i>	97a	24	93	11 (<i>S</i>)
2	<i>pseudo-geminal</i>	97b	2	78	78 (<i>R</i>)
3	<i>pseudo-ortho</i>	98a	24	74	35 (<i>S</i>)
4	<i>pseudo-ortho</i>	98b	4	96	51 (<i>S</i>)
5	<i>ortho</i>	99a	24	79	62 (<i>S</i>)
6	<i>ortho</i>	99b	48	72	44 (<i>R</i>)
7	<i>pseudo-geminal</i>	100	4	93	87 (<i>R</i>)



addition to *N*-diphenylphosphinoylimine (Scheme 1.48, Table 1.44).⁶⁹

Initial screening showed the phenyl-substituted ligand **101a** to give the highest enantiomeric excess (91%) for the addition to *N*-diphenylphosphinoyl benzalimine. A range of imines were then screened using ligand **101a**, with the *para*-benzyl-substituted imine giving the highest enantiomeric excess of 95%, with an isolated yield of 81% after 48 h at room temperature (Table 1.44, entry 5). Interestingly, the *para*-fluoro-substituted imine was almost unreactive (Table 1.44, entry 8).



5. Mono(oxazoline) *N,S*-Ligands

Cyclopenta[*b*]thiophene-alkyloxazoline ligands **102** have been prepared by Ricci and applied in palladium-catalyzed allylic alkylation (Scheme 1.6).⁷⁰ Ligands **102a–d** all resulted in high yields of the dimethyl 1,3-diphenylprop-2-enylmalonate product, with slightly higher reactivity rates being observed for the (*S*)-configured ligands (Table 1.45, entry 2). Changing the ratio of ligand/catalyst had no significant effect on yield or enantioselectivity (Table 1.45,

Scheme 1.48

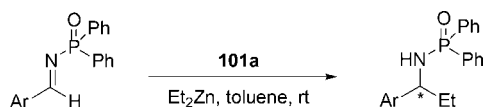
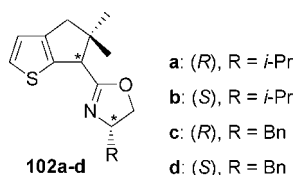


Table 1.44. Enantioselective Diethylzinc Addition of Aromatic Imines in the Presence of Ligand 101

entry	Ar	yield (%)	ee (%)
1	Ph	80	91
2	4-ClC ₆ H ₄	76	88
3	4-BrC ₆ H ₄	85	94
4	4-MeOC ₆ H ₄	78	94
5	4-BnOC ₆ H ₄	81	95
6	piperonyl	83	92
7	β -naphthyl	84	86
8	4-FC ₆ H ₄	trace	

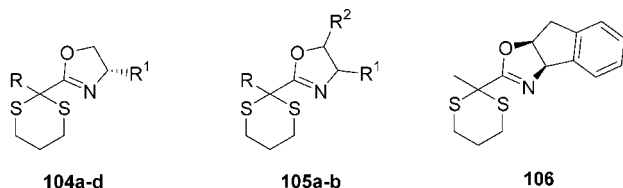
entry 3). Interestingly, both (*R*)- and (*S*)-configured ligands led to the (*S*)-product.



A new range of *N,S* ligands containing a rigid three ring skeleton **103** was also developed by Ricci.⁷¹ The ligands were successfully applied in the copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcone (Scheme 1.49, Table 1.46).

Ligands **103a–e** promoted good levels of enantioselectivities, with diethyl ether as solvent, resulting in slightly enhanced enantioselectivities compared to the case of toluene (Table 1.46, entries 2, 6, 8). Substituents on the aryl ring had a negligible effect on the stereochemical outcome of the reaction (Table 1.46, entries 3,4). A significant improvement in the enantioselectivity was obtained using ligand **103d**, which contains a methyl group at position 5 (Table 1.46, entry 6). The presence of an additional methyl group at position 6, however, had a detrimental effect, most likely due to its close proximity to the metal chelation site of the oxazoline nitrogen (Table 1.46, entry 8).

Ricci has extended this work to include new oxazoline-1,3-dithianes **104–106**, and these ligands were applied in the enantioselective palladium-catalyzed allylic substitution (Scheme 1.6) and 1,4-conjugate addition of Et₂Zn to enones (Scheme 1.49).⁷²



a: R = H, R¹ = Bn

a: R¹ = Me, R² = Ph

b: R = Me, R¹ = Bn

b: R¹ = Ph, R² = Ph

c: R = Me, R¹ = *i*-Pr

d: R = Me, R¹ = *t*-Bu

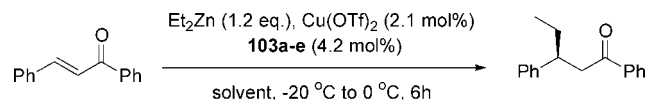
For palladium-catalyzed allylic substitution, ligands **104–106** all gave excellent yields (>94%), with the best enantioselectivity being obtained using ligand (*S*)-**104d**, which

Table 1.45. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligands 102a–d

entry	ligand	solvent	time (h)	yield (%)	ee (%) (conf)
1	102b	CH ₂ Cl ₂	70	91	70 (<i>S</i>)
2	102d	CH ₂ Cl ₂	30	93	73 (<i>S</i>)
3 ^a	102d	CH ₂ Cl ₂	60	94	74 (<i>S</i>)

^a Reaction using ligand (5 mol %) and Pd catalyst (2.5 mol %).

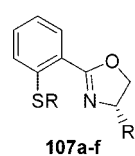
Scheme 1.49

Table 1.46. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et₂Zn to Chalcone Using Ligands 103a–e

Entry	Ligand	Solvent	Yield (%)	ee (%) (Conf.)
1	103a	toluene	61	51 (<i>S</i>)
2	103a	Et ₂ O	51	53 (<i>S</i>)
3	103b	toluene	58	47 (<i>S</i>)
4	103c	toluene	55	43 (<i>S</i>)
5	103d	toluene	58	70 (<i>R</i>)
6	103d	Et ₂ O	49	79 (<i>R</i>)
7	103e	toluene	58	58 (<i>R</i>)
8	103e	Et ₂ O	40	65 (<i>R</i>)

gave an ee of 90% (*S*). For the conjugate addition to chalcone, the yields varied from 60 to 80% and the highest ee's were obtained using ligands (*S*)-**104b** (62% (*S*)) and **106** (*R*).

Claver has reported the facile two-step synthesis of oxazoline-thioether ligands **107**, from 2-fluorobenzonitrile.⁷³



a: R = Me, R¹ = Ph

b: R = Me, R¹ = *i*-Pr

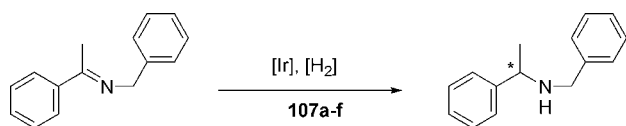
c: R = Ph, R¹ = Ph

d: R = Ph, R¹ = *i*-Pr

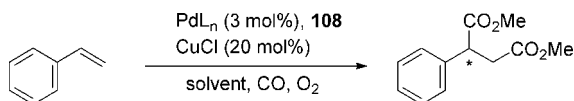
e: R = *t*-Bu, R¹ = Ph

f: R = *t*-Bu, R¹ = *i*-Pr

Scheme 1.50

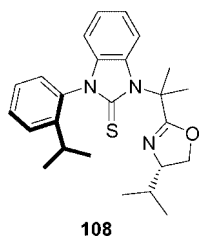


Scheme 1.51



The ligands were applied in the hydrogenation of *N*-(α -methyl)benzylidenebenzylamine (Scheme 1.50) and resulted in moderate to excellent conversions (32–100%), but only ligand **107a** afforded any enantioselectivity (15% ee).

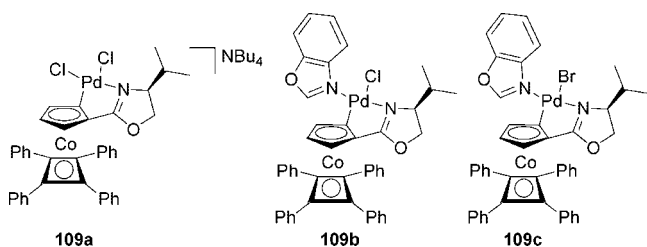
Marder and Yang have reported the synthesis of thiourea ligand **108** and its application in the palladium-catalyzed carbonylation of styrene (Scheme 1.51, Table 1.47).⁷⁴



$[\text{PdCl}(\text{C}_3\text{H}_5)]_2$ as the Pd source gave the best isolated yield (95%) and enantiomeric excess (75%). The ratio of Pd/ligand was also found to be important, with an increase in yield from 84% to 95%, and an enhancement of enantiomeric excess from 67% to 75% observed by increasing the amount of ligand present.

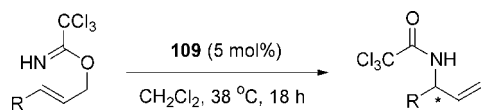
6. Miscellaneous Mono(oxazoline) Ligands

Overman has carried out extensive work on the asymmetric rearrangement of allylic trichloroacetimidates (Scheme 1.52, Table 1.48) using palladium(II) complexes of the COP family, for example **109a–c**. Each complex led to excellent enantiomeric excesses (>95%) for both substrates shown, with other substrates being converted with levels of induction in excess of 91%.⁷⁵

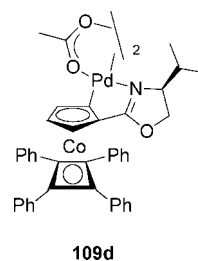


The structurally similar COP-OAc **109d** was applied in the catalytic asymmetric intramolecular aminopalladation reaction (Scheme 1.53) with a yield of 82% and an enantioselectivity of 87%.⁷⁶

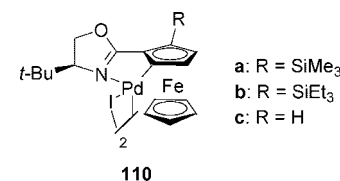
Scheme 1.52



A range of ferrocenyloxazoline palladacycle catalysts **110** have been applied by Overman in the rearrangement of *N*-(4-trifluoromethylphenyl)benzimidates (Scheme 1.54, Table 1.49).⁷⁷



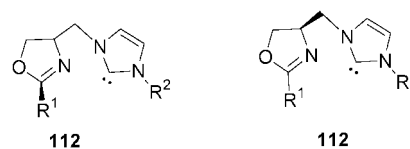
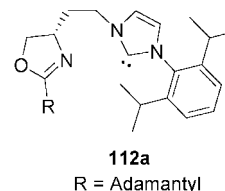
The results show the importance of the presence of the silyl group *ortho* to the oxazoline. In its absence (**110c**), the enantiomeric excesses dropped from 91% to 46% (Table 1.49, entries 1, 5). The best overall results were obtained with the *Z*-imidate, with catalyst **110a** and **110b** giving excellent enantiomeric excesses of 91% and 90%, respectively (Table 1.49, entries 1, 3).



Mixed oxazoline–carbene ligands have been reported by the groups of Gade, Bellemin-Lapponnaz, and Pfaltz.^{78–80}

As an example, catalysts **111** have been applied in the hydrosilylation of ketones (Scheme 1.55, Table 1.50).⁷⁹

Initial screening revealed catalyst **111c** to be the most active and stereoselective, and it was thus applied in the hydrosilylation of a range of ketones. Both aromatic and aliphatic ketones were converted into their corresponding alcohols with excellent yield and enantioselectivities. Substitution of the aromatic ring had little effect on either yield or enantioselectivity (Table 1.50, entries 1–4). The naphthyl-substituted ketone afforded the highest enantioselectivity of 91%. Aliphatic ketones were also successful substrates, with *t*-Bu-substituted ketone affording the highest overall ee of 95%, although the product yield (70%) was significantly lower than those of the other substrates (Table 1.50, entry 6).



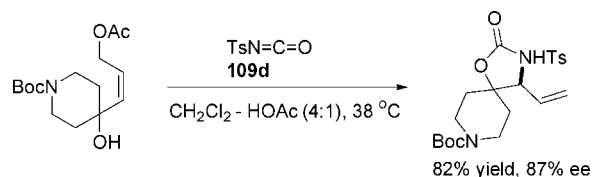
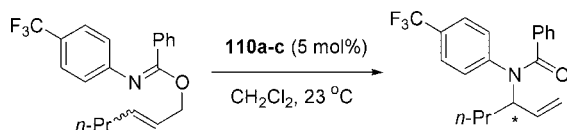
- b: R¹ = *t*-Bu, R² = Me
c: R¹ = *t*-Bu, R² = *i*-Pr
d: R¹ = *t*-Bu, R² = Neopentyl
e: R¹ = *t*-Bu, R² = Isobutyl
f: R¹ = *t*-Bu, R² = Me
g: R¹ = *t*-Bu, R² = *i*-Pr
h: R¹ = *t*-Bu, R² = Neopentyl
i: R¹ = *t*-Bu, R² = Isobutyl

Table 1.47. Pd-Catalyzed Carbonylation of Styrene Using Thiourea Ligand 108

entry	PdL _n	Pd/108	solvent	temp (deg)	time (h)	yield (%)	ee (%)
1	Pd(OAc) ₂	1:1	MeOH	50	24	77	60
2	[PdCl(C ₃ H ₅) ₂] ₂	1:1	MeOH	20	52	84	67
3	[PdCl(C ₃ H ₅) ₂] ₂	1:2	MeOH	20	52	95	75
4	[PdCl(C ₃ H ₅) ₂] ₂	1:2	MeOH/THF	20	52	94	66

Table 1.48. Asymmetric Allylic Trichloroacetimidate Rearrangement Using 109a–c

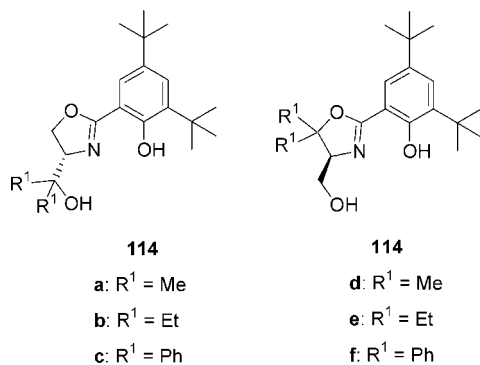
entry	R (imidate)	catalyst	ee (%)
1	CH ₂ CH ₂ Ph	109b	97
2	CH ₂ CH ₂ Ph	109a	97
3	CH ₂ CH ₂ Ph	109c	96
4	Me	109b	95
5	Me	109a	95

Scheme 1.53**Scheme 1.54**

Pfaltz has synthesized and applied a range of chiral *N*-heterocyclic carbene oxazoline ligands **112** in the iridium-catalyzed enantioselective hydrogenation of *trans*- α -methylstilbene. The [Ir-COD] complexes of ligands **112a–i** gave excellent yields, with the majority being >99%. The enantioselectivities were very good, with **112b–d** giving ee's of 84–90%. Similar levels of enantioselection were observed for **112f–i**. The highest enantioselectivity was obtained using **112a**, which resulted in 98% ee.⁸⁰

Sigman has designed a new oxazoline-containing ligand **113**, derived from (*S*)-camphor sulfonic acid and has achieved an enantioselectivity of 90% in the enantioselective hetero-Diels–Alder reaction (Scheme 1.56).⁸¹

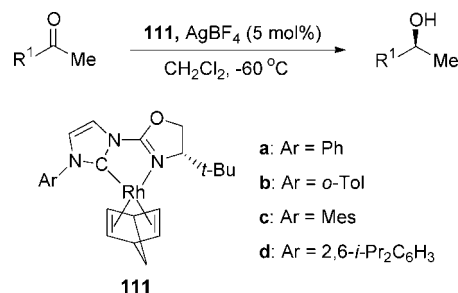
Hayashi has applied ligands **114a–f** as Schiff bases in the enantioselective addition of diketene to benzaldehyde (Scheme 1.57, Table 1.51).⁸²



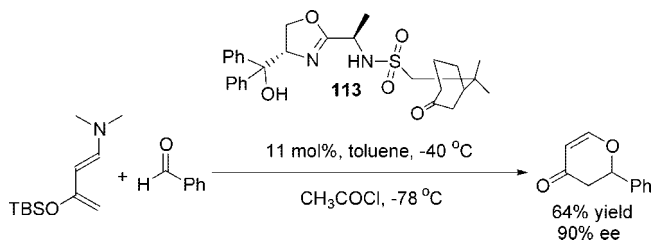
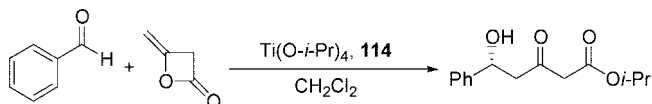
Methyl-substituted ligand **114a** and ethyl-substituted **114e** afforded the highest enantiomeric excesses of 90% and 87%, respectively (Table 1.51, entries 1, 5). These two optimum ligands were subsequently applied in the addition of diketene

Table 1.49. Enantioselective Imidate Rearrangement Using Palladacycle 110

entry	catalyst	imidate isomer	time (days)	yield (%)	ee (%) (conf)
1	110a	<i>Z</i>	3	67	91 (<i>R</i>)
2	110a	<i>E</i>	2	57	79 (<i>S</i>)
3	110b	<i>Z</i>	6	89	90 (<i>R</i>)
4	110b	<i>E</i>	2.5	76	76 (<i>S</i>)
5	110c	<i>Z</i>	2	15	46 (<i>R</i>)
6	110c	<i>E</i>	2	77	69 (<i>S</i>)

Scheme 1.55**Table 1.50. Asymmetric Hydrosilylation of Ketones Using Catalyst 111c**

entry	R ¹	yield (%)	ee (%)
1	Ph	92	90
2	naphthyl	99	91
3	4-MeOC ₆ H ₄	92	88
4	4-FC ₆ H ₄	90	91
5	H ₃ C(CH ₂) ₅	95	79
6	<i>t</i> -Bu	70	95
7	adamantyl	96	89

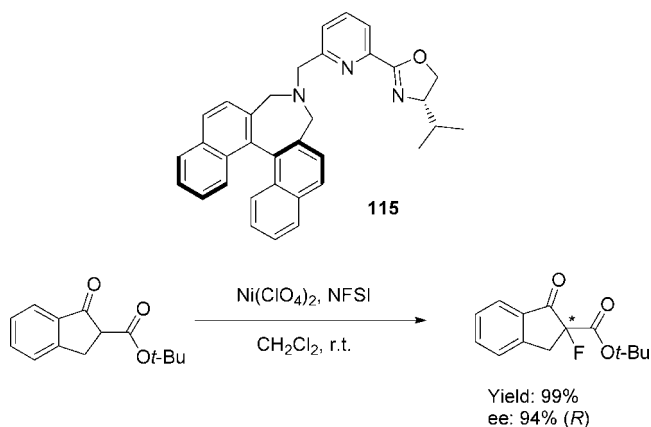
Scheme 1.56**Scheme 1.57**

to a range of aromatic and aliphatic aldehydes. The best results were obtained using **114a**, which afforded enantiomeric excesses of up to 92% and 93% for the addition to (*E*)-cinnamaldehyde and 2-furfural, respectively.

