Recent Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis

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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.

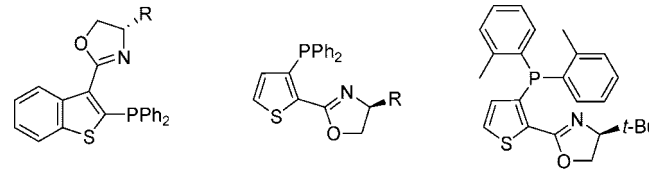
Since the first report in 1986 of the use of chiral oxazoline-based ligands in asymmetric catalysis, a diverse range of ligands with one, two, or more oxazoline rings incorporating various heteroatoms, additional chiral elements, and specific structural features have been used with great success in a 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]



1
a: R = *i*-Pr
b: R = *t*-Bu
c: R = Ph

2
a: **R** = *i*-Pr
b: **R** = *t*-Bu

2c

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.

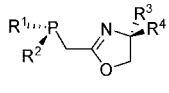
Pat Guiry graduated with an Honours B.Sc. degree in chemistry from University College Dublin (UCD) in 1986. He stayed at UCD for his Ph.D., working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his Ph.D., he 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 Frosst 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.

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]

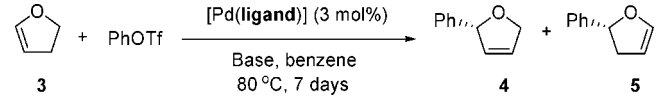


9

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

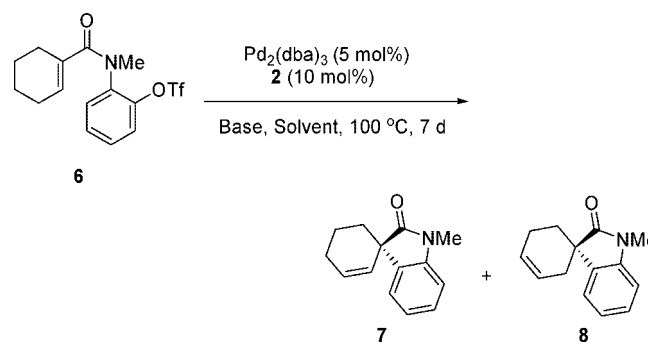


Table 1.1. Asymmetric Phenylation of 2,3-Dihydrofuran Using Ligands 1 and 2

entry	ligand	base	yield (%) of **4** (**5**)	ee (%) of **4** (*R*)
1	**1c**	*i*-Pr_2NH	66 (8)	77
2	**1a**	Proton sponge	23 (6)	89
3	**1a**	*i*-Pr_2NH	33 (7)	87
4	**2a**	Et_3N	17 (1)	81
5	**2a**	Proton sponge	18 (2)	82
6	**2b**	Et_3N	90 (9)	95
7	**2b**	Proton sponge	72 (8)	91
8	**2b**	*i*-Pr_2NH	97 (2)	95

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

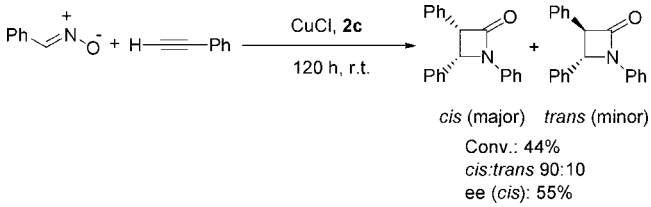
entry	ligand	base	solvent	conv (%)	**7**:**8**	ee (%) of **7** (*R*)
1	**2b**	PMP[b]	toluene	67	99:1	68
2	**2b**	proton sponge	toluene	59	98:2	76
3	**2b**	DIPEA	toluene	9	94:6	60
4	**2b**	K_2CO_3	toluene	3	65:35	62
5[a]	**2b**	Cy_2NMe	toluene	60	98:2	72

[a] Reaction carried out at 140 °C. [b] 1,2,2,6,6-Pentamethylpiperidine.