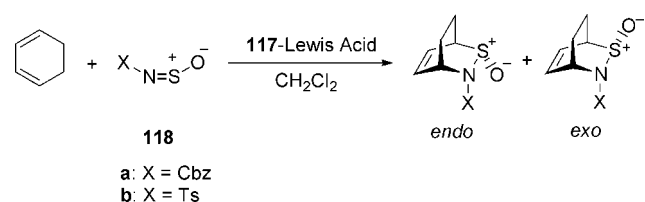
Iwasa has applied ligand **115**, which contains both axial chirality and carbon-centered chirality in the asymmetric fluorination of the β -keto ester 2-*tert*-butoxycarbonyl-1-indanone (Scheme 1.58), and achieved an enantiomeric

Table 1.51. Enantioselective Addition of Diketene to Benzaldehyde Using 114a–f

entry	ligand	yield (%)	ee (%)
1	114a	67	90
2	114b	46	77
3	114c	14	56
4	114d	55	62
5	114e	47	87
6	114f	77	62

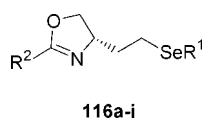
Scheme 1.58**Table 1.52. Asymmetric Pd-Catalyzed Allylic Alkylation Using Ligand Class 116**

entry	ligand	R ¹	R ²	yield (%)	ee (%) (<i>R</i>)
1	116a	Ph	Ph	99	85
2 ^a	116a	Ph	Ph	99	91
3	116b	Bn	Ph	93	79
4	116c	4-ClC ₆ H ₄	Ph	85	63
5	116d	4-MeOC ₆ H ₄	Ph	81	75
6	116e	2,4,6-Me ₃ C ₆ H ₂	Ph	95	87
7	116f	3-CF ₃ C ₆ H ₄	Ph	83	54
8	116g	<i>t</i> -Bu	Ph	91	37

^a Cs₂CO₃/CH₂Cl₂ used as the base/solvent system.**Scheme 1.59**

excess of 94% when Ni(ClO₄)₂ was employed as the Lewis acid and NFSI used as the electrophilic source of fluoride.⁸³

Chiral organoselenium compounds **116a–j** have been developed by Braga and evaluated as chiral ligands in palladium-catalyzed asymmetric allylic alkylation (Scheme 1.6).⁸⁴

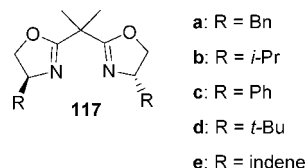


The nature of the group attached to the selenium atom and the oxazoline substituent both appear to play a role in the enantioselection of the reaction. The best results were achieved with **116a**, which bears a phenyl group on the Se and a phenyl on the oxazoline. This ligand furnished the alkylated product in 91% ee with 99% yield (Table 1.52, entry 2).

7. Bis(oxazoline) Ligands

7.1. Bis(oxazoline) Ligands with One Carbon Separating the Oxazoline Rings

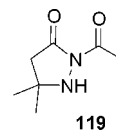
Due to the recent review of C₂-symmetric bis(oxazoline) ligands by Desimoni and Jørgensen, only applications of these ligands reported from 2006 onward will be described here.⁸⁵



Gautun has applied **117c** in the hetero Diels–Alder reactions of *N*-sulfinyl dienophiles **118** (Scheme 1.59, Table 1.53). The reaction proceeded smoothly with very good yields, excellent diastereoselectivities favoring the *endo* product, and excellent enantioselectivities being reported in the presence of either TMSOTf or TIPSOTf. The best results were obtained using Cu(OTf)₂ as the Lewis acid, TMSOTf as the additive, and dienophile **2a** (Table 1.53, entry 2). After 4 h, a diastereoselectivity of >95:<5 and an enantiomeric excess of 98% was obtained. Interestingly, leaving the reaction for an additional 18 h led to a significant loss in ee to 89% (Table 1.53, entry 1).⁸⁶

Sibi has reported the application of **117c** to the enantioselective Diels–Alder reaction (Scheme 1.24) and obtained an enantioselectivity of 95% (*R*) in the presence of additive **119**.⁸⁷

Reiser has applied **117c** in the Mukaiyama aldol reaction between methyl pyruvate and 1-phenyl-1-(trimethylsiloxy)ethane and obtained 100% yield and an enantiomeric excess of 64% (Scheme 1.60).⁸⁸



Fustero utilized ligand **117c** in the generation of difluorinated amino acid derivatives (Scheme 1.61). The addition of allylzinc bromide in the presence of **117c** led to the formation of the desired diene system in 20% yield and with 50% enantiomeric excess.⁸⁹

Yamazaki has successfully applied **117d** in the enantioselective Friedel–Crafts reactions of reactive ethenetricarboxylates and acyl-substituted methylenemalonates (Scheme 1.62, Table 1.54).⁹⁰

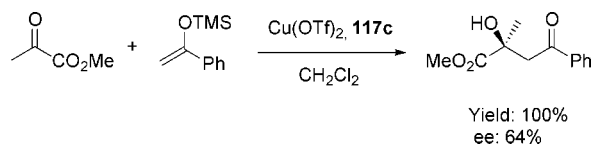
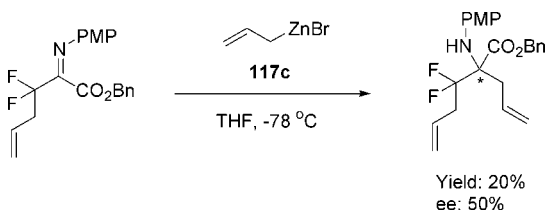
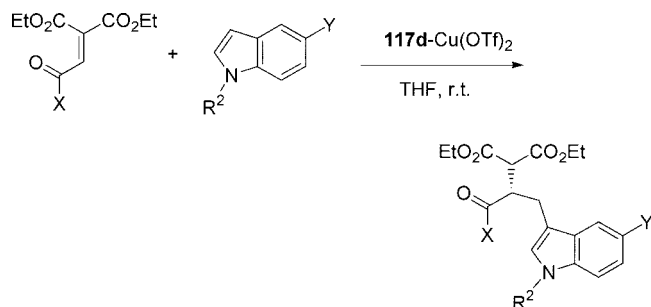
Cu(OTf)₂ complexes of **117d** catalyzed the addition of a range of indoles to a range of ethenetricarboxylates with very good yields and enantioselectivities. *N*-Methylindole was particularly successful, adding to the Ph-substituted carboxylate with a yield of 87% and an enantiomeric excess of 95% (Table 1.54, entry 2).

Zhou has achieved enantiomeric excesses of up to 90% in the asymmetric Friedel–Crafts alkylation of indole with nitroalkenes employing Zn(OTf)₂ complexes of **117c**.⁹¹

Ligand **117c** has also proven to be successful in the enantioselective Diels–Alder reaction between pyridine *N*-oxides **120** and a variety of dienes (Scheme 1.63, Table 1.55).⁹²

Table 1.53. Enantioselective Hetero-Diels–Alder Reaction Using Ligand **113c**

entry	<i>N</i> -sulfine	additive	Lewis acid	time (h)	yield (%)	endo/exo	ee (%)
1	118a	TMSOTf	117c -Cu(OTf) ₂	22	85	>95:<5	89
2	118a	TMSOTf	117c -Cu(OTf) ₂	4	68	>95:<5	98
3	118a	TMSOTf	117c -Cu(OTf) ₂	1	54	90:10	94
4	118b	TMSOTf	117c -Zn(OTf) ₂	22	86	>95:<5	97
5	118b	TMSOTf	117c -Zn(OTf) ₂	4	83	>95:<5	96
6	118a	TMSOTf	117c -Zn(OTf) ₂	1	82	>95:<5	94
7	118c	TIPSOTf	117c -Zn(OTf) ₂	4	62	>95:<5	90

Scheme 1.60**Scheme 1.61****Scheme 1.62****Table 1.54. Enantioselective Addition of Indoles Using Ligand **117d****

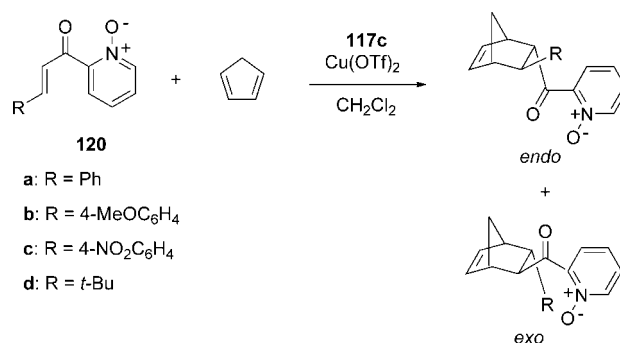
entry	X	R ²	Y	yield (%)	ee (%)
1	OBn	Me	H	74	86
2	Ph	Me	H	87	95
3	Ph	H	Cl	75	93

The reactions proceeded with excellent yields in very short reaction times (maximum 30 min). There was little variation in the diastereoselectivity (95:5 – 97.5:2.5) or enantiomeric excess (95–96%) for dienophiles **120a**–**c** (Table 1.55, entries 1–3), but the *t*-Bu-substituted dienophile **120d** resulted in a moderate diastereoselectivity of 78:22 (Table 1.55, entry 4). Dienophile **120a** was reacted with a range of linear dienes, with diastereoselectivities of up to 99:1 and enantiomeric excess of 94% obtained.

Nakamura and Toru have applied a range of bis(oxazoline) ligands in the enantioselective Strecker reaction, with **117c** in the presence of Cu(OTf)₂ affording the best enantiomeric excess of 94%. Indene-substituted ligand **117e** led to an ee of 80%.⁹³

Ligand **117e** has recently been applied by Kim in the enantioselective Friedel–Crafts alkylations of indoles with α -phosphoric enones (Scheme 1.64), with an optimal enantiomeric excess of 98%.⁹⁴

Ligand **117c** has been applied by Ma in the first known example of a Cu-catalyzed enantioselective tandem Nazarov

Scheme 1.63**Table 1.55. Enantioselective Diels–Alder Reaction Using Cu(OTf)₂–**117c****

entry	dienophile	time (h)	yield (%)	endo/exo	ee (endo) (%)
1	120a	0.3	98	97.5:2.5	96
2	120b	0.3	95	97:3	95
3	120c	0.01	93	95:5	96
4	120d	0.5	92	78:22	93

cyclization for the synthesis of organofluorine compounds with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters. The highest yield obtained was 80% with an excellent *cis/trans* ratio of >49:1 and an enantioselectivity of 95.5% (Scheme 1.65).⁹⁵

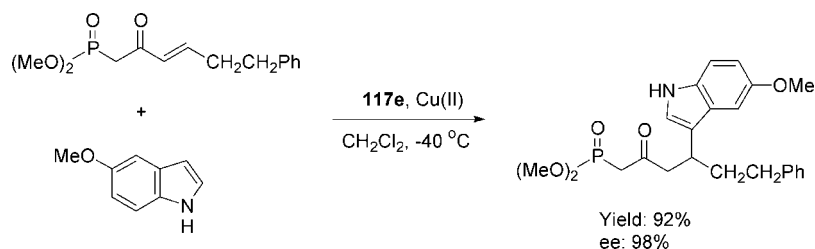
Nakamura and Toru have applied ligands **117c** and **117e** in the enantioselective Mannich-type reaction of imines in the presence of Lewis acids (Scheme 1.66).⁹⁶ The nature of the aromatic substitution on the imine group proved crucial, with only 2-pyridylimines giving satisfactory enantioselectivities. Phenyl-substituted ligand **117c** formed a significantly more active and selective catalyst with an optimum yield of 86% and ee of 86%, compared to the indene variant **117e**, which provided an ee of 71% but a disappointing yield of 24%.

A range of bis(oxazoline) ligands have been applied by Chemler in the Cu-catalyzed enantioselective intramolecular carboamination of alkenes (Scheme 1.67, Table 1.56).⁹⁷ Initial screening of ligands showed that ligand **117c** gave the highest asymmetric induction, and this ligand was then applied in the cyclization of a range of γ -alkenyl arylsulfonamides. The yields obtained were in the range 45–85% yield with excellent enantioselectivities of between 80–94% for a range of substrates.

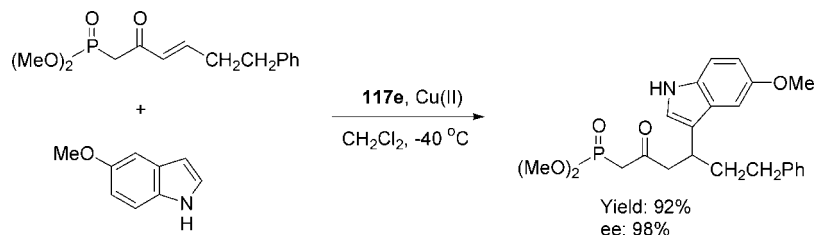
(*R,R*)-**117c** has been applied by Gade and Bellemin-Laponnaz in the copper-catalyzed α -amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate, and they obtained a yield of 93% and an enantiomeric excess of 98% (Scheme 1.68).⁹⁸

Analogues of the BOX ligand class **117** have also been prepared, with varying substitution patterns on both the oxazoline ring and the one-carbon bridge which links the two oxazoline rings.

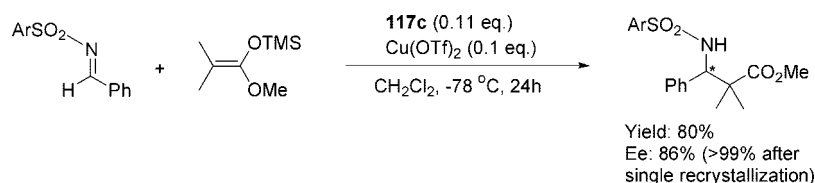
Scheme 1.64



Scheme 1.65



Scheme 1.66



Scheme 1.67

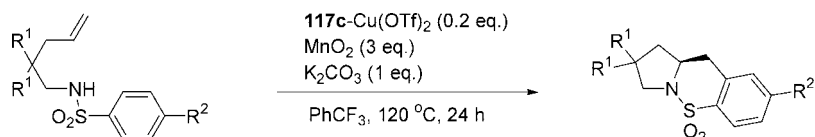
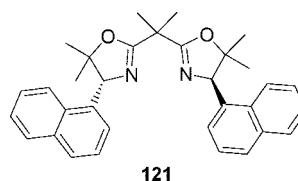


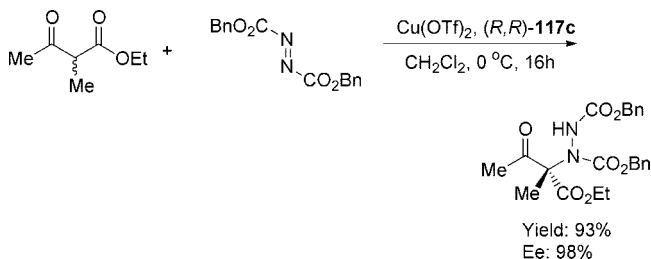
Table 1.56. Cu-Catalyzed Enantioselective Carboamination Using Ligand 117c

entry	substrate	yield (%)	ee (%)
1	R ¹ = Me, R ² = Me	85	92
2	R ¹ = Me, R ² = H	73	92
3	R ¹ = Me, R ² = Cl	45	92
4	R ¹ = Me, R ² = OMe	75	94
5	R ¹ = Ph, R ² = Me	78	94
6	R ¹ = CH ₂ (CH ₂) ₂ CH ₃ , R ² = Me	83	92
7	R ¹ = CH ₂ (CH ₂) ₃ CH ₃ , R ² = Me	68	92

Ph₃CPF₆/**121**, which gave a 91% yield, 88:12 *trans/cis* ratio, and 96% ee for the *trans*-isomer (Table 1.57, entry 5). These results were reproduced using a lower catalyst loading of 0.2 mol %.



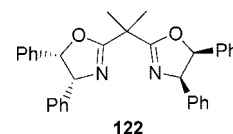
Scheme 1.68



Itagaki has prepared and applied ligand **121** in the copper-catalyzed asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) (Scheme 1.69, Table 1.57).⁹⁹

The reactions proceeded with very good yield and *trans* selectivity for a range of Cu systems. The enantiomeric excess of the *trans*-isomer was excellent in all cases (94–96%), with the *cis*-isomer affording ee's in the range 71–74%. The best overall result was obtained using CuCl/

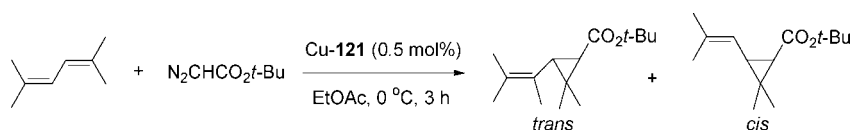
Ligand **122** has been applied in the Friedel–Crafts alkylation of aromatic ethers with trifluoropyruvate. A yield of 78% and an enantiomeric excess of 93% was reported for the reaction between ether **123** and **124** (Scheme 1.70).¹⁰⁰



Ligand **122** has also been applied in the enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes, with enantioselectivities of up to 86% reported.¹⁰¹

Jørgensen has applied the Cu complex of ligand **122** in the enantioselective addition of 1-methoxy-3-(trimethylsiloxy)butadiene **125** to 5-bromo-*N*-oxypyridine-2-carbaldehyde **126** (Scheme 1.71).¹⁰² Screening of a range of Lewis

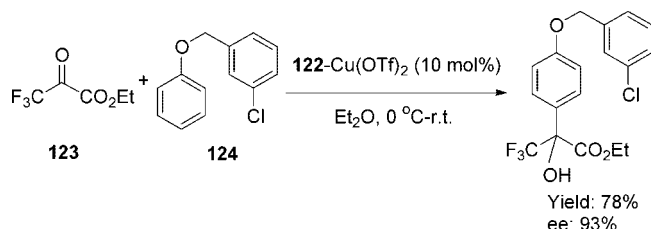
Scheme 1.69

Table 1.57. Asymmetric Cyclopropanation of DMHD Using Cu(1) Complexes of **121**

entry	catalyst system	yield (%)	<i>trans/cis</i>	ee (<i>trans</i>) (%)	ee (<i>cis</i>) (%)
1	Cu(OTf)/ 121	83	87:13	96	71
2	Cu(CH ₃ CN) ₄ PF ₆ / 121	82	87:13	95	70
3	CuCl/AgPF ₆ / 121	87	88:12	96	74
4	CuCl/AgSbPF ₆ / 121	88	88:12	94	73
5	CuCl/Ph ₃ CPF ₆ / 121	91	88:12	96	74
6 ^a	CuCl/Ph ₃ CPF ₆ / 121	92	88:12	96	71

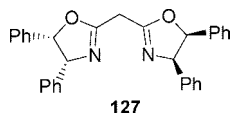
^a 0.2 mol % of catalyst utilized.

Scheme 1.70



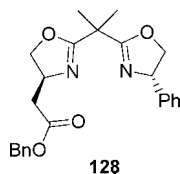
acids and solvents resulted in an optimum enantiomeric excess of 93% using Cu(OTf)₂ and toluene/CH₂Cl₂ (4:1).

These reaction conditions were then applied to the addition of diene **125** to a range of aldehyde substrates, with the most successful substrate being 6-phenyl-*N*-oxypyridine-2-carbaldehyde, which gave the desired product in 49% yield and with an enantiomeric excess of 95%.



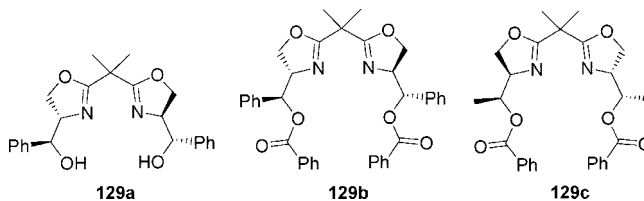
Ligand **127** is structurally related to **122** and has been applied by Singh in the enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes to afford enantiomeric excess of 57–86% for the alkylation of a range of indoles using various nitroolefins.¹⁰¹

The C₁-symmetric ligand **128** has been synthesized by Orlandi and applied in the Cu(II)-catalyzed Mukaiyama aldol reaction with a highest enantiomeric excess of 55%.¹⁰³

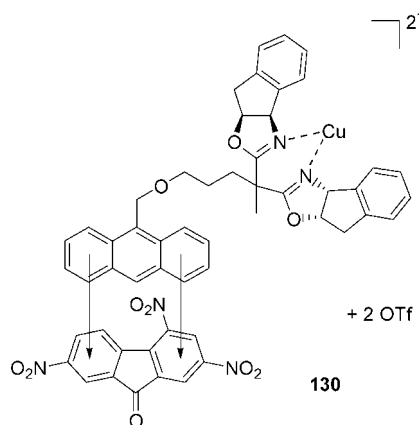


Aït-Haddou has developed new dihydroxy bis(oxazoline) ligands **129a–c**.¹⁰⁴ They were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate

with dimethyl malonate using sodium hydride as the base (Scheme 1.6). Ligand **129a** gave a yield of 98% and an ee of 92% after 2 h. Ligand **129b** afforded similar results with a yield of 98% and ee of 90% after 24 h; ligand **129c** was the most selective, affording the product in 95% yield and an ee of 97% after 16 h.

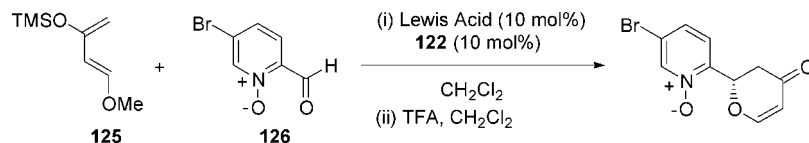


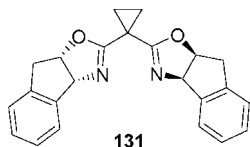
The charge-transfer complex **130** has been applied by Schulz in the copper-catalyzed Diels–Alder reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one with a diastereoselectivity of up to 97% and an enantiomeric excess up to 94%.¹⁰⁵ No loss of activity or stereoselectivity was observed after recycling the catalyst up to 12 times.



The indene-derived ligand **131**, which contains a cyclopropyl linkage, has been applied in a number of catalytic asymmetric transformations.

Scheme 1.71





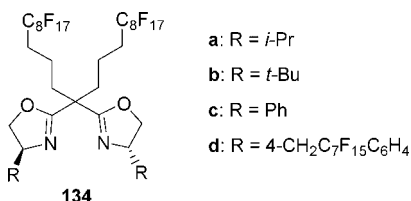
Lautens has applied ligand **131** in the enantioselective catalytic ring expansion of methylenecyclopropane carboxamides, with the highest enantioselectivity of 86% reported for the reaction of cyclopropane **132** with *N*-tosylaldimine **133**, using a 1.5:1 ratio of 10:MgI₂ (Scheme 1.72).¹⁰⁶

In an extension to Sibi's previous work, ligand **131** was applied to the enantioselective 1,3-dipolar cycloadditions of nitrones and nitrile oxides, resulting in enantioselectivities of 98% and 99%, respectively.¹⁰⁷

The application of ligand **131** in the enantioselective Michael addition (Scheme 1.73) has been reported by Nichols as a key step in the synthesis of pyrrolidine-based PDE₄ inhibitors.¹⁰⁸

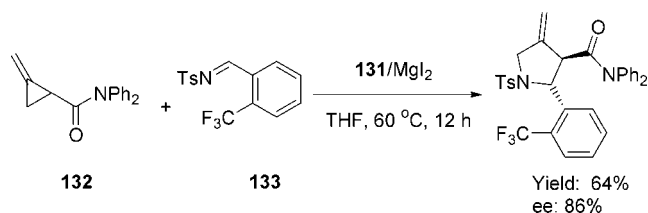
The C₂-symmetric ligand class **134** has been applied in the enantioselective cyclopropanation of styrene by Sinou (Scheme 1.74). Cu(I) complexes of ligand **134b** gave the best *trans/cis* ratio of 62:38 with enantiomeric excesses of 84% and 81%, respectively.¹⁰⁹

In an extension to this work, Sinou has also reported the application of **134c** in the copper-catalyzed glyoxylate-ene reaction and using a solid/liquid extraction methodology for recycling the catalyst.¹¹⁰ These catalysts gave moderate to high enantioselectivities and were successfully reused. The best result obtained was for the reaction of α -methylstyrene and ethyl glyoxylate, with a yield of 78% and enantiomeric excess of 88% after five runs (Scheme 1.75).

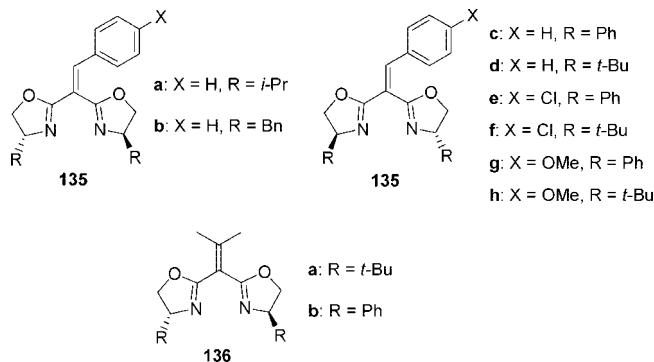
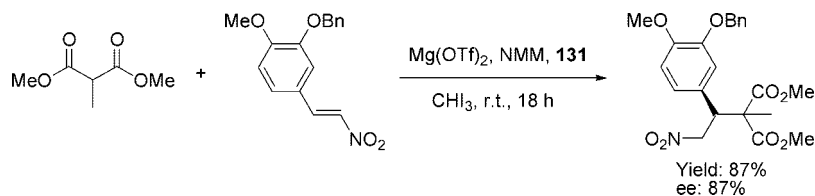


Ligand **134d** was applied in the palladium-catalyzed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate with quantitative yield and an enantiomeric excess of 92%. The enantioselective allylic oxidation of cyclohexene utilizing Cu-**134d** led to a yield of 43% and ee of 50%.¹¹¹

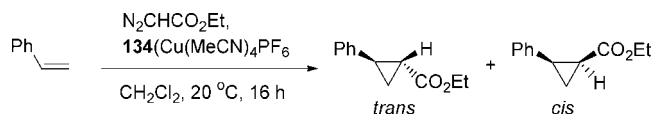
Scheme 1.72



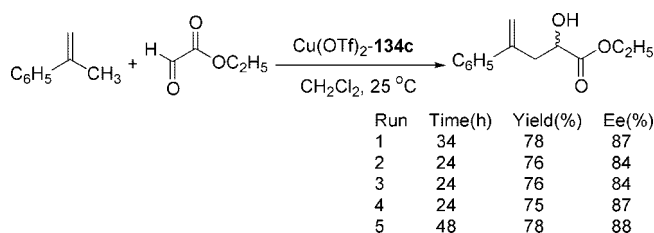
Scheme 1.73



Scheme 1.74

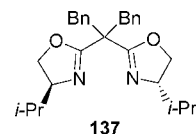


Scheme 1.75



Burke has developed aryld-Box **135**, a new family of chiral bis(oxazolines) containing an aryldene bridging unit. The ligands have been successfully applied in the Cu(I)-catalyzed cyclopropanation of styrene (Scheme 1.74). The most successful ligands were those with *t*-Bu-substituted oxazoline rings **135d** and **135f**, which afforded enantiomeric excesses of 77% and 78%, and *trans/cis* ratios of 62:38 and 65:35, respectively.¹¹²

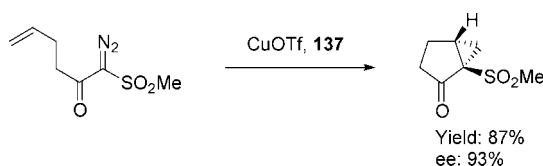
The structurally related ligand **136** has been applied in the Cu-catalyzed cyclopropanation of styrenes with **136a**, giving yields of up to 69%, typical *trans/cis* ratios of 60:40, and ee's of up to 60%.¹¹³



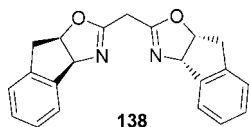
Ligand **137** was applied by Nakada in the intramolecular enantioselective cyclopropanation of 2-diazo-3-oxo-6-heptenoic mesityl ester with an isolated yield of 87% and an enantiomeric excess of 93% (Scheme 1.76).¹¹⁴

Ma has applied bis(oxazoline) ligand **138** in the Cu-catalyzed enantioselective addition of activated terminal alkynes to 1-acylpyridinium salts (Table 1.58).¹¹⁵ A range of alkynes were successfully added to the 1-acylpyridinium chloride salt. Methyl propiolate gave an excellent enanti-

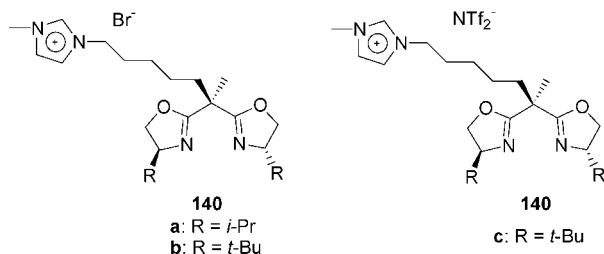
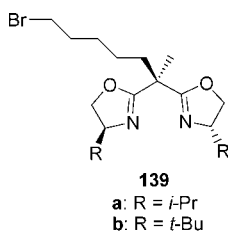
Scheme 1.76



oselectivity of 95% with a good yield of 74% (Table 1.58, entry 1). Increasing the size of the propiolate to benzyl propiolate gave a significantly lower ee of 86% (Table 1.58, entry 2). A similar trend was observed using ynones, with the smaller 1-pentyn-3-one giving the highest ee of 99% (Table 1.58, entry 4).



This IndaBOX ligand **138** has also been utilized by Kim in the copper-catalyzed Diels–Alder reaction in ionic liquids.¹¹⁶ Using [Bmim]SbF₆ as the ionic liquid, good to excellent yields and enantioselectivities of up to 97% were obtained using cyclopentadiene with a range of β -substituted dienophiles (Scheme 1.77). This methodology led to a significant enhancement in rate, yield, and enantioselectivity compared to the previously reported homogeneous reaction.¹¹⁷

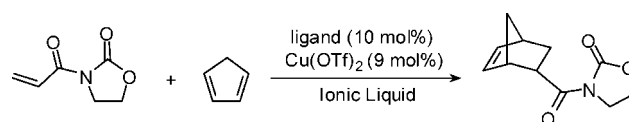


A range of new bis(oxazolines) **139** and **140** have been applied in the enantioselective Cu-catalyzed Diels–Alder reaction (Scheme 1.77). The optimum results were obtained

Table 1.58. Enantioselective Addition of 1-Alkynes to 1-Acylpyridinium Salt Using Cu-138

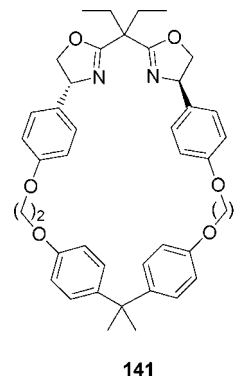
entry	R	yield (%)	ee (%)
1	CO ₂ CH ₃	74	95
2	CO ₂ Bn	81	85
3	COCH ₃	69	93
4	COCH ₂ CH ₃	65	99
5	CO(CH ₂) ₃ CH ₃	70	91
6	CO(CH ₂) ₄ CH ₃	68	90

Scheme 1.77

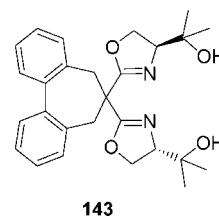
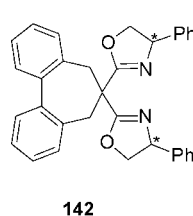


using ligands **139b** and **140c**, which both gave 100% conversion and enantioselectivities (*endo*) of 93% and 84%, respectively.¹¹⁸

A range of chiral macrocyclic bis(oxazoline) ligands have been developed by Žinic. These ligands were applied in the enantioselective cyclopropanation of styrene with diazoacetate, with ligand **141** giving a 7:93 *cis:trans* ratio, with enantioselectivities of 59–65% ee, respectively.¹¹⁹



Du has reported the application of ligands **142** and **143**, in which the two oxazoline rings are linked by a dibenzocycloheptadiene unit in the addition of diethylzinc to aldehydes (Scheme 1.41) and the palladium-catalyzed asymmetric allylic alkylation of dimethyl malonate (Scheme 1.6).



The use of both (*R*)- and (*S*)-**142** in palladium-catalyzed asymmetric allylic alkylation gave yields of 87% and 86%, and enantioselectivities of 87% and 86%, respectively.

The application of **143** in the enantioselective diethylzinc addition to benzaldehyde (Scheme 1.41) gave an optimized yield of 86% and ee of 87%. Other aldehydes were also successful substrates, with 4-chlorobenzaldehyde giving an ee of 96%.¹²¹

7.2. Bis(oxazoline) Ligands with Other Linkers

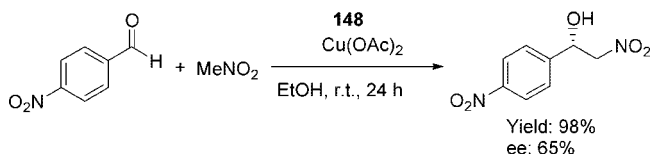
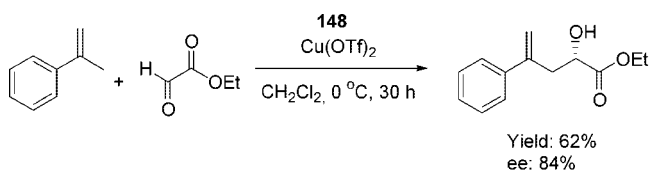
Bis(oxazoline) ligands with a range of bridges linking the chiral oxazoline rings have been developed and applied in metal-catalyzed asymmetric transformations.

Pfaltz has described a class of anionic bis(oxazoline) ligands **144** (boraBOX), in which a tetrasubstituted boron atom bridges the two oxazoline rings.¹²²

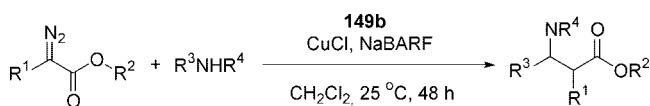
These ligands have been applied in the enantioselective cyclopropanation of styrene (Scheme 1.74, Table 1.59).

The boraBOX complexes showed similar reactivities to the corresponding BOX complexes. Bulkier substituents at the stereogenic centers of the boraBOX ligands induced

Scheme 1.81

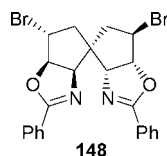


Scheme 1.82

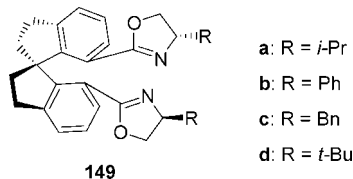
Table 1.62. Catalytic Asymmetric NH Insertion Using Cu Complexes of **149b**

entry	R ¹	R ²	R ³	R ⁴	yield (%)	ee (%)
1	Me	Et	Ph	H	94	98
2	Me	Et	4-ClC ₆ H ₄	H	92	98
3	Me	Et	4-BrC ₆ H ₄	H	95	98
4	Me	Et	3-BrC ₆ H ₄	H	96	98
5	Me	Et	2-MeOC ₆ H ₄	H	86	98
6	Me	Et	1-naphthylC ₆ H ₄	H	89	98
7	Me	Et	2-naphthylC ₆ H ₄	H	91	98

This area had been further advanced with the synthesis of ligand class **149** and its application in the catalytic asymmetric N–H insertion of amines with diazoesters (Scheme 1.82, Table 1.62).¹²⁷



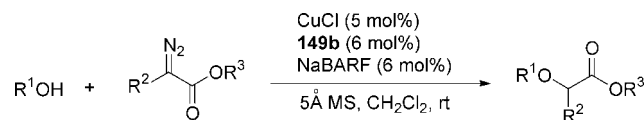
Initial screening of the ligand class showed Ph-substituted **149b** to be the most active and stereoselective, and this was thus applied in the NH insertion of a range of amines with various diazoesters. All the substituted anilines underwent the insertion reaction with high reactivity; complete conversions were achieved within 2 h. The nature of the aniline had little effect on the enantioselectivities obtained, with excellent ee's reported in all cases.