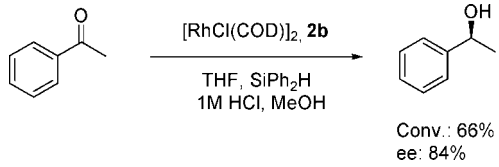
Table 1.3. Asymmetric Pd-Catalyzed Allylic Alkylation Using Ligand Class 9

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

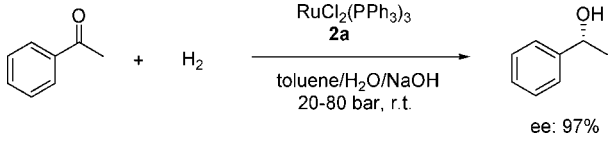
Scheme 1.3



Scheme 1.4



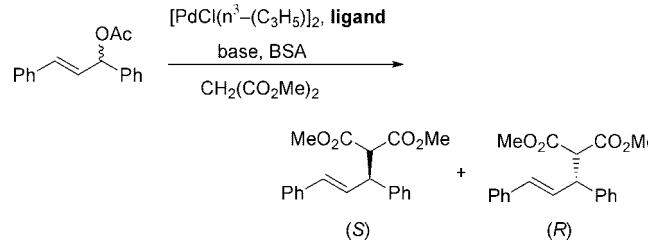
Scheme 1.5



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

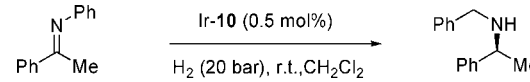


Table 1.4. Enantioselective Imine Hydrogenation Using Ligand Class 10

entry	ligand (mol %)	H_2 (atm)	temp (°C)	time (h)	conv (%)	ee (%) (*S*)
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

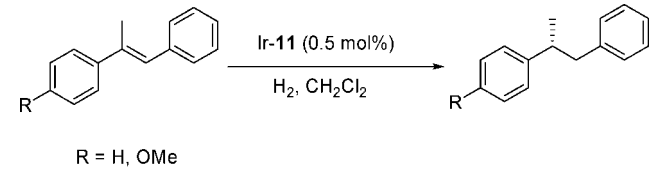
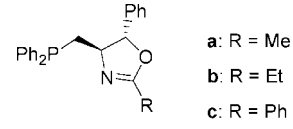


Table 1.5. Asymmetric Hydrogenation of Methylstilbene Derivatives Using Ir Complexes of 11

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

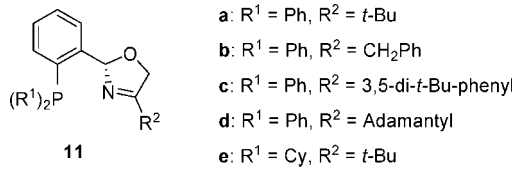
of room temperature, low catalyst loading, and low H_2 pressure (Table 1.4, entry 4). The methyl- and phenyl-substituted ligands **4a** and **4c** gave low selectivities of 10% and 7%, respectively.



10

Zhang has developed new conformationally rigid phosphinooxazolines 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).

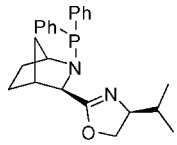


11

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 H_2, but in contrast, **11d** and **11e** gave near quantitative conversions (Table 1.5, entries 7, 8). Increasing the H_2 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]

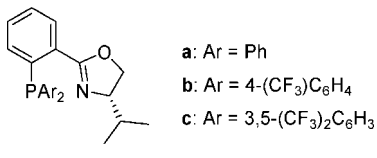
Andersson has applied a new chiral phosphinooxazoline ligand **12** in the iridium-catalyzed asymmetric hydrogenation of acyclic aromatic *N*-arylamines (Scheme 1.9, Table 1.6).[11]



12

Initial hydrogenation of the model substrate (R = R^1 = 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 phosphinooxazolines **13** in the iridium-catalyzed allylic alkylation (Scheme 1.10) of linear substrates of type **14** has been reported by Helmchen.[12]



13

The results obtained clearly show the importance of both electronic and steric effects during the reaction (Table 1.7). Thus, the CF_3-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 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 cycloaddtions of azomethine ylides with α,β-unsaturated carboxylic esters (Scheme 1.11, Table 1.8).[13]