The application of the Spirobox ligand (*S,S,S,S*)-**149b** in the enantioselective insertion of carbenoids into the O–H bonds of phenols has been reported by Zhou (Scheme 1.83, Table 1.63).¹²⁸

Using optimized conditions, a variety of phenols were examined in the copper-catalyzed asymmetric carbenoid insertion reaction. All substituted phenols, including naphthols, underwent the insertion reaction in 3 h and provided

Scheme 1.83

Table 1.63. Asymmetric Catalytic Carbenoid Insertion into O–H Bonds of Phenols Using Ligand **149b**

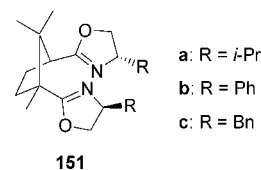
entry	R ¹	R ²	R ³	yield (%)	ee (%)
1	Ph	Me	Et	87	99
2	2-MeC ₆ H ₄	Me	Et	71	98
3	2-MeOC ₆ H ₄	Me	Et	68	95
4	2-PhC ₆ H ₄	Me	Et	83	99.2
5	3-MeC ₆ H ₄	Me	Et	79	99.3
6	3-MeOC ₆ H ₄	Me	Et	71	99
7	3-BrC ₆ H ₄	Me	Et	78	99
8	3-PhC ₆ H ₄	Me	Et	82	99
9	4-MeC ₆ H ₄	Me	Et	88	99
10	4-MeOC ₆ H ₄	Me	Et	78	99
11	4- <i>t</i> BuC ₆ H ₄	Me	Et	70	98
12	4-ClC ₆ H ₄	Me	Et	83	99.1
13	4-BrC ₆ H ₄	Me	Et	85	99.6
14	4-MeO ₂ CC ₆ H ₄	Me	Et	62	99
15	2,4-Me ₂ C ₆ H ₃	Me	Et	80	99
16	3,5-Ph ₂ C ₆ H ₃	Me	Et	84	99
17	1-naphthyl	Me	Et	77	99.1
18	2-naphthyl	Me	Et	83	98
19	Ph(CH ₂) ₃	Me	Et	63	59
20	PhCH=CHCH ₂	Me	Et	85	61
21	Ph	Ph	Et	71	10
22	Ph	Me	Et	70	98
23	Ph	Me	<i>t</i> -Bu	80	99

the corresponding α -aryloxypropionates in good yields and excellent enantioselectivities of $\geq 95\%$ regardless of the nature or position of the substituents (Table 1.63, entries 1–18). Aliphatic alcohols also underwent O–H insertion, although with lower enantioselectivities (Table 1.63, entries 19, 20). Changing R² of the α -diazoester from methyl to phenyl had a detrimental effect on enantioselectivity to 10% (Table 1.63, entry 21). The reaction was not sensitive to the size of the R³ group of the α -diazoester, with similar results obtained with both ethyl and *tert*-butyl groups.

The cyclohexane-linked bis(oxazoline) ligand **150** (cH-BOX) has been applied in the copper-catalyzed asymmetric aziridation of chalcones (Scheme 1.84) and furnished enantioselectivities of 80–99% for a range of chalcone substrates.¹²⁹

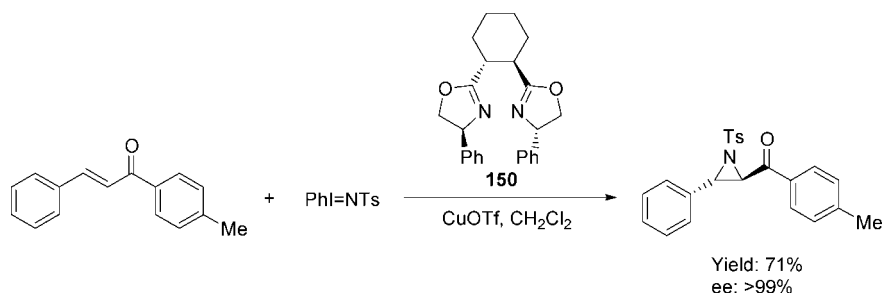
Camphoric acid derived ligands **151** have been applied by You in the Cu-catalyzed cyclopropanation of styrene (Scheme 1.74).

Ligand **151b** afforded the highest enantiomeric excess of 29% and was subsequently applied in the cyclopropanation of 1,1-diphenylethene with diazoacetate, resulting in an enantiomeric excess of 81%.¹³⁰

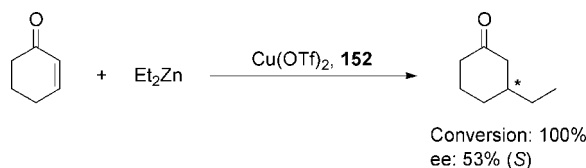


Ligands derived from tartaric acid have been synthesized by Barros and applied in the enantioselective addition of diethylzinc to chalcone, with the phenylglycinol-derived ligand **152** affording the best enantiomeric excess of 53% (Scheme 1.85).¹³¹

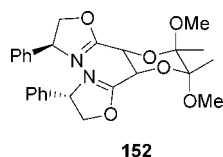
Scheme 1.84



Scheme 1.85

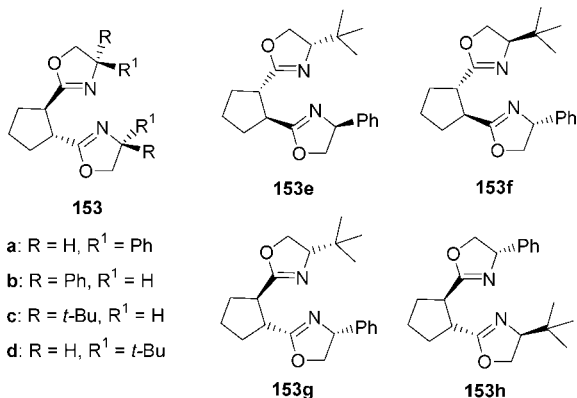


Bolm has developed a range of C_2 -symmetric and C_1 -symmetric bis(oxazoline) containing ligands **153** for application in a range of asymmetric metal-catalyzed transformations. There are relatively few examples of C_1 -symmetric bis(oxazoline)-containing ligands reported.⁵⁶



In the enantioselective Diels–Alder reaction, ligand **153b** gave the optimum enantiomeric excess of 71% with a 99% yield and an *endo:exo* ratio of 85:15 (Scheme 1.86).

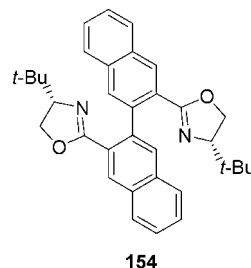
Ligand **153g** provided the best enantiomeric excess of 26% with a conversion of 90% for the ruthenium-catalyzed transfer hydrogenation of acetophenone (Scheme 1.5).



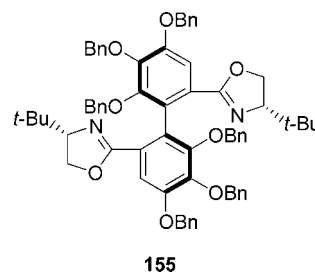
In the enantioselective cyclopropanation of styrene, *ent*-**153d** provided a yield of 72% and a *trans:cis* ratio of 63:37 with enantiomeric excesses of 83% and 87%, respectively (Scheme 1.74).¹³²

Bis(oxazoline) ligands containing a biaryl backbone have recently been developed and applied with some success in asymmetric catalysis.

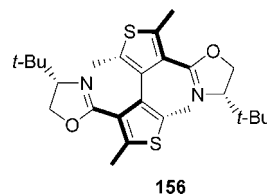
Ligand **154** with an axial-unfixed biaryl backbone has been applied in the enantioselective Cu(I)-catalyzed cyclopropanation of styrene (Scheme 1.74), with a *trans:cis* ratio of 83:17 and enantiomeric excesses of 96% and 89%, respectively.¹³³



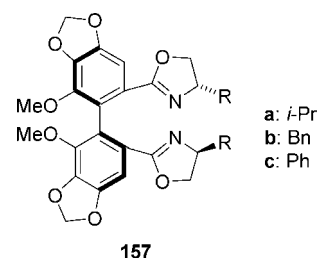
Ligand **155** has furnished an enantiomeric excess of 82% in the Cu(I)-catalyzed cyclopropanation of styrene (Scheme 1.74), with a *trans:cis* ratio of 59:41 and yield of 41%.¹³⁴



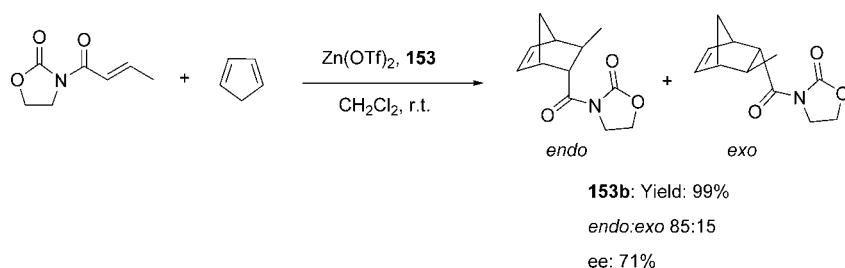
Bis(oxazoline) ligand **156** with a 3,3'-bithiophene backbone has also been applied in the Cu(I)-catalyzed cyclopropanation of styrene (Scheme 1.74) with an enantiomeric excess of 67%, a yield of 81%, and a *trans:cis* ratio of 67:33.¹³⁵



Ligand class **157** has been applied in the asymmetric pinacol coupling reaction. Ligand **157a**, with *i*-Pr-substituted oxazoline rings, afforded the highest enantiomeric excess of 81% for the pinacol coupling of benzaldehyde and was subsequently applied to the pinacol coupling of a range of aromatic aldehydes (Scheme 1.87, Table 1.64).¹³⁶



Scheme 1.86



Scheme 1.87

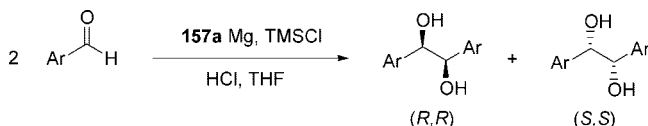
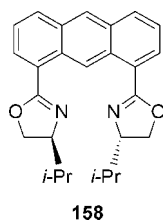


Table 1.64. Asymmetric Pinacol Coupling of Aromatic Aldehydes Using 157a

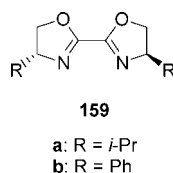
entry	aldehyde	yield (%)	ee (%)
1	C ₆ H ₅ CHO	81	81 (<i>R,R</i>)
2	4-MeC ₆ H ₄ CHO	84	83 (<i>R,R</i>)
3	4-MeOC ₆ H ₄ CHO	86	79 (<i>R,R</i>)
4	1-naphthaldehyde	86	78 (<i>R,R</i>)

The asymmetric pinacol couplings proceeded with excellent yield and very good enantioselectivity. The best substrate was *p*-tolualdehyde, which gave the desired pinacol product in 84% yield and 83% enantiomeric excess, with no *meso* product detected (Table 1.64, entry 2).

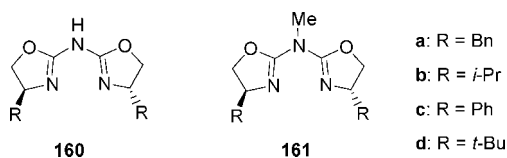
The AnBOX ligand **158** has been applied by Xu in the catalytic Cu-catalyzed aziridination of α,β -unsaturated ketones (Scheme 1.88), and it furnished an excellent yield of 92% and an enantiomeric excess of 92% for the aziridination of the *para*-tolyl-substituted ester.¹³⁷



Bis(oxazoline) ligands **159**, in which the oxazoline rings are joined directly to each other, have been applied in the [2,3]-Wittig rearrangement (Scheme 1.89) and cycloisomerization of 1,6-enynes (Scheme 1.90).¹³⁸



Azabis(oxazoline) ligands **160** and the methylated derivatives **161** have been applied in a range of asymmetric transformations.



Mayoral reported the successful recycling of **161d** in the asymmetric copper-catalyzed cyclopropanations of alkenes **162** in ionic liquid (Scheme 1.91).¹³⁹

After the second run using **161d** in the cyclopropanation of alkene **162**, a yield of 20% was reported, with a **163/164** ratio of 71:29. The enantioselectivity of **163** was 80% (*R*), and the enantiomeric excess of **155** was 98% (*R*).

Ligands **161b** and **161c** were applied by Reiser in the Co(II)-catalyzed conjugate reduction of α,β -unsaturated carbonyl compounds (Scheme 1.92, Table 1.65).¹⁴⁰

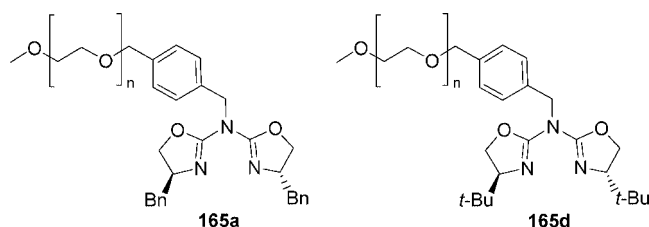
Ligand **161c** was found to be slightly more active than **161b**, while maintaining the same level of enantioselection (Table 1.65, entries 1, 2), and was thus investigated in the conjugate reduction of a range of aromatic and aliphatic aldehydes. Excellent yields and enantioselectivities were obtained in all cases. Most noteworthy was the success using the TBDMSO-protected ester (Table 1.65, entry 8) due to its potential in the synthesis of γ -butyrolactones.

Ligands **161b–d** have also been applied in the Mukaiyama aldol reaction between methyl pyruvate and 1-phenyl-1-(trimethylsilyloxy)ethane (Scheme 1.93). The best result was obtained using the *t*-Bu-substituted oxazoline ligand **161d**, which afforded 100% yield and an enantiomeric excess of 91%.¹⁴¹

Ligand classes **160** and **161** were applied by Reiser in the Cu(II)-catalyzed benzylation of (*rac*)-**163** to monobenzylation product **164** (Scheme 1.94, Table 1.66).¹⁴²

Of the members of ligand class **160**, benzyl-substituted **160a** afforded the highest enantiomeric excess of 97% with the highest selectivity factor of 160 (Table 1.66, entry 1). The selectivity of the process was improved using the *N*-methylated ligand **161a**, affording an enantioselectivity of 99% and a selectivity factor of 751 (Table 1.66, entry 6), in the presence of 0.5 mol % of both CuCl₂ and ligand.

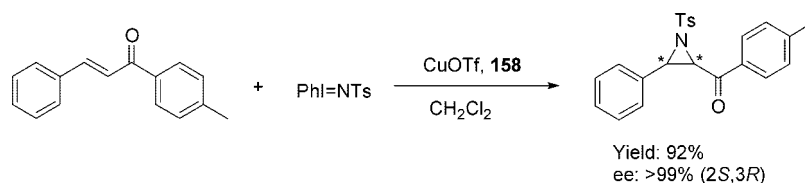
Subsequent immobilization of **160a** onto MeOPEG₅₀₀₀ afforded **165a**, which was repeatedly applied in the asymmetric benzylation of **163** and afforded a yield of 41% and an enantiomeric excess of 98% after 5 cycles.



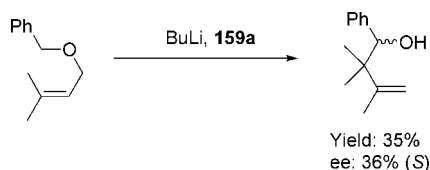
Application of ligand **165d** in the cyclopropanation of styrene has been reported to give enantiomeric excesses of up to 91%.¹⁴³

Reiser has also applied members of ligand classes **160** and **161** to the enantioselective 1,4-addition to benzyldiene malonates (Scheme 1.95).

Scheme 1.88



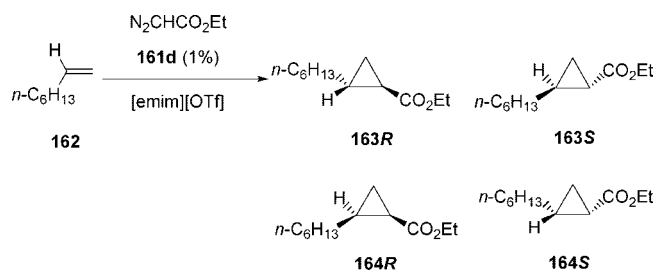
Scheme 1.89



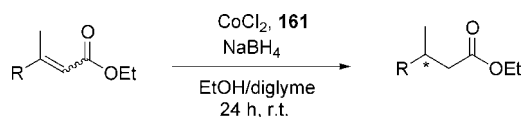
Scheme 1.90



Scheme 1.91



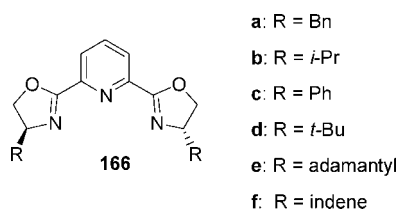
Scheme 1.92



Ligand **160b** gave the highest enantioselectivity of >99%, with a yield of 97%, using Cu(OTf)₂ and a Cu/ligand ratio of 1:1.04 for [R = Ph, R¹ = H]. Using these optimal conditions, **160b** was applied to the addition of a range of malonates to a series of indoles, with [R = *p*-ClC₆H₄, R¹ = H] providing the best enantiomeric excess of 98% with a yield of 91%.¹⁴⁴

Pybox ligand **166** has been applied by Gautun in the asymmetric Cu-catalyzed Diels–Alder reaction of *N*-sulfinyl dienophiles, with **166d** affording an enantiomeric excess of >95%.¹⁴⁵

The application of **166** in the enantioselective Diels–Alder reaction of **167** and diene **168** has been described by Shibasaki and Kanai (Scheme 1.96, Table 1.67).¹⁴⁶

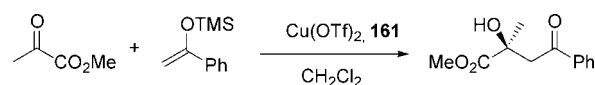


The phenyl-substituted ligand **166c** afforded superior yields and enantioselectivities compared to its *i*-Pr analogue.

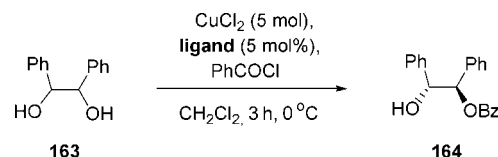
Table 1.65. Enantioselective Conjugate Reduction of α,β -Unsaturated Esters Using **161b** and **161c**

Entry	Ligand	R	Yield (%)	ee (%) (Conf.)
1	161b		82	96 (S)
2	161c		88	96 (R)
3	161c		87	96 (S)
4	161c		86	92 (S)
5	161c		89	94 (R)
6	161c		86	93 (R)
7	161c		86	97 (S)
8	161c		85	95 (S)

Scheme 1.93



Scheme 1.94

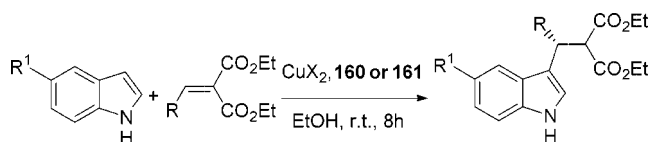
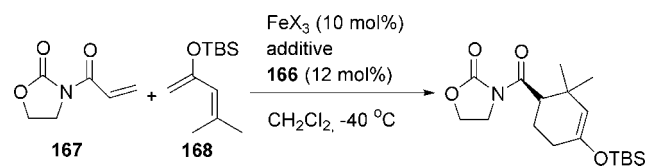


A high enantioselectivity was obtained when the catalyst was prepared from FeBr₃ and AgSbF₆ in a 1:2 ratio (Table 1.67, entry 4). The best result was obtained when the reaction was carried out using FeBr₃ and AgSbF₆ at –50 °C, which gave an ee of 92%, with a chemical yield of 75% (Table 1.67, entry 6).

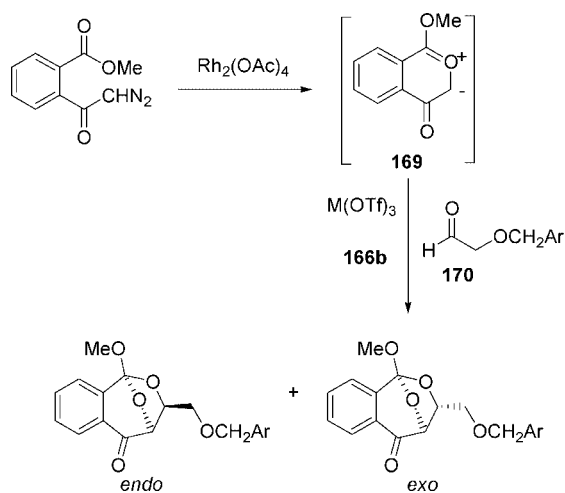
Pybox-*i*-Pr (**166b**) has been applied by Suga in the asymmetric cycloaddition of 2-benzopyryrium-*r*-olate **169**

Table 1.66. Enantioselective Cu-Catalyzed Benzoylation of 163 Using Ligands 160 and 161

entry	ligand	yield (%)	ee (%)	conf	selectivity factor
1	160a	45	97	<i>R,R</i>	160
2	160b	38	68	<i>R,R</i>	7.8
3	(<i>ent</i>)- 160c	48	87	<i>S,S</i>	35
4	160d	49	33	<i>R,R</i>	2.6
5	161a	45	99	<i>R,R</i>	501
6 ^a	161a	49	99	<i>R,R</i>	751
7	(<i>ent</i>)- 161c	46	93	<i>S,S</i>	66

^a Reaction performed with 0.5 mol % CuCl₂ and 0.5 mol % **161c**.**Scheme 1.95****Scheme 1.96****Table 1.67. Enantioselective Diels-Alder Reaction Using 166**

entry	ligand	additive (mol %)	FeX ₃	time (h)	yield (%)	ee (%)
1	166b	AgSbF ₆ (20)	FeBr ₃	16	12	22
2	166c	AgClO ₄ (30)	FeBr ₃	23	71	64
3	166c	AgSbF ₆ (10)	FeBr ₃	16	36	82
4	166c	AgSbF ₆ (20)	FeBr ₃	16	64	86
5	166c	AgSbF ₆ (30)	FeBr ₃	16	42	80
6 ^a	166c	AgSbF ₆ (4)	FeBr ₃	7	75	92
7	166c	none	Fe(ClO ₄) ₃	21	35	76

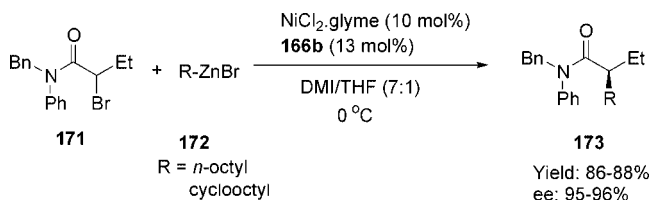
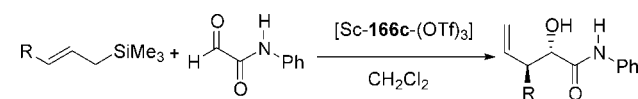
^a Reaction was performed at -50 °C.**Scheme 1.97**

with benzyloxacetaldehyde derivatives **170** (Scheme 1.97, Table 1.68).¹⁴⁷

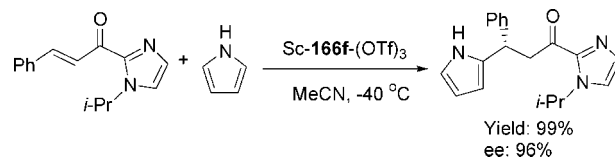
The yields in all reactions were excellent, with the exception of the electron-rich *p*-methoxyphenyl-substituted reagent, which afforded a yield of 53% (Table 1.68, entry 3). The *endo:exo* ratio was very good, with the *endo*-adduct favored in all cases. The best result was obtained with benzyloxacetaldehyde, which resulted in a yield of 96% and

Table 1.68. Enantioselective Cycloaddition of 169 and 170 Using Ligand 166b

entry	Ar	temp (°C)	yield (%)	<i>endo:exo</i>	ee (%)	
1	Ph	-10	96	88:12	91	18
2	2-MeOC ₆ H ₄	-10	82	85:15	82	15
3	4-MeOC ₆ H ₄	-10	53	91:9	89	12
4	4-FC ₆ H ₄	-10	97	82:18	93	22
5	4-ClC ₆ H ₄	-25	84	73:27	86	10
6	4-BrC ₆ H ₄	-25	77	67:33	83	5

Scheme 1.98**Scheme 1.99****Table 1.69. Enantioselective Sakurai-Hosomi Additions Using a Scandium Complex of Ligand 166c**

entry	R	cat. loading	temp (°C)	<i>anti:syn</i>	yield (%)	ee (%)
1	Me	10	-20	26:1	89	95
2	(<i>Z</i>)-Me	10	-20	1:4	76	94
3	Et	10	-20	32:2	76	91
4	<i>n</i> -Pr	10	-20	29:1	71	93
5	Ph	15	r.t.	99:1	67	99
6	4-MeC ₆ H ₄	15	r.t.	99:1	75	99
7	4-MeOC ₆ H ₄	15	r.t.	99:1	64	97
8	4-FC ₆ H ₄	15	r.t.	99:1	73	99
9	2-MeC ₆ H ₄	15	r.t.	9:1	64	99
10	β -naphthyl	15	r.t.	99:1	89	97

Scheme 1.100

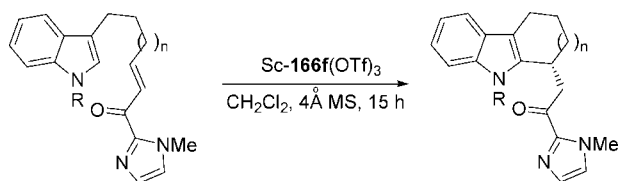
an 88:12 *endo:exo* ratio, with the *endo*-product having an enantiomeric excess of 91%.

Fu has successfully applied ligand **166b** in the asymmetric nickel-catalyzed Negishi cross-coupling of secondary α -bromo amides with organozinc reagents. For example, α -bromo amide **171** has been coupled with **172** using hexylzinc bromide to give the corresponding amides **173** (Scheme 1.98).¹⁴⁸

Evans has applied the Sc(OTf)₃ complex of ligand **166c** to the asymmetric Sakurai-Hosomi addition reaction (Scheme 1.99, Table 1.69).¹⁴⁹

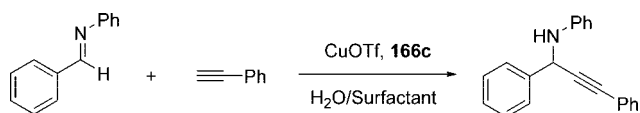
Use of (*E*)-crotyltrimethylsilane as the substrate afforded good *anti*-diastereoselection of 26:1 and excellent enantiomeric excess of 95% (Table 1.69, entry 1). Allylation of unbranched (*E*)-alkyl-substituted silanes resulted in good yields and excellent enantio- and diastereoselectivities (Table 1.69, entries 3, 4). (*Z*)-Crotyltrimethylsilane afforded the *syn*-product with excellent enantiomeric excess (94%) and a

Scheme 1.101

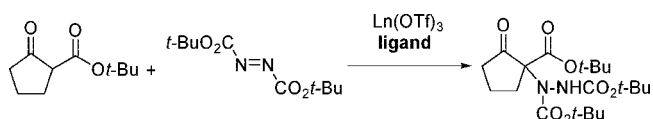
Table 1.70. Intramolecular Alkylations of Tethered Indoles Using Scandium-Triflate Complexes of **166f**

entry	R	n	mol % cat.	temp (°C)	yield (%)	ee (%)
1	H	0	5	0	99	9
2	Bn	1	5	0	99	9
3	H	1	2	−40	99	97
4	H	1	5	−40	99	96
5	H	1	20	−40	99	98
6	H	1	50	−40	99	79
7	H	2	10	0 to rt	decomp	

Scheme 1.102



Scheme 1.103



moderate *syn*-diastereoselectivity of 4:1 (Table 1.69, entry 2). Increasing both the reaction temperature and catalyst loading had a very positive effect on both diastereo- and enantioselectivities. Using these conditions, an *anti:syn* ratio of 99:1 and an enantiomeric excess of 99% was obtained for the majority of substrates (Table 1.69, entries 5–10).

Evans has also successfully applied the scandium complexes of indene-derived ligand **166f** to the enantioselective pyrrole alkylations of α,β -unsaturated 2-acyl imidazoles with excellent enantioselectivities (Scheme 1.100).¹⁵⁰

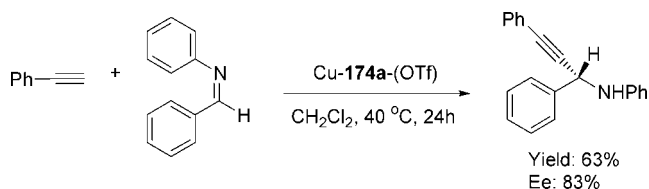
Scandium complexes of ligand **166f** has also been applied by Evans in a wide range of enantioselective Friedel–Crafts alkylations utilizing a variety of indoles and various β -substituted α,β -unsaturated phosphonates and α,β -unsaturated 2-acyl imidazoles.¹⁵¹ The ligand was also applied in the more challenging intermolecular Friedel–Crafts alkylation (Scheme 1.101, Table 1.70).

As was observed with previous examples, there was an inverse relationship between enantioselectivity and amount of catalyst utilized (Table 1.70, entries 3–6). The reactions to form the six-membered rings were successful, with excellent yields and enantioselectivities (Table 1.70, entries 3–6). However, the corresponding reactions to form the five and seven membered rings were unsuccessful.

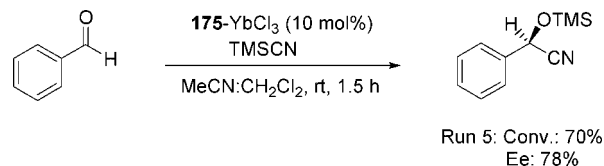
Ligand **166c** was applied by Li and Chan in the asymmetric addition of alkynes to imines in water (Scheme 1.102). In the absence of surfactant, an enantioselectivity of 80% and yield of 77% were obtained. However, adding stearic acid led to an increase in both yield and enantioselectivity to 86% and 85% ee, respectively.¹⁵²

Vallribera has applied complexes of **166b** and **166e** in the enantioselective electrophilic amination of ketoesters (Scheme 1.103). The adamantyl-substituted **166e** afforded an ee of 86%, with the less sterically demanding ligand **166b** affording an enantiomeric excess of >95%.¹⁵³

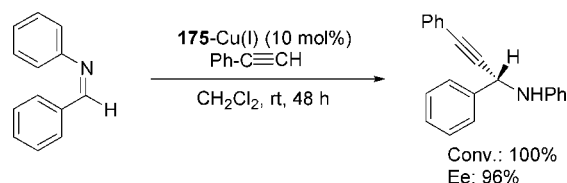
Scheme 1.104



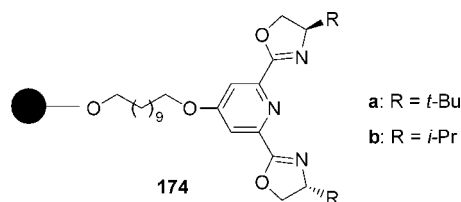
Scheme 1.105



Scheme 1.106

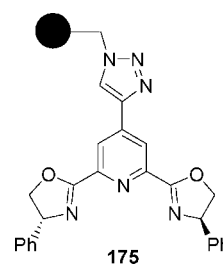


Polymer-bound versions of type **174** derived from the Pybox ligand class **166** have also been applied in asymmetric catalysis. Portnoy has applied **174a** in the reaction of phenyl acetylene and benzylidene aniline (Scheme 1.104) and obtained an enantiomeric excess of 83%.¹⁵⁴



Martínez-Merino and Mayoral have reported the application of Ru-**174b** in the cyclopropanation of styrene (Scheme 1.74) and obtained excellent *trans/cis* ratios of up to 90/10 with ee's up to 88%.¹⁵⁵

Moberg and Levacher have developed a click-pybox resin **175** and applied it in a range of metal-catalyzed transformations.¹⁵⁶

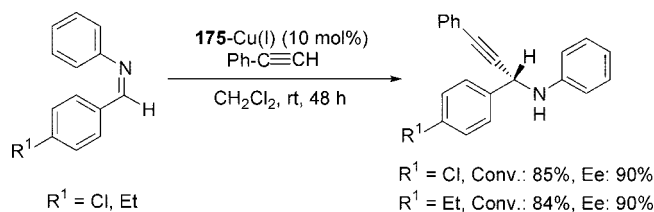


In the asymmetric Yb-catalyzed enantioselective silylcyanation of benzaldehyde, an optimum enantioselectivity of 78% was obtained after four runs (Scheme 1.105).

In the Cu-catalyzed enantioselective addition of phenylacetylene to benzylidene aniline, an enantioselectivity of 96% was obtained (Scheme 1.106).

In the Cu-catalyzed enantioselective alkynylation of arylimines, good to excellent conversions (73–100%) and excellent enantioselectivities (80–90%) were obtained for a range of imines (Scheme 1.107).

Scheme 1.107



Scheme 1.108

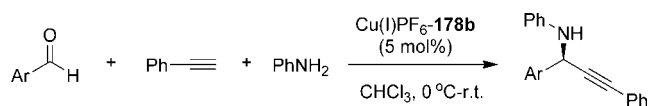
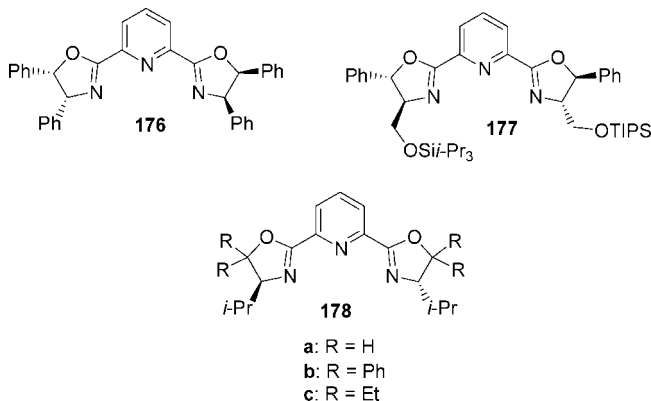


Table 1.71. Enantioselective Propargylamine Synthesis Using Ligand 178b

entry	Ar	time (h)	yield (%)	ee (%) (conf)
1	4- <i>i</i> -PrC ₆ H ₄	20	89	95 (<i>R</i>)
2	4-NO ₂ C ₆ H ₄	28	82	94 (<i>R</i>)
3	3-MeC ₆ H ₄	12	91	96 (<i>R</i>)
4	4-ClC ₆ H ₄	24	94	96 (<i>R</i>)
5	3-FC ₆ H ₄	28	85	93 (<i>R</i>)
6	3-BrC ₆ H ₄	26	92	91 (<i>R</i>)
7	3,5-(Me) ₂ C ₆ H ₃	12	98	95 (<i>R</i>)
8	3-Cl-4-FC ₆ H ₃	26	97	91 (<i>R</i>)
9	2-ClC ₆ H ₄	12	93	98 (<i>S</i>)

Substituted variants of Pybox (**166**) have also been developed. Ligand **176** afforded an ee of 48% in the enantioselective copper-catalyzed allylic alkylation of cycloheptene.¹⁵⁷

Ligand **177** has been applied by Desimoni in the Mukaiyama-aldol reaction and afforded an enantiomeric excess of 85%. Replacing the methyl of the pyruvate moiety with a benzyl group resulted in an increase in enantiomeric excess to 99.5%.¹⁵⁸



Singh has applied ligand class **178** to the enantioselective one-pot, three-component synthesis of propargylamines (Scheme 1.108, Table 1.71).¹⁵⁹ Initial screening using benzaldehyde as the substrate showed that ligand **178b** induced the highest levels of enantioselectivity, and this was then applied to reactions involving a range of aldehydes.

In all reactions the chemical yield was excellent, and the enantioselectivities were also very high, with both electron-rich and electron-poor aldehydes giving 94–95% ee (Table 1.71, entries 1, 2). A maximum of 98% ee was obtained using 2-chlorobenzaldehyde (Table 1.71, entry 9).

In 2004, Nakada reported the successful application of ligands **179a–c** in the catalytic asymmetric propargylation of aldehydes (Scheme 1.109, Table 1.72).¹⁶⁰ Ligands **179c**

Scheme 1.109

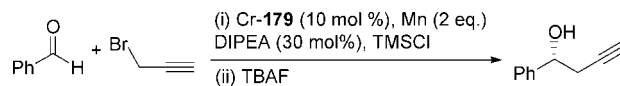
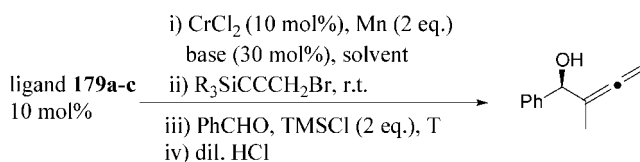


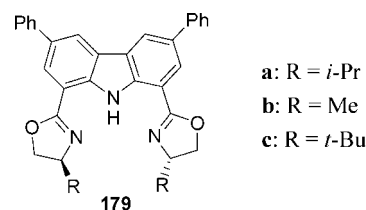
Table 1.72. Asymmetric NHK Propargylation using Ligands 179a–c

entry	ligand	time (h)	yield (%)	ee (%)
1	179a	16	94	26 (<i>S</i>)
2	179a	16	78	24 (<i>S</i>)
3	179b	18	80	28 (<i>S</i>)
4	179b	24	74	24 (<i>S</i>)
5	179c	60	75	71 (<i>R</i>)

Scheme 1.110



provided the highest enantiomeric excess of 71% (*R*) for the propargylation of benzaldehyde (Table 1.72, entry 5). This ligand was then applied in the propargylation of a range of aliphatic and aromatic aldehydes, with an enantiomeric excess of 98% (*R*) being obtained for *t*-BuCHO.