Scheme 1.9

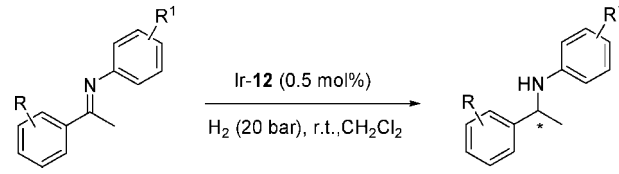
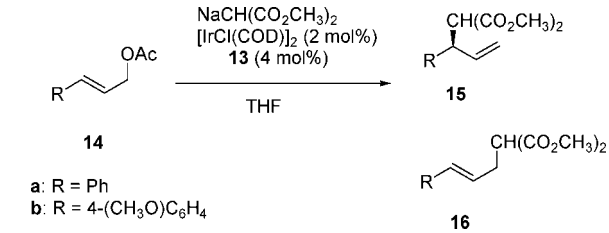


Table 1.6. Asymmetric Hydrogenation of Acyclic *N*-Arylamines Catalyzed by Ir Complexes of 12

entry	R	R^1	time (h)	conv (%)	ee (%) (conf)
1	H	H	2	98	90 (*R*)
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



14

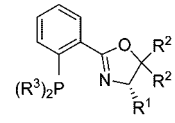
a: R = Ph
b: R = 4-(CH3O)C6H4

15

16

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



17

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

Scheme 1.11

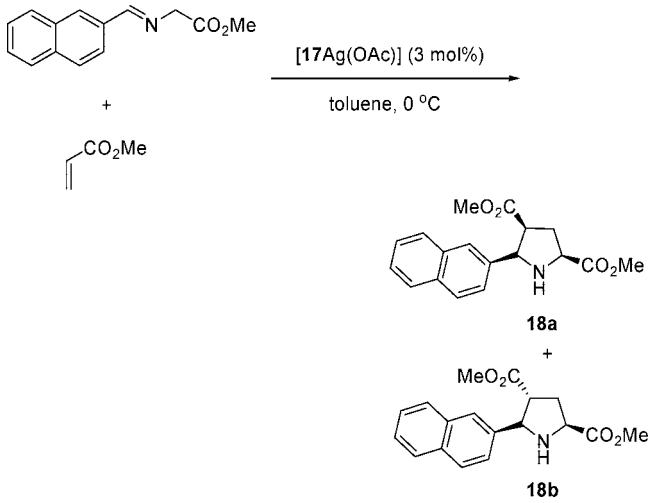
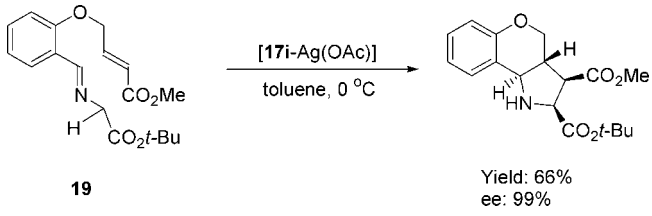


Table 1.8. Asymmetric Ag(I)-Catalyzed Intermolecular [3 + 2] Cycloaddition Using Ligand Class 17

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]

Moberg has developed new phosphino-4-(1-hydroxyalkyl)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 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.

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

entry	ligand	conv (%)	ee (%) (conf)
1[a]	**20a**	99	95 (*R*)
2[a]	**20b**	100	95 (*R*)
3[a]	**20c**	100	92 (*R*)
4[a]	**20d**	100	88 (*R*)
5[a]	**21a**	100	97 (*S*)
6[a]	**21b**	100	98 (*S*)
7[a]	**21c**	100	88 (*S*)
8[a]	**21d**	100	99 (*S*)
9[b]	**20a**	100	93 (*R*)
10[b]	**20b**	100	91 (*R*)
11[b]	**21c**	100	76 (*S*)
12[b]	**21d**	81	97 (*S*)

[a] Reaction carried out at 0 °C. [b] Reaction carried out at 25 °C.