More recently, Nakada has reported the first enantioselective Nozaki–Hiyama–Kishi allenylation of terminally silylated propargyl halides using ligands **179a–c** (Scheme 1.110, Table 1.73).¹⁶¹

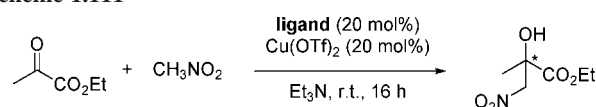
The reaction with ligand **179a** took 8 h to complete and again generated the (*R*) product with 52% ee (Table 1.73, entry 1). The reaction with ligand **179b** was complete after 6 h and generated the (*R*) product in 90% yield with 64% ee (Table 1.73, entry 2). Interestingly, the reaction using ligand **179c** led to a lowering and reversal of enantiomeric excess to 29% (*S*) (Table 1.73, entry 3). Screening of solvents and bases showed propionitrile and DIPEA to give the best results (Table 1.73, entries 4–12). Decreasing the reaction temperature to 0 °C led to a longer reaction time but an increase in enantioselection (Table 1.73, entry 9). The silyl group of the propargyl halide also affected the enantiomeric excess, with the bulkier TES, TIPS, DMPS, and MDPS groups not enhancing enantiomeric excess (Table 1.73, entries 13–16) but the smaller DMS group affording the highest enantioselectivity of 80% (Table 1.73, entry 17).

A range of additives were then screened, with the presence of DMI (1 equiv) leading to an increase in both yield (97%) and enantioselectivity (83%). Applying the optimal reaction conditions to the allenylation of a range of aldehydes did not result in enhanced enantioselectivities, with the highest ee of 82% being obtained with 4-ClC₆H₄CHO.

Guiry has previously reported the first synthesis of bis(oxazoline) ligands of type **180**, which are structurally similar to Nakada's ligand **179** but contain an *N*-phenylaniline unit linking the two chiral oxazoline rings. The key

Table 1.73. Asymmetric NHK Allenylation of Benzaldehyde

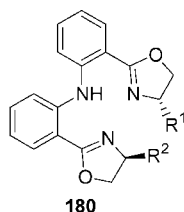
entry	ligand	solvent	temp (°C)	base	R ₃ Si	time (h)	yield (%)	ee (%) (R)
1	179a	THF	rt	DIPEA	TMS	8	92	52
2	179b	THF	rt	DIPEA	TMS	6	90	64
3	179c	THF	rt	DIPEA	TMS	12	92	29 ^a
4	179b	DME	rt	DIPEA	TMS	12	72	61
5	179b	MeCN	rt	DIPEA	TMS	12	74	60
6	179b	EtCN	rt	DIPEA	TMS	12	83	71
7	179b	CH ₂ Cl ₂	rt	DIPEA	TMS	24	49	57
8	179b	DMF	rt	DIPEA	TMS	48	56	74
9	179b	EtCN	0	DIPEA	TMS	16	80	76
10	179b	EtCN	0	K ₂ CO ₃	TMS	16	72	76
11	179b	EtCN	0	γ-collidine	TMS	16	65	76
12	179b	EtCN	0	pyridine	TMS	30	64	65
13	179b	EtCN	0	DIPEA	TES	24	81	74
14	179b	EtCN	0	DIPEA	TIPS	30	49	66
15	179b	EtCN	0	DIPEA	DMPS	24	66	73
16	179b	EtCN	0	DIPEA	MDPS	30	79	73
17	179b	EtCN	0	DIPEA	DMS	16	81	80

^a (S) product.**Scheme 1.111****Table 1.74. Enantioselective Henry Reaction Using Ligands 180b and 180d**

entry	ligand	solvent	yield (%)	ee (%) (S)
1	180b	ClCH ₂ CH ₂ Cl	32	76
2	180b	CH ₂ Cl ₂	43	80
3 ^a	180b	CH ₂ Cl ₂	29	82
4	180d	ClCH ₂ CH ₂ Cl	32	19
5	180d	CH ₂ Cl ₂	23	32

^a Reaction was performed at −20 °C.

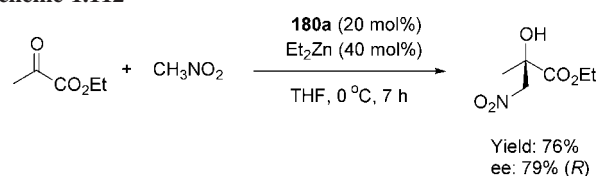
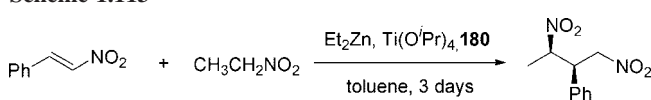
step in the synthesis involved an aryl amination which allowed the preparation of both C₂-symmetric (**180a–d**) and C₁-symmetric (**180e–j**) ligands.¹⁶²



- 180a** R¹ = Bn, R² = Bn **180f** R¹ = *t*-Bu, R² = Bn
180b R¹ = *i*-Pr, R² = *i*-Pr **180g** R¹ = *t*-Bu, R² = *i*-Pr
180c R¹ = Ph, R² = Ph **180h** R¹ = *i*-Pr, R² = Ph
180d R¹ = *t*-Bu, R² = *t*-Bu **180i** R¹ = *t*-Bu, R² = Ph
180e R¹ = Ph, R² = Bn **180j** R¹ = Bn, R² = *i*-Pr

Da and Xu have applied two examples of Guiry's bis(oxazoline) C₂-symmetric ligands **180b** and **180d** in the enantioselective Henry reaction (Scheme 1.111, Table 1.74).¹⁶³

The yields using both ligands were low, with the less bulky **180b** exhibiting slightly higher reactivity. Ligand **180d** gave poor yields and enantioselectivities (Table 1.74, entries 4 and 5). The best enantioselectivity was achieved at −20 °C using **180b**, which afforded a moderate yield of 29% and a very good enantiomeric excess of 82% (Table 1.74, entry 3).

Scheme 1.112**Scheme 1.113****Table 1.75. Asymmetric Michael Addition of Nitroethane to β-Nitrostyrene Using Ligands 180a–d**

entry	ligand	conv (%)	yield (%)	syn/anti	ee (%) (syn)
1	180a	46	44	3.8:1	71
2	180b	52	43	5.8:1	80
3	180c	96	82	6.1:1	91
4	180d	26	21	100:0	78

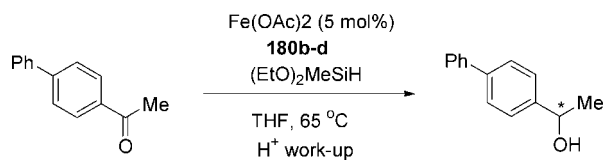
These ligands were subsequently more successfully applied in a zinc-catalyzed enantioselective Henry reaction (Scheme 1.112), with benzyl-substituted **180a** affording the highest enantioselectivity of 79%.¹⁶⁴

Du has also applied symmetric ligands **180a–d** in the asymmetric Michael addition of nitroethane to β-nitrostyrene (Scheme 1.113, Table 1.75).¹⁶⁵

The best ligand in terms of enantioselectivity for this asymmetric transformation was the bis(phenyl)-substituted ligand **180c**, which afforded a 91% ee, with a good *syn/anti* ratio of 6:1 and a yield of 82% (Table 1.75, entry 3). This enantioselectivity was increased to >99% ee following recrystallization. Ligand **180d** afforded the best diastereoselectivity, with the exclusive formation of the *syn* product in a very good ee of 78%, but both the yield and conversion were low (Table 1.75, entry 3). Ligand **180c** was also successfully applied to the Michael addition to a range of nitroalkanes and nitroalkenes.

Nishiyama has reported the application of **180b** and **180d** in the iron-catalyzed hydrosilylation of ketones (Scheme 1.114), resulting in yields of 82% and 75%, respectively. Ligand **180b** afforded an enantiomeric excess of 57%, with the bulkier **173d** affording an enantiomeric excess of 79%.¹⁶⁶

Scheme 1.114



Guiry has reported the application of ligand class **180** in the Nozaki–Hiyama–Kishi allylation, crotylation, and methallylation of aldehydes (Table 1.76).¹⁶⁷

The reactions proceeded with excellent conversions after 16 h at room temperature, with no byproduct detected. Of the four symmetric ligands, only the diisopropyl-substituted ligand (**180b**) afforded a significant level of enantioselectivity of 69% ee (Table 1.76, entry 1). Interestingly, the highest enantioselectivity was obtained using the nonsymmetric ligand **180f**, which gave an ee of 87% (Table 1.76, entry 3). Both the extent and sense of the asymmetric induction were highly dependent on the nature and combination of the substituents on the oxazoline rings, with small changes in structure translating into large variations in enantiodiscrimination.

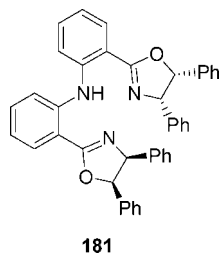
The optimal ligand **180f** was then used in the allylation of a range of aliphatic and aromatic aldehydes, with enantiomeric excesses of 87–91% reported and with the best aldehyde substrate being the linear aliphatic heptaldehyde.

Application in the crotylation of a range of aldehydes resulted in *syn/anti* ratios of up to 80:20, with *p*-methoxybenzaldehyde and heptaldehyde affording excellent enantiomeric excesses of up to 92% (Table 1.77). The *tert*-butyl/phenyl-substituted ligand **180i** afforded the highest *anti/syn* selectivity of 88:12 (Table 1.77, entry 4). As was observed for the reactions with allyl bromide, the highest level of enantiodiscrimination was achieved using the nonsymmetric *tert*-butyl/benzyl-substituted ligand **180f**, which afforded 82% ee (1*R*, 2*R*) for *anti*-2-methyl-1-phenylbut-3-en-1-ol and 90% ee (1*R*, 2*S*) for the *syn* diastereomer.

More recently, ligand **180f** has been applied by Hargaden and Guiry in the methallylation of a range of aldehydes (Scheme 1.115).¹⁶⁸

The methallylation of benzaldehyde using methallyl bromide resulted in an ee of 95%, whereas using methallyl chloride resulted in an ee of 99.5%. The optimum aliphatic aldehyde was heptaldehyde, affording an enantiomeric excess of 89%.

Ligand **180c**, together with its analogue **181**, has been applied by Du in the enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes (Scheme 1.116).¹⁶⁹

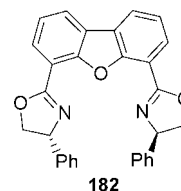


Both **180c** and **181** furnished the desired product in 99% yield, with enantiomeric excesses of 83% and 90%, respectively.

Ligand **181** has also been applied in the zinc-catalyzed enantioselective Friedel–Crafts alkylation of methoxyfuran with β -nitrostyrene, and it afforded an optimum yield of

85% and an enantioselectivity of 94% (Scheme 1.117). A range of nitroalkanes were also used as substrates, with enantioselectivities of 62–96% being reported.¹⁷⁰

Willis has applied DBFox ligand **182** in the direct catalytic enantioselective Mannich reaction (Scheme 1.118, Table 1.78).¹⁷¹



Excellent yields of up to 98% and enantioselectivities of up to 99% were obtained for the addition of isothiocyanate-substituted oxazolidinone to a range of *N*-Ts imines.

Functionalized aryl imines were shown to be excellent substrates for this reaction, with both electron-donating and electron-withdrawing groups and with a number of halo-substituted examples giving excellent yields and enantiomeric excesses (Table 1.78, entries 1–3).

Heteroaromatic imines were also successfully employed, with ee's up to 99% (Table 1.78, entries 4–6). Of particular interest was the indolyl substrate (Table 1.78, entry 4), which provides a potentially useful β -tryptophan derivative.

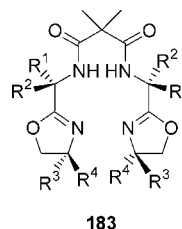
This bis(phenyl)-substituted ligand **182** was also applied to the enantioselective addition of nitrones to activated cyclopropanes (Scheme 1.119).¹⁷²

Good to excellent enantioselectivities (71–99%) were obtained using a range of substituted cyclopropanes and various nitrones. The optimum selectivity and enantioselectivity were obtained with the substrate where R^1 and $\text{R}^2 = (\text{CH}_2)_5$, which gave a yield of 54% and enantioselectivity of 99%.

8. Tetradentate Bis(oxazoline) Ligands

Adolfsson has synthesized a series of highly modular chiral 2-(aminoalkyl)oxazolines **183** and reported their application in the enantioselective addition of diethylzinc to aldehydes (Scheme 1.120, Table 1.79).¹⁷³

Ligand class **183** was initially investigated in the diethylzinc addition to benzaldehyde (Table 1.79, entries 1–6). The reactions proceeded with excellent yield, with the exception of **183f**, which afforded poor yield and enantioselectivity (Table 1.79, entry 6). The optimum ligand was found to be **183e**, furnishing an ee of 90% (Table 1.79, entry 5). This ligand was successfully applied in the diethylzinc addition to other aldehydes, with the best substrate being *meta*-nitrobenzaldehyde, which was converted to its alcohol adduct in an ee of 97% (Table 1.79, entry 8).



- a: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = i\text{-Pr}$
- b: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$, $\text{R}^4 = i\text{-Pr}$
- c: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = i\text{-Pr}$
- d: $\text{R}^1 = \text{H}$, $\text{R}^2 = i\text{-Pr}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = i\text{-Pr}$
- e: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$, $\text{R}^4 = \text{Me}$
- f: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = i\text{-Pr}$

Monari and Umani-Ronchi have applied bis(oxazoline) ligands **184** and **185** to palladium-catalyzed allylic alkylation (Scheme 1.6). Although ligands **184** and **185** did not provide

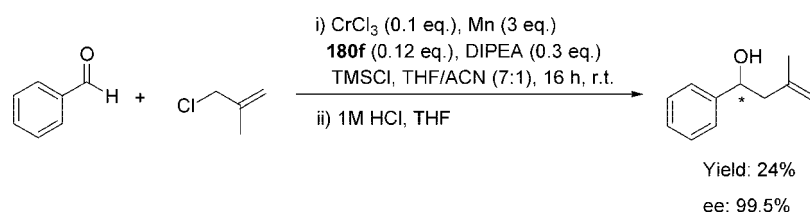
Table 1.76. NHK Allylation of Benzaldehyde Using Ligands 180a–j

i) CrCl₃ (0.1 eq.), Mn (3 eq.)
180a–j (0.12 eq.), DIPEA (0.3 eq.)
 TMSCl, THF/MeCN (7:1), 16 h, r.t.
 ii) 1M HCl, THF

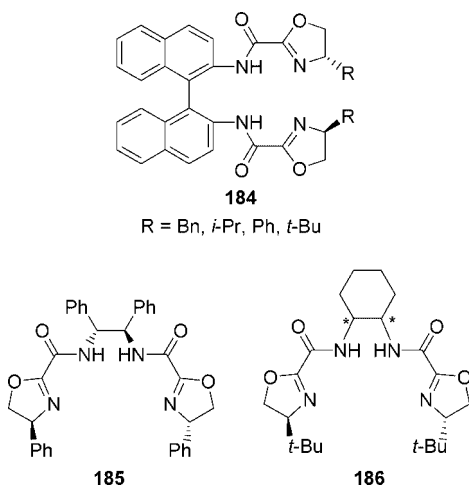
entry	ligand	R ¹	R ²	X	yield (conv) (%)	ee (%) (conf)
1	180b	<i>i</i> -Pr	<i>i</i> -Pr	Br	78 (96)	69 (<i>S</i>)
2	180c	Ph	Ph	Br	60 (99)	44 (<i>S</i>)
3	180f	<i>t</i> -Bu	Bn	Br	87 (100)	87 (<i>R</i>)
4	180f	<i>t</i> -Bu	Bn	Cl	10 (19)	74 (<i>R</i>)
5	180f	<i>t</i> -Bu	Bn	I	88 (98)	80 (<i>R</i>)
6	180g	<i>t</i> -Bu	<i>i</i> -Pr	Br	97 (100)	71 (<i>R</i>)

Table 1.77. NHK Crotylation of Benzaldehyde Using Ligands 180

entry	ligand	yield (conv) (%)	anti/syn	ee (%) (conf) anti	syn
1	180c	74 (98)	87:13	64 (1 <i>S</i> , 2 <i>S</i>)	7 (1 <i>S</i> , 2 <i>R</i>)
2	180f	77 (94)	77:23	82 (1 <i>R</i> , 2 <i>R</i>)	90 (1 <i>R</i> , 2 <i>S</i>)
3	180g	79 (100)	77:23	56 (1 <i>R</i> , 2 <i>R</i>)	66 (1 <i>R</i> , 2 <i>S</i>)
4	180i	80 (88)	88:12	4 (1 <i>R</i> , 2 <i>R</i>)	48 (1 <i>R</i> , 2 <i>S</i>)

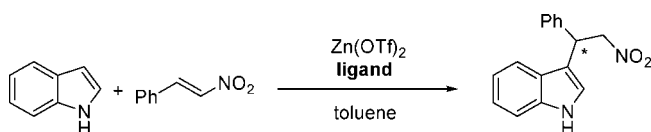
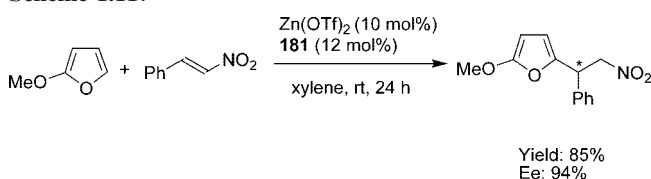
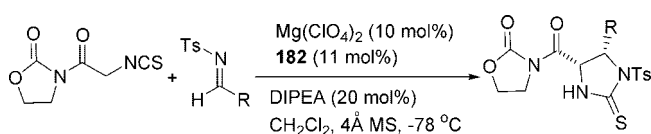
Scheme 1.115

satisfactory enantioselectivities (<45%), ligand **186** resulted in an ee of 98%.¹⁷⁴



Zhang has developed a new class of *N,N,O,O*-bis(oxazoline) ligands of type **187** and has applied them in the enantioselective addition of diethylzinc to aldehydes (Scheme 1.41). For the addition to benzaldehyde, **187b** afforded the highest enantiomeric excess of 87%, with a yield of 93%. This ligand was then applied in the addition to a range of arylaldehydes, with the best substrate being *p*-methoxybenzaldehyde, which was converted to the desired product with 92% yield and 92% ee.¹⁷⁵

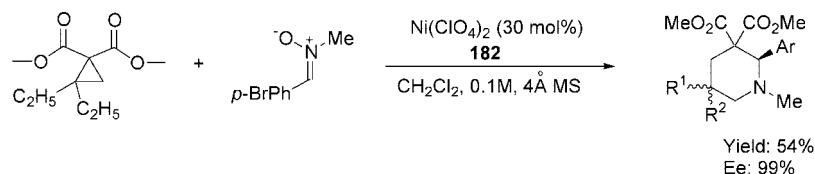
Zhang has developed novel air-stable *C*₂-symmetric tetrasubstituted ruthenocene-based ligands **188** and applied them in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate (Scheme 1.6).¹⁷⁶ The best result was obtained using the *t*-Bu-

Scheme 1.116**Scheme 1.117****Scheme 1.118****Table 1.78. Enantioselective Addition of Isothiocyanate-Substituted Oxazolidinone to a Range of *N*-Ts Imines Using Ligand 182**

entry	R	yield	syn/anti	ee (%)
1	Ph	94	12:88	96
2	4-MeC ₆ H ₄	96	12:88	99
3	4-BrC ₆ H ₄	86	16:84	98
4	2- <i>N</i> -Ts-indolyl	99	10:90	99
5	2-Np	94	7:93	98
6	2-thiophenyl	95	13:87	90

substituted ligand **188b**, which gave >95% isolated yield and an ee of 98% after 30 min at room temperature.