Scheme 1.13

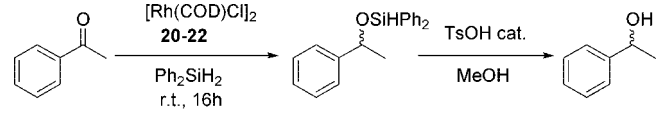
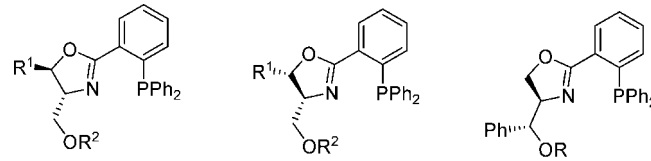


Table 1.10. Enantioselective Hydrosilylation of Acetophenone Using Ligands 20 and 22

entry	ligand	conv (%)	ee (%) (conf)
1	**20a**	100	12 (*S*)
2[a]	**20a**	100	63 (*S*)
3	**20b**	100	70 (*S*)
4[a]	**20b**	100	60 (*S*)
5	**22a**	100	66 (*R*)
6[a]	**22a**	97	91 (*R*)
7[a,b]	**22a**	100	95 (*R*)
8	**22b**	100	56 (*R*)
9	**22b**	100	87 (*R*)

[a] $AgBF_4$ added. [b] Reaction was carried out at 0 °C.

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 $AgBF_4$ 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).



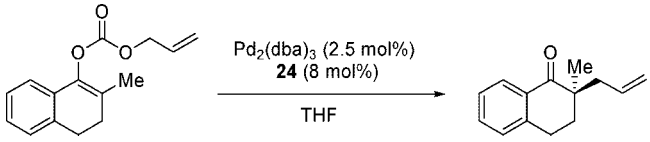
20
a: R^1 = Me, R^2 = H
b: R^1 = Me, R^2 =Me
c: R^1 = Ph, R^2 = H
d: R^1 = Ph, R^2 = Me

21
a: R^1 = Me, R^2 = H
b: R^1 = Me, R^2 = Me
c: R^1 = Ph, R^2 = H
d: R^1 = Ph, R^2 = Me

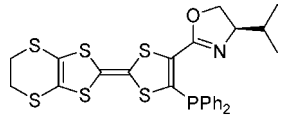
22
a: R = H
b: R = Me

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

Scheme 1.14



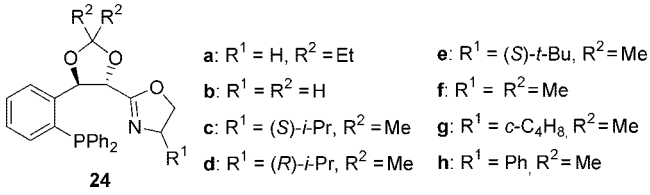
and Avarvari.[16a] In the asymmetric palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6), an enantiomeric excess of 85% (*R*) was obtained after 18 h at room temperature.



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 phosphinooxazoline 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).

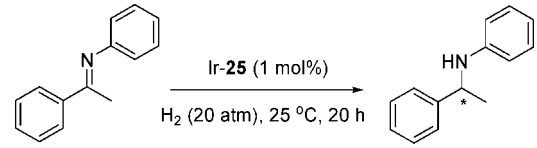
Zhou has synthesized new chiral phosphinooxazoline ligands **25** and reported their application in the iridium-catalyzed hydrogenation of imines (Scheme 1.15).[18] Using the iridium complex of (*S*,*S*)-**25a**, *N*-(1-phenylethylidene)aniline was hydrogenated with 98% conversion and 76% ee (Table 1.11, 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

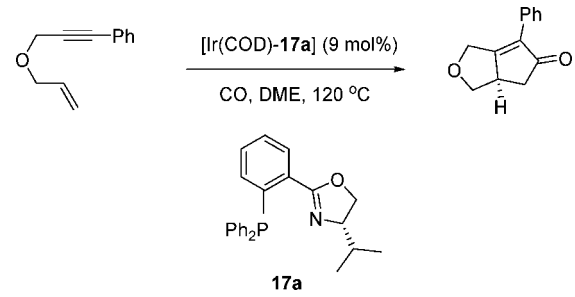
entry	ligand	solvent	conv (%)	ee (%)
1	(*S*,*S*)-**25a**	CH_2Cl_2	96	76
2	(*S*,*R*)-**25a**	CH_2Cl_2	7	0
3	(*S*,*S*)-**25b**	CH_2Cl_2	18	74
4	(*S*,*S*)-**25c**	CH_2Cl_2	98	81
5	(*S*,*S*)-**25c**	THF	65	79
6	(*S*,*S*)-**25c**	toluene	98	82
7	(*S*,*S*)-**25c**	EtOAc	40	74
8	(*S*,*S*)-**25c**	MeOH	8	nd
9	(*S*,*S*)-**25c**	ether	99	87
10	(*S*,*S*)-**25d**	ether	99	88
11	(*S*,*S*)-**25e**	ether	>99	90
12[a]	(*S*,*S*)-**25e**	ether	>99	89
13[b]	(*S*,*S*)-**25e**	ether	70	90
14[c]	(*S*,*S*)-**25e**	ether	>99	93
15[c,d]	(*S*,*S*)-**25e**	*t*-BuOMe	>99	93

[a] 0.5 mol% catalyst used. [b] 0.1 mol % catalyst used. [c] Reaction carried out at ambient H_2 pressure at 10 °C. [d] 4 Å MS used.

Scheme 1.15



Scheme 1.16



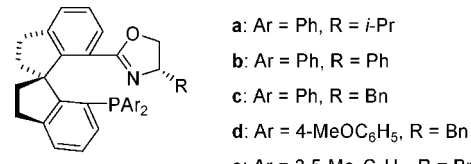
17a

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

entry	P_{CO} (bar)	yield (%)	ee (%)
1	1.4	51	97 (*R*)
2	1.6	61	96 (*R*)
3	1.8	71	94 (*R*)
4	2.0	81	92 (*R*)
5	2.2	85	91 (*R*)

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

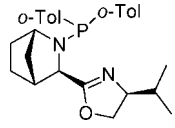
Pfaltz has applied iridium complexes of the PHOX ligand **17a** to the asymmetric catalytic intramolecular Pauson−Khand reaction (Scheme 1.16, Table 1.12).[19]

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 $C(CO_2Me)_2$ 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]

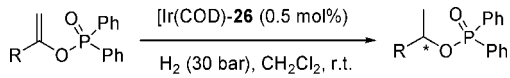


26

The synthesis and application of phosphinooxazoline 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 CF_3 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

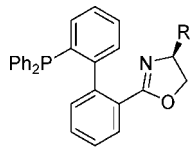


27

2.2. Phosphinooxazoline 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]

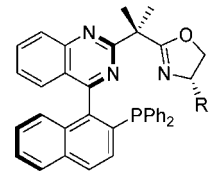


30
a: R = *i*-Pr
b: R = *t*-Bu

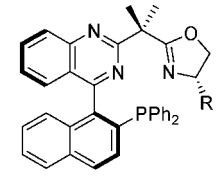
The ligands were applied in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (Scheme 1.6, Table 1.15).

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]



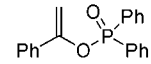
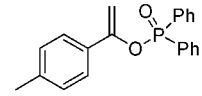
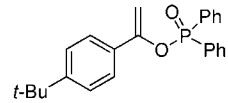
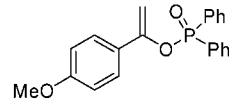
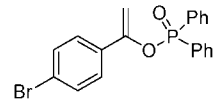
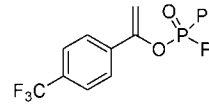
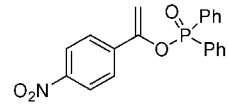
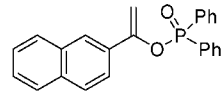
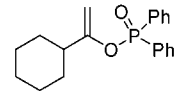
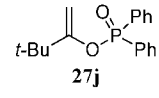
31
a: R = *i*-Pr
c: R = *t*-Bu



31
b: R = *i*-Pr
d: R = *t*-Bu

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	 **27a**	>99	95 (*R*)
2	 **27b**	>99	95 (*R*)
3	 **27c**	>99	95 (*R*)
4	 **27d**	>99	95 (*R*)
5	 **27e**	>99	95 (*R*)
6	 **27f**	>99	95 (*R*)
7	 **27g**	>99	95 (*R*)
8	 **27h**	>99	95 (*R*)
9	 **27i**	>99	95 (*R*)
10	 **27j**	>99	95 (*R*)