Scheme 1.119



Scheme 1.120

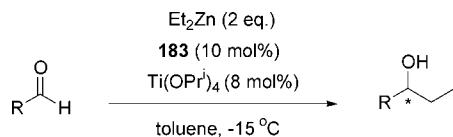
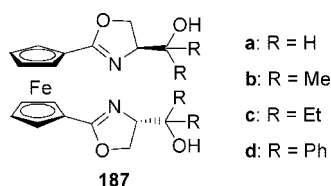
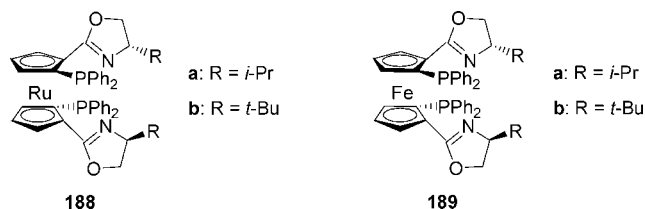


Table 1.79. Enantioselective Addition of Diethylzinc to Aldehydes Using Ligand 183

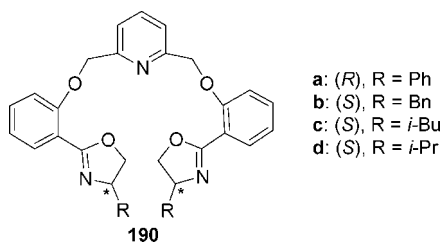
entry	ligand	R	yield (%)	ee (%) (conf)
1	183a	Ph	87	78 (<i>S</i>)
2	183b	Ph	85	70 (<i>S</i>)
3	183c	Ph	90	79 (<i>S</i>)
4	183d	Ph	93	73 (<i>R</i>)
5	183e	Ph	92	90 (<i>S</i>)
6	183f	Ph	18	25 (<i>S</i>)
7	183e	3-MeC ₆ H ₄	95	91 (<i>S</i>)
8	183e	3-NO ₂ C ₆ H ₄	94	97 (<i>S</i>)
9	183e	4-NO ₂ C ₆ H ₄	95	94 (<i>S</i>)



Ligand **188a** and its ferrocene analogue **189** were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with an enamine (Scheme 1.121).¹⁷⁷

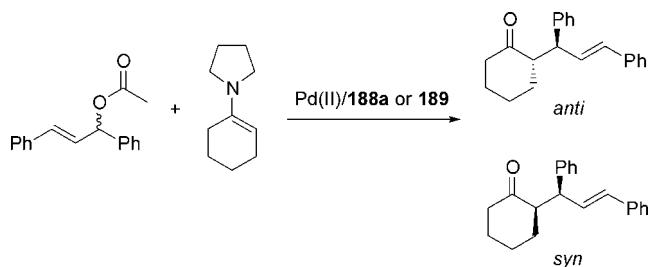


Isolated yields of 60–90% were obtained, with typical *anti*/*syn* ratios of 60:40 and enantioselectivities of up to 99% using **189b**. In general, the enantioselectivity using the ruthenocene-containing ligands was found to be slightly inferior.



Novel chiral semicrown ether-like ligands **190** have been developed by Wang, Du, and Xu and applied in the cyclopropanation of styrene (Scheme 1.74).¹⁷⁸ The (*R*)-phenyl-substituted ligand was shown to give the best yield

Scheme 1.121

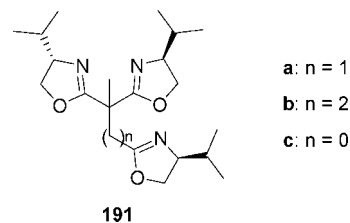


of 80% and a *trans*/*cis* ratio of 82:18, with ee's of 84% and 65%, respectively.

9. Tris(oxazoline) and Tetra(oxazoline) Ligands

There are relatively few examples of metal complexes of tris(oxazoline) ligands being applied in asymmetric catalysis. Tang has reported the application of ligand **191** in the enantioselective Friedel–Crafts reaction between indoles **192** and alkylidene malonates **193** to give alkylated indoles **194** (Scheme 1.122, Table 1.80a and b).¹⁷⁹

The enantioselectivity obtained for the alkylation of indole **192** ($\text{R} = \text{H}$) was altered by changing the ester group on the benzylidene malonate **193**, such that the ee improved with increasing ester size: methyl < ethyl < *tert*-butyl (Table 1.80a).



A wide variety of indoles **192** were subsequently applied in the reaction, with excellent enantioselectivities reported for 4- or 5-substituted indoles (Table 1.80b, entries 2, 3, and 4).

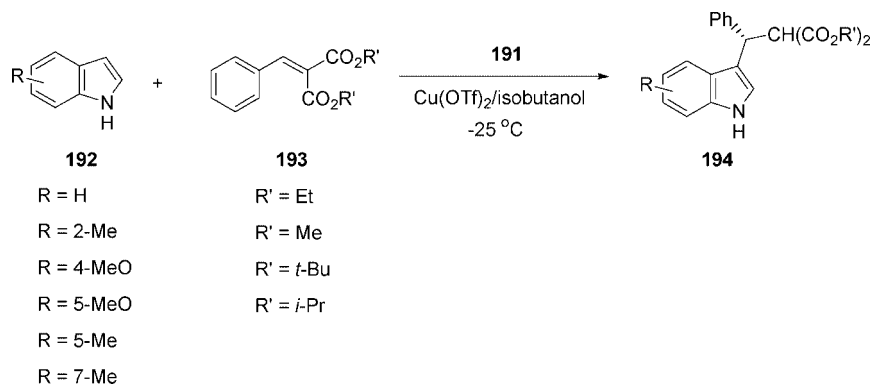
Tang also reported the tolerance of the catalyst system to water, with the enantioselectivity being maintained with a H_2O /catalyst ratio of 50 mmol.¹⁸⁰

The sidearm on the oxazoline structure was also modified (**191b**, **191c**), with both new ligands resulting in slightly lower enantioselectivities of 91% and 87%, respectively, for the reaction of unsubstituted indole and alkylidene malonate.

Subsequently, ligand **191** was modified, with an additional ten members comprising a range of substitution patterns, for example, **191d–f**. Three such ligands resulted in the highest enantiomeric excesses of 90%, 90%, and 91%, respectively, when applied in the enantioselective alkylation of indole by alkylidene malonate.¹⁸¹

A similar ligand motif **191g** with a linking chiral center was applied in the 1,3-dipolar cycloaddition of nitrones **195** to alkylidene malonates **196** (Scheme 1.123, Table 1.81).¹⁸²

Scheme 1.122

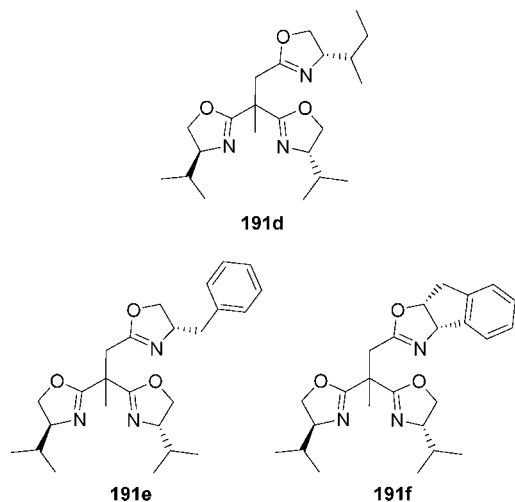
Table 1.80. (a) Effects on Enantioselective Indole Alkylation Using **191a**

Effect of Ester Group				
entry	R	R'	conv (%)	ee (%)
1	H	Et	99	94
2	H	Me	93	91
3	H	<i>t</i> -Bu	90	98
4	H	<i>i</i> -Pr	26	91

Effect of Indole Substituent				
entry	R	R'	yield (%)	ee (%)
1	2-Me	Et	99	-53
2	4-MeO	Et	90	+98
3	5-MeO	Et	79	+94
4	5-Me	Et	89	+95
5	7-Me	Et	82	+89

Ligand **191f** has also been applied to the enantioselective cycloaddition of a variety of cyclopropanes with nitrones (Scheme 1.124).

The ester groups of the cyclopropane had a small effect on the enantioselectivity, with the benzyl diester and ethyl diester giving higher ee (up to 97%) than the corresponding methyl diester (90% ee) (Table 1.82, entries 1–3). Both electron-rich and electron-poor α -aryl nitrones proceeded with excellent enantio- and diastereoselectivities (of up to 97% and 13:1, Table 1.82, entries 4–7). A range of vinyl- and styryl-substituted cyclopropanes and nitrones also reacted smoothly with good diastereoselectivity and enantioselectivity (Table 1.82, entries 9–12), highlighting the applicability of this reaction.¹⁸³

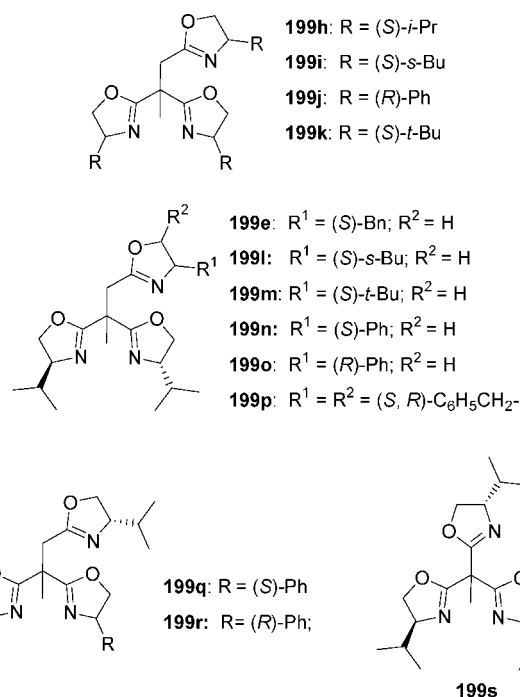
Table 1.81. Application of Tris(oxazoline) **191g** in Enantioselective 1,3-Dipolar Cycloaddition between Nitrones **195** and Alkenes **196**

entry	R ¹ /R ²	R ³ /R ⁴	yield (%)	197 / 198	ee (%)
1	Ph/Et	4-CH ₃ C ₆ H ₄ /Ph	93	>99/1	91
2 ^a	Ph/Et	4-BrC ₆ H ₄ /Ph	76	>99/1	95
3	Ph/Et	Ph/Ph	94	97/3	95
4	4-CH ₃ C ₆ H ₄ /Et	Ph/Ph	95	95/5	92
5	4-NO ₂ C ₆ H ₄ /Me	Ph/Ph	93	97/3	94
6	4-BrC ₆ H ₄ /Et	Ph/Ph	99	95/5	95
7	Ph/Me	Ph/4-CF ₃ C ₆ H ₄	100	92/8	98
8	Ph/Me	Ph/4-CH ₃ OC ₆ H ₄	94	95/5	96
9	Ph/Me	4-BrC ₆ H ₄ /Ph	92	>99/1	98
10	Ph/ <i>i</i> -Bu	4-BrC ₆ H ₄ /Ph	95	>99/1	96
11 ^a	Cy/Et	4-BrC ₆ H ₄ /Ph	91	90/10	89

^a Using 6.7 mol % of **191g**.

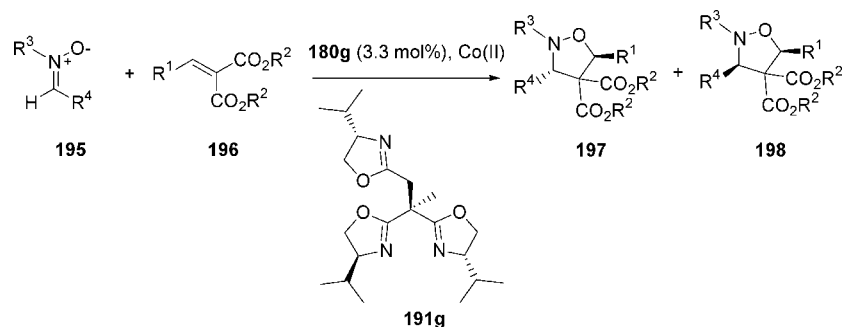
Ligand **191g** was also applied by Reiser in the enantioselective alkylation of indole by alkylidene malonate with a yield of 90% and enantiomeric excess of 93%.¹⁸⁴

In 2006, Tang reported the application of a range of tris(oxazoline) ligands **199** in the enantioselective synthesis of β -lactams using the Kinugasa reaction (Scheme 1.125, Table 1.82).¹⁸⁵

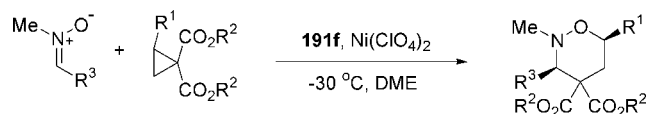


The results show that the pendant oxazoline rarely influences the enantioselectivity of the Kinugasa reaction (Table

Scheme 1.123



Scheme 1.124



Scheme 1.126

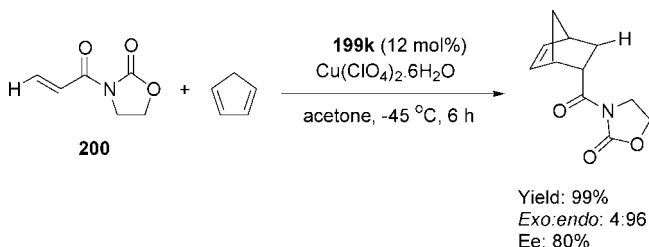


Table 1.82. Asymmetric Cycloaddition of Cyclopropanes with Nitrones Using Ligand 191f

entry	R ¹	R ²	R ³	time (days)	yield (%)	dr	ee (%)
1	Ph	Me	Ph	3	82	13:1	90
2	Ph	Bn	Ph	4	62	10:1	97
3	Ph	Et	Ph	4	88	11:1	95
4	Ph	Et	4-BrC ₆ H ₄	4	85	12:1	97
5	Ph	Et	4-MeO ₂ CC ₆ H ₄	4	97	11:1	97
6	Ph	Et	4-MeC ₆ H ₄	4	80	12:1	96
7	Ph	Et	4-MeOC ₆ H ₄	4	92	13:1	90
8	Ph	Et	2-furyl	4	99	13:1	93
9	Ph	Et	styryl	3	76	4:1	92
10	vinyl	Et	Ph	3	88	6:1	80
11	styryl	Et	Ph	5	84	5:1	80
12	Ph	Et	Ph	5	74	11:1	93

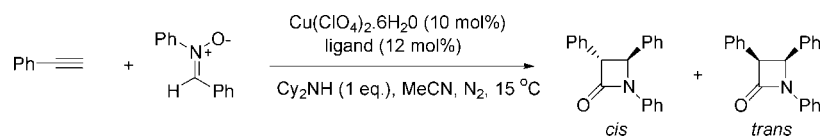
Table 1.83. Application of Ligands 199e and 199h–s in the Asymmetric Kinugasa Reaction

entry	ligand	time (h)	yield (%)	cis/trans	ee (%)
1	199h	15	60	13/1	80
2	199i	11	71	20/1	80
3	199j	6 days	47	13/1	–70
4	199e	11	56	9/1	58
5	199l	15	51	9/1	66
6	199m	14	51	10/1	75
7	199n	12	56	9/1	61
8	199o	15	60	10/1	56
9	199p	11	56	10/1	61
10	199q	32	52	9/1	58
11	199r	80	51	10/1	–52
12	199s	25	47	12/1	49

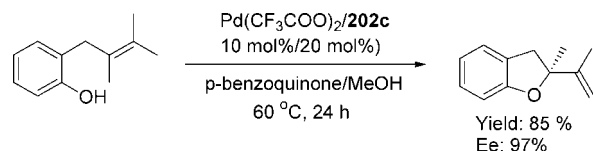
1.83, entries 5–9). For example, **199n** and **199o** with opposite chiral centers gave similar enantioselectivities (Table 1.83, entries 7, 8). Increasing the steric hindrance diminished the reaction rate dramatically, with ligand **199k** not giving any desired lactam product.

Ligand **199h** was also applied by Tang in the copper-catalyzed cyclopropanation of alkenes with aryldiazoacetates. A range of alkenes was tested, with the optimum enantiose-

Scheme 1.125



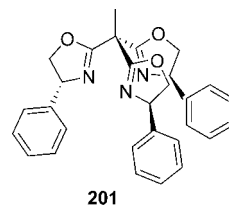
Scheme 1.127



lectivity of 95% being obtained using *p*-methoxystyrene and ethyl phenyldiazoacetate.¹⁸⁶

The *tert*-butyl-substituted ligand **199k** has also been utilized by Tang in the copper-catalyzed enantioselective Diels–Alder reaction of cyclopentadiene with acryloyl-2-oxazolidinones or ketoesters. The best results were obtained with the oxazolidinone-type dienophile systems (Scheme 1.126). Although good enantioselectivities (80–82%) and high *exolendo* ratios were obtained at low temperatures (–20 to –78 °C), the yields in some cases were very poor (20–21%). The best result was found using dienophile **200** at –45 °C for 6 h, which gave the product in 99% yield, an *exolendo* ratio of 4:96, and an enantiomeric excess of 80%.¹⁸⁷

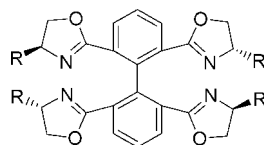
Gade and Bellemin-Lapomnaz have reported the application of tris(oxazoline) ligand **201** in the α -amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate (Scheme 1.68) and obtained a yield of 91% and enantiomeric excess of 99%.⁹⁸



201

Zhang has developed a new class of tetra(oxazoline) containing ligands **202** and reported their application in the

Pd(II)-catalyzed asymmetric Wacker-type cyclization of allylphenols.¹⁸⁸ Initial screening showed that the Ph-substituted ligand **191c** afforded the best enantioselectivity of 97% using 2-(2,3-dimethyl-2-butenyl)phenol as substrate (Scheme 1.127).