Scheme 1.18

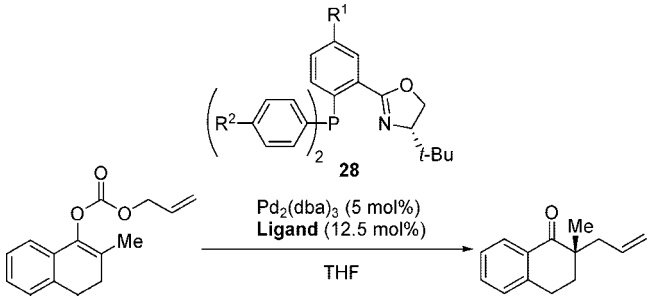


Table 1.14. Asymmetric Allylation Using Ligand 28

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

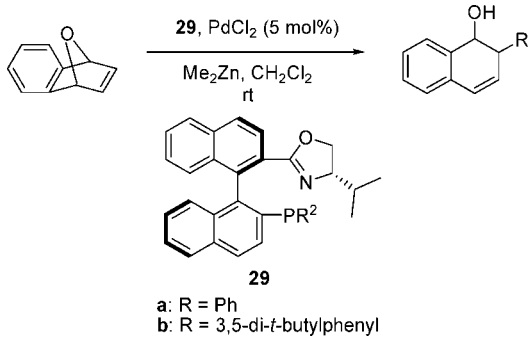


Table 1.15. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligand Class 30

entry	ligand	solvent	yield (%)	ee (%) (conf)
1	**30a**	THF	96	83 (*S*)
2	**30a**	CH_2Cl_2	89	82 (*S*)
3	**30b**	THF	97	88 (*S*)
4	**30b**	CH_2Cl_2	96	90 (*S*)

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

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

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

2.3. Phosphinooxazoline 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]

Phosphinooxazolines **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

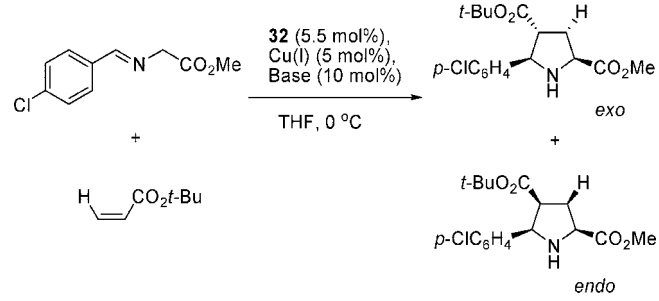
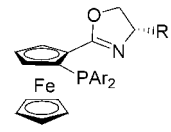


Table 1.17. Enantioselective Cu(I)-Catalyzed [3 + 2] Cycloaddition Using Ligand Class 32

entry	Cu(I)	ligand	yield of *exo* (%)	yield of *endo* (%)	ee of *exo* (%)
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.

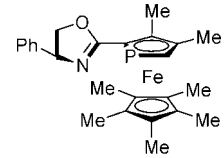
1.17, entries 1−5). The highest *exo* selectivity and enantiomeric excess was obtained using the *t*-Bu-substituted ligand **32d** (Table 1.17, entry 4). The yield and enantiomeric excess obtained using this ligand was further improved to 91% ee by applying $CuClO_4$ and conducting the reaction at a 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.



32

a: Ar = Ph, R = *i*-Pr
b: Ar = 3,5-$(Me)_2C_6H_3$, R = *i*-Pr
c: Ar = Ph, R = *t*-Bu
d: Ar = 3,5-$(Me)_2C_6H_3$, R = *t*-Bu
e: Ar = 3,5-$(Me)_2C_6H_3$, R = Ph
f: Ar = 3,5-$(Me)_2C_6H_3$, 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]



33

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

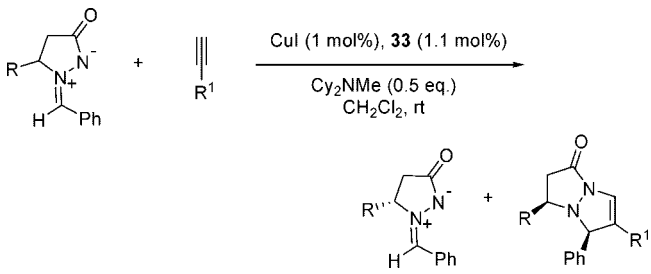


Table 1.18. Kinetic Resolution of Azomethine Imines Using Ligand 33

entry	R	R^1	s^a	yield (%)^b	ee (%)^b
1	Ph	CO_2Et	53	42	99
2	Ph	CON(Me)Ph	30	42	91
3	Ph	4-(trifluoromethyl)phenyl	53	39	99
4	Ph	CO_2Et	53	42	99
5	Ph	CON(Me)Ph	54	44	99
6	3-BrC_6H_4	CO_2Et	15	31	98
7	*i*-Pr	CON(Me)Ph	76	40	97
8	*t*-Bu	CON(Me)Ph	51	48	93