202 a: R = *t*-Bu
b: R = *i*-Pr
c: R = Ph

This ligand was then applied in the cyclization of a range of allylphenols, with good isolated yields and excellent enantioselectivities (95–99%) reported for a range of electron-withdrawing and electron-donating aromatic systems.

10. Conclusion

This review reports on developments in the design and application of oxazoline-based ligands in asymmetric catalysis since 2004, when the area was previously reviewed.

The broad utility of this class of ligands in catalytic asymmetric synthesis is demonstrated by the high levels of enantiocontrol induced in a wide range of metal-catalyzed transformations including oxidations, reductions, cycloadditions, and carbon–carbon bond forming reactions.

The enantiocontrolling ability of the chiral oxazoline ligand in a metal-catalyzed reaction is determined both 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.

For phosphinooxazoline ligands, palladium-catalyzed asymmetric allylic alkylation, iridium-catalyzed enantioselective hydrogenation of unfunctionalized alkenes, and the asymmetric Heck reaction are particularly successful processes and proceed with good levels of enantioselection.

In contrast, *N,N*- and *N,N,N*-mono- and -bis(oxazoline) ligands have been applied with considerable success to 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.

Mono(oxazoline) *N,O*-ligands and oxazoline-containing ligands with secondary chelating hydroxy groups have been applied in the asymmetric addition of diethylzinc and diphenylzinc to aldehydes.

Although this review shows extensive research in over the past three years 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 both the development of new ligands and their application in newly developed metal-catalyzed asymmetric transformations.

11. References

- McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.
- Kilroy, T. G.; Cozzi, P. G.; End, N.; Guiry, P. J. *Synlett* **2004**, *11*, 1879.
- Fitzpatrick, M. O.; Coyne, A. G.; Guiry, P. J. *Synlett* **2006**, *18*, 3150.
- Coyne, A. G.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *48*, 199.
- Coyne, A. G.; Guiry, P. J. *Tetrahedron Lett.* **2007**, *48*, 747.
- Naud, F.; Malan, F.; Spindler, F.; Rüggerberg, C.; Schmidt, A. T.; Blaser, H.-U. *Adv. Synth. Catal.* **2006**, *348*, 47.
- Danjo, H.; Higuchi, M.; Yada, M.; Imamoto, T. *Tetrahedron Lett.* **2004**, *45*, 603.
- Ezhova, M. B.; Patrick, B. O.; James, B. R.; Waller, F. J.; Ford, M. E. *J. Mol. Catal. A* **2004**, *71*.
- Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513.
- Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460.
- Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825.
- García-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459.
- Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, *9*, 1431.
- Frölander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. J. *Org. Chem.* **2005**, *70*, 9882.
- Frölander, A.; Moberg, C. *Org. Lett.* **2007**, *9*, 1371.
- (a) Réthoré, C.; Suisse, I.; Agbossou-Niedercorn, F.; Guilmón, E.; Llusar, R.; Fourmigué, M.; Avarvari, N. *Tetrahedron* **2006**, *62*, 11942. (b) Réthoré, C.; Riobé, F.; Fourmigué, M.; Avarvari, N.; Suisse, I.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2007**, *18*, 1877.
- Trudeau, S.; Morken, J. P. *Tetrahedron* **2006**, *62*, 11470.
- Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 12886.
- Lu, Z.-L.; Neumann, E.; Pfaltz, A. *Eur. J. Org. Chem.* **2007**, *25*, 4189.
- Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659.
- Tani, K.; Behenna, D. C.; McFadden, R.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529.
- Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Organometallics* **2004**, *23*, 2295.
- Zhang, W.; Xie, F.; Yoshinaga, H.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2006**, *8*, 1185.
- Fekner, T.; Müller-Bunz, H.; Guiry, P. J. *Org. Lett.* **2006**, *8*, 5109.
- Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241.
- Suárez, A.; Downey, W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.
- Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055.
- Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, Z.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979.
- Fukuzawa, S.; Yahara, Y.; Kamiyama, A.; Hara, M.; Kikuchi, S. *Org. Lett.* **2005**, *7*, 5809.
- Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 550.
- Naud, F.; Spindler, F.; Rueggerberg, C. J.; Schmidt, A. T.; Blaser, H.-U. *Org. Process Res. Dev.* **2007**, *11*, 519.
- Palmer, A. M.; Nettekoven, U. *Tetrahedron: Asymmetry* **2007**, *18*, 2381.
- Geisler, F. M.; Helmchen, G. *J. Org. Chem.* **2006**, *71*, 2486.
- Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 585.
- Franco, D.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M.; Maestro, M. A.; Mahía, J. *Organometallics* **2004**, *23*, 3197.
- Smidt, S. S.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023.
- McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282.
- Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159.
- Bronger, R. P. J.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 1094.
- Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.
- Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943.
- Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Org. Lett.* **2005**, *7*, 5597.
- Mata, Y.; Pàmies, O.; Diéguez, M. *Chem.—Eur. J.* **2007**, *13*, 3296.
- Mata, Y.; Diéguez, M.; Pàmies, O.; Biswas, K.; Woodward, S. *Tetrahedron: Asymmetry* **2007**, *18*, 1613.
- Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646.
- Pàmies, O.; Claver, C.; Diéguez, M. *J. Mol. Catal. A* **2006**, *249*, 207.
- Hou, X.-L.; Sun, N. *Org. Lett.* **2004**, *6*, 4399.
- Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151.
- Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.
- Whelligan, D. K.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 4609.
- Trifonova, A.; Källström, K. E.; Andersson, P. G. *Tetrahedron* **2004**, *60*, 3393.
- McManus, H. A.; Barry, S. M.; Andersson, P. G.; Guiry, P. J. *Tetrahedron* **2004**, *60*, 3405.

- (53) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293.
- (54) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933.
- (55) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076.
- (56) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.
- (57) Lee, J. Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837.
- (58) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752.
- (59) Hargaden, G. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, *25*, 4235.
- (60) Barros, M. T.; Maycock, C. D.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2004**, 1820.
- (61) Bolm, C.; Zani, L.; Rudolph, J.; Schiffrers, I. *Synthesis* **2004**, 2173.
- (62) Li, M.; Zhu, X.-Z.; Yuan, K.; Cao, B.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 219.
- (63) Gluszyńska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2004**, *15*, 3289.
- (64) Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407.
- (65) Chai, Z.; Liu, Z.-Y.; Wu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, 2442.
- (66) Wu, X.-W.; Zhang, T.-Z.; Yuan, K.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 2357.
- (67) Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Chanqin, M.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, 8611.
- (68) Bolm, C.; Whelligan, D. K. *Adv. Synth. Catal.* **2006**, *348*, 2093.
- (69) Yan, G.; Wu, Y.; Lin, W.; Zhang, X. *Tetrahedron: Asymmetry* **2007**, *18*, 2643.
- (70) Bonini, B.-F.; Giordano, L.; Fochi, M.; Comes-Franchini, M.; Bernardi, L.; Capitò, E.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1043.
- (71) Bonini, B. F.; Capitò, E.; Comes-Franchini, M.; Ricci, A.; Bottoni, A.; Bernardi, L.; Miscione, G. P.; Giordano, L.; Cowley, A. R. *Eur. J. Org. Chem.* **2004**, 4442.
- (72) Capitò, E.; Bernardi, L.; Comes-Franchini, M.; Fini, F.; Fochi, M.; Pollicino, S.; Ricci, A. *Tetrahedron: Asymmetry* **2006**, *16*, 3232.
- (73) Guio, E.; Claver, C.; Castillón, S. J. *Organomet. Chem.* **2004**, *689*, 1911.
- (74) Liang, B.; Liu, J.; Gao, Y.-X.; Wongkhan, K.; Shu, D.-X.; Lan, Y.; Li, A.; Batsanov, A. S.; Howard, J. A. H.; Marder, T. B.; Chen, J.-H.; Yang, Z. *Organometallics* **2007**, *26*, 4756.
- (75) (a) Kirsch, S.; Overman, L.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101. (b) Prasad, R. S.; Anderson, C. E.; Richards, C. J.; Overman, L. E. *Organometallics* **2005**, *24*, 77. (c) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031.
- (76) Kirsch, S.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 2859.
- (77) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648.
- (78) Gade, L. H.; Bellemin-Laponnaz, S. *Coord. Chem. Rev.* **2007**, *251*, 718.
- (79) Gade, L. H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014.
- (80) Nanchen, S.; Pfaltz, A. *Chem.—Eur. J.* **2006**, 4550.
- (81) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473.
- (82) Chu, C.; Morishita, K.; Tanaka, T.; Hayashi, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2672.
- (83) Shibatomi, K.; Tsuzuki, Y.; Nakata, S.; Sumikawa, Y.; Iwasa, S. *Synlett* **2007**, *4*, 551.
- (84) (a) Braga, A. L.; Lüdtke, D. S.; Sehnem, J. A.; Alberto, E. E. *Tetrahedron* **2005**, *61*, 11664. (b) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Braga, R. C. *Synlett* **2006**, *10*, 1453.
- (85) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.
- (86) Endeshaw, M. M.; Bayer, A.; Hansen, L. K.; Gautun, O. R. *Eur. J. Org. Chem.* **2006**, 5249.
- (87) Sibi, M. P.; Manyem, S.; Palencia, H. J. *Am. Chem. Soc.* **2006**, *128*, 13660.
- (88) Fraile, J. M.; Pérez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1680.
- (89) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; del Pozo, C.; Sanz-Cervera, J. F.; Simón, A. *Org. Lett.* **2006**, *8*, 4129.
- (90) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739.
- (91) Jia, Y.-X.; Zhu, S.-F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75.
- (92) Barroso, S.; Blay, G.; Pedro, J. R. *Org. Lett.* **2007**, *9*, 1983.
- (93) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2006**, *47*, 7599.
- (94) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281.
- (95) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053.
- (96) (a) Nakamura, S.; Sano, H.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Tetrahedron: Asymmetry* **2007**, *48*, 5565. (b) Nakamura, S.; Sano, H.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2007**, *48*, 5565.
- (97) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948.
- (98) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wade-pohl, H.; Gade, L. H. *Chem.—Eur. J.* **2007**, *13*, 9912.
- (99) Itagaki, M.; Masumoto, K.; Suenobu, K.; Yamamoto, Y. *Org. Process Res. Dev.* **2006**, *10*, 245.
- (100) Zhao, J.-L.; Sui, J.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127.
- (101) Singh, P. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 1127.
- (102) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240.
- (103) Orlandi, S.; Benaglia, M.; Dell'Anna, G.; Celentano, G. J. *Organomet. Chem.* **2007**, *692*, 2120.
- (104) Ait-Haddou, H.; Hoarau, O.; Cramailé, D.; Pezet, F.; Daran, J.-C.; Balavoine, G. G. A. *Chem.—Eur. J.* **2004**, *10*, 699.
- (105) Chollet, G.; Rodriguez, F.; Schulz, E. *Org. Lett.* **2006**, *8*, 539.
- (106) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591.
- (107) Sibi, M. P.; Stanley, L. M.; Nie, X.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395.
- (108) Nichols, P. J.; deMattei, J. A.; Barnett, B. R.; LeFur, N. A.; Chuang, T.-H.; Piscopio, A. D.; Koch, K. *Org. Lett.* **2006**, *8*, 1495.
- (109) Bayardon, J.; Holczknecht, O.; Pozzi, G.; Sinou, D. *Tetrahedron: Asymmetry* **2006**, *17*, 1568.
- (110) Kolodziuk, R.; Goux-Henry, C.; Sinou, D. *Tetrahedron: Asymmetry* **2007**, *18*, 2782.
- (111) Bayardon, J.; Sinou, D. *Tetrahedron: Asymmetry* **2005**, *16*, 2965.
- (112) da Palma Carreiro, E.; Chercheja, S.; Moura, N. M. M.; Gertrudes, C. S. C.; Burke, A. J. *Inorg. Chem. Commun.* **2006**, *9*, 823.
- (113) da Palma Carreiro, E.; Chercheja, S.; Burke, A. J.; Prates Ramalho, J. P.; Rodrigues, A. I. *J. Mol. Catal. A* **2005**, *236*, 38.
- (114) Takeda, H.; Honma, M.; Ida, R.; Sawada, T.; Nakada, M. *Synlett* **2007**, *4*, 579.
- (115) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300.
- (116) Yeom, C.-E.; Kim, H. W.; Shin, Y. J.; Kim, B. M. *Tetrahedron Lett.* **2007**, *48*, 9035.
- (117) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.
- (118) Doherty, S.; Goodrich, P.; Hardacre, C.; Knight, J. G.; Nguyen, M. T.; Părvulescu, V. I.; Paun, C. *Adv. Synth. Catal.* **2007**, *349*, 951.
- (119) Portada, T.; Roje, M.; Raza, Z.; Çaplar, V.; Žinic, M.; Sunjić, V. *Eur. J. Org. Chem.* **2007**, 838.
- (120) Fu, B.; Du, D.-M.; Xia, Q. *Synthesis* **2004**, *2*, 221.
- (121) Fu, B.; Du, D.-M.; Wang, J. *Tetrahedron: Asymmetry* **2004**, *15*, 119.
- (122) (a) Mazet, C.; Köhler, V.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4888. (b) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879.
- (123) Tsuchiya, Y.; Kanazawa, Y.; Shiomi, T.; Kobayashi, K.; Nishiyama, H. *Synlett* **2004**, *14*, 2493.
- (124) Kanazawa, Y.; Nishiyama, H. *Synlett* **2006**, *19*, 3343.
- (125) Shiomi, T.; Ito, J.; Yamamoto, Y.; Nishiyama, H. *Eur. J. Org. Chem.* **2006**, 5594.
- (126) Kato, T.; Marubayashi, K.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3693.
- (127) (a) Liu, B.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 634. (b) Liu, B.; Zhu, S.-F.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.
- (128) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616.
- (129) Ma, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2005**, *70*, 10155.
- (130) Tan, Q.; Wen, J.; Li, D.; Li, H.; You, T. *J. Mol. Catal. A* **2005**, *242*, 113.
- (131) Barros, M. T.; Maycock, C. D.; Faisca Phillips, A. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2946.
- (132) Atodiresi, I.; Schiffrers, I.; Bolm, C. *Tetrahedron: Asymmetry* **2006**, *17*, 620.
- (133) Zhang, W.; Xie, F.; Matsuo, S.; Imahori, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **2006**, *17*, 767.
- (134) Khanbabaee, K.; Basceken, S.; Flörke, U. *Eur. J. Org. Chem.* **2007**, 831.
- (135) Benaglia, M.; Benincori, T.; Mussini, P.; Pilati, T.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2005**, *70*, 7488.
- (136) Wen, J.; Tan, Q.; You, T. *J. Mol. Catal. A* **2006**, *258*, 159.
- (137) Ma, L.; Jiao, P.; Zhang, Q.; Du, D.-M.; Xu, J. *Tetrahedron: Asymmetry* **2007**, *18*, 878.
- (138) (a) Barrett, I. M.; Breedon, S. W. *Tetrahedron: Asymmetry* **2004**, *15*, 3015. (b) Zhang, Q.; Xu, W.; Lu, X. *J. Org. Chem.* **2005**, *70*, 1505.
- (139) Fraile, J. M.; García, J. I.; Herreras, C. I.; Mayoral, J. A.; Reiser, O.; Vaultier, M. *Tetrahedron Lett.* **2004**, *45*, 6765.

- (140) Geiger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249.
- (141) Fraile, J.; Pérez, I.; Mayoral, J.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1680.
- (142) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325.
- (143) Werner, H.; Herréras, C. I.; Glos, M.; Gissibl, A.; Fraile, J. M.; Pérez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 125.
- (144) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099.
- (145) Bayer, A.; Endeshaw, M. M.; Gautun, O. R. *J. Org. Chem.* **2004**, *69*, 7198.
- (146) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387.
- (147) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47.
- (148) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.
- (149) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071.
- (150) Evans, D. A.; Fandrick, K. *Org. Lett.* **2006**, *8*, 2249.
- (151) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029.
- (152) Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 396.
- (153) Commelles, J.; Pericas, A.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; García-Granda, S.; Rocas-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077.
- (154) Weissberg, A.; Halak, B.; Portnoy, M. *J. Org. Chem.* **2005**, *70*, 4556.
- (155) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **2005**, *70*, 5536.
- (156) Tilliet, M.; Lundgren, S.; Moberg, C.; Levacher, V. *Adv. Synth. Catal.* **2007**, *349*, 2079.
- (157) Bayardon, J.; Sinou, D.; Guala, M.; Desimoni, G. *Tetrahedron: Asymmetry* **2004**, *15*, 3195.
- (158) Desimoni, G.; Faita, G.; Piccinini, F.; Toscanini, M. *Eur. J. Org. Chem.* **2006**, 5228.
- (159) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405.
- (160) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977.
- (161) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252.
- (162) McManus, H. A.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 8566.
- (163) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433.
- (164) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712.
- (165) Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.
- (166) Nishiyama, H.; Furuta, A. *Chem. Commun.* **2007**, *7*, 760.
- (167) McManus, H. A.; Cozzi, P.-G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551.
- (168) Hargaden, G. C.; McManus, H. A.; Cozzi, P.-G.; Guiry, P. J. *Org. Biomol. Chem.* **2007**, *5*, 763.
- (169) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115.
- (170) Liu, H. L.; Xu, J.; Du, D.-M. *Org. Lett.* **2007**, *9*, 4725.
- (171) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociek-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.
- (172) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 16–5764.
- (173) Västilä, P.; Pastor, I. M.; Adolfsson, H. *J. Org. Chem.* **2005**, *70*, 2921.
- (174) Albano, V. G.; Bandini, M.; Monari, M.; Marcucci, E.; Piccinelli, F.; Umani-Ronchi, A. *J. Org. Chem.* **2006**, *71*, 6451.
- (175) Hua, G.; Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 385.
- (176) Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 585.
- (177) Liu, D.; Xie, F.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 7591.
- (178) Wang, Z.-Y.; Du, D.-M.; Xu, J.-Z. *Synth. Commun.* **2005**, *35*, 299.
- (179) Zhou, J.; Ye, M.-C.; Tang, Y. *J. Comb. Chem.* **2004**, *6*, 301.
- (180) Ye, M.-C.; Li, B.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6108.
- (181) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309.
- (182) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, 1677.
- (183) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918.
- (184) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099.
- (185) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576.
- (186) Xu, Z.-H.; Zhu, S.-N.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *Chem. Commun.* **2007**, 1960.
- (187) Zhou, J.; Tang, Y. *Org. Biomol. Chem.* **2004**, *2*, 429.
- (188) Zhang, Y. J.; Wang, F.; Zhang, W. *J. Org. Chem.* **2007**, *72*, 9208.

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