[a] Selectivity factor. [b] Yield and ee of the dipole.

Scheme 1.22

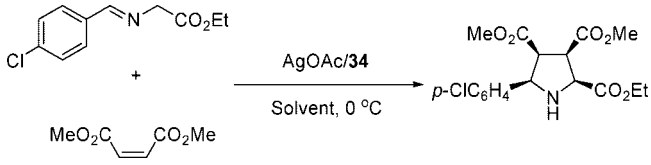
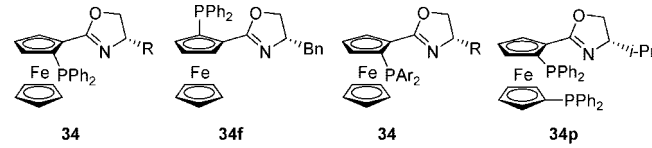


Table 1.19. AgOAc-Catalyzed Asymmetric Cyloaddition Using Ligand Class 34

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_2O	93	88
7	**34e**	Et_2O	98	81
8	**34f**	Et_2O	96	78[a]
9	**34g**	Et_2O	91	84
10	**34h**	Et_2O	88	89
11	**34i**	Et_2O	89	83
12	**34j**	Et_2O	94	94
13[b]	**34j**	Et_2O	88	98
14[c]	**34j**	Et_2O	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 Et_2O (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



34 **34f** **34** **34p**

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

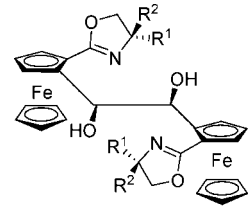
g: R = Bn, Ar = 4-$MeOC_6H_4$
h: R = Bn, Ar = 3,5-$Me_2C_6H_3$
i: R = Bn, Ar = 3,5-$(CF_3)_2C_6H_3$
j: R = Bn, Ar = 4-$CF_3C_6H_4$
k: R = *i*-Pr, Ar = Ph
l: R = *i*-Pr, Ar = 4-$CF_3C_6H_4$
m: R = *i*-Pr, Ar = 4-$MeOC_6H_4$
n: R = *i*-Pr, Ar = 3,5-$Me_2C_6H_3$
o: R = *i*-Pr, Ar = 3,5-$(CF_3)_2C_6H_3$

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 CF_3 substituent gave a mixture of *exo:endo* isomers (73:27), whereas **34o** with two CF_3 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]



37

a: R^1 = *i*-Pr, R^2 = H
b: R^1 = *t*-Bu, R^2 = H
c: R^1 = Ph, R^2 = H
d: R^1 = Bn, R^2 = H
e: R^1 = R^2 = 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

Scheme 1.23

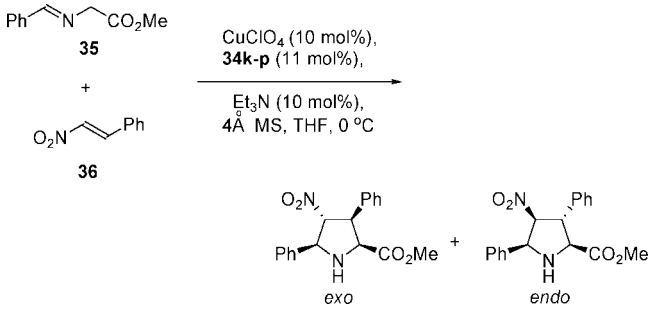


Table 1.20. Enantioselective Cycloaddition of 35 and 36 Using Ligands 34k−p

entry	ligand	yield (%)	*exo*/*endo*	ee (%)
1	**34k**	58	only *exo*	97
2	**34l**	67	73:27	95
3	**34m**	65	only *exo*	98
4	**34n**	49	only *exo*	98
5	**34o**	62	18:82	88
6	**34p**	37	49:51	92

Scheme 1.24

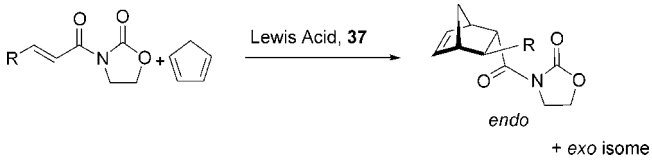
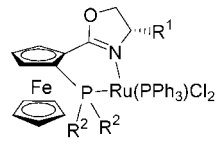


Table 1.21. Enantioselective Diels−Alder Reaction Using Ligand 37a

entry	Lewis acid	conv (%)	*endo*/*exo*	ee *endo* (%) (conf)
1	$La(OTf)_3$	99	88:12	16 (*R*)
2	$Sc(OTf)_3$	99	77:23	48 (*R*)
3	$Sm(OTf)_3$	99	81:19	15 (*R*)
4	$Yb(OTf)_3$	99	80:20	70 (*R*)
5	$Yb(ClO_4)_3$	77	74:26	15 (*S*)
6	$Yb(OTf)_3$	99	74:26	50 (*R*)
7	$Mg(ClO_4)_2$	63	82:18	40 (*R*)

used in the hydrogenation of 3,5-bistrifluoromethyl acetophenone on a 140 kg scale at 20 bar and 25 °C with enantiomeric excesses of >95% reported.[31]



38

a: R^1 = *i*-Pr, R^2 = Ph
b: R^1 = *t*-Bu, R^2 = Ph
c: R^1 = Ph, R^2 = Ph
d: R^1 = *i*-Pr, R^2 = 3,5-$Me_2C_6H_3$
e: R^1 = Ph, R^2 = 4-$CF_3C_6H_4$
f: R^1 = *i*-Pr, R^2 = 3,5-$(Me)_2$-4(MeO)C_6H_2

Palmer and Nettekoven have reported the application of **38a** in the asymmetric reduction of O-protected ketone **40** (Scheme 1.26) with complete conversion and enantiomeric excesses of up to 90%.[32]

Helmchen has reported the synthesis of chiral phosphinooxazolines with a pentamethylferrocene backbone **41** and their application in the palladium-catalyzed allylic alkylation of cyclic substrates (Scheme 1.27, Table 1.23).[33]

Ligands **41a−e** were initially applied in the allylic alkylation of substrate where $n = 2$. The best result was obtained using **41b**, which gave almost complete conversion and an enantiomeric excess of 81% (Table 1.23, entry 2), with very poor results being reported using **41d** and **41e**.

Scheme 1.25

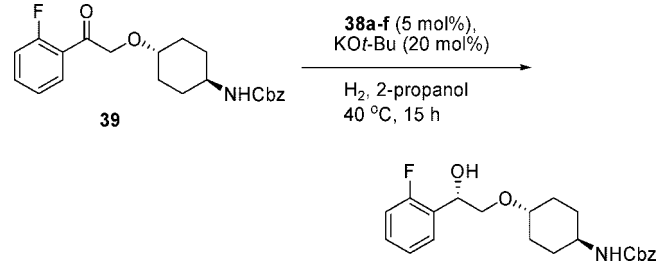
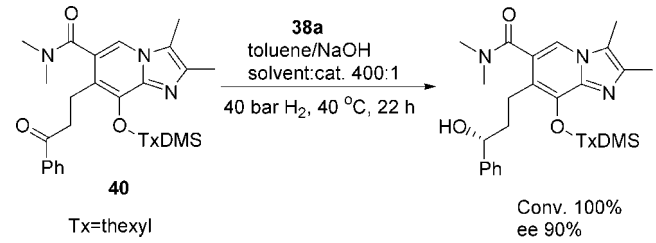


Table 1.22. Enantioselective Hydrogenation of Ketone 39 Using Complexes 38

entry	ligand	ee (%)
1	**38a**	78
2	**38b**	86
3	**38c**	83
4	**38d**	75
5	**38e**	81
6	**38f**	78
7[a]	**38b**	93
8[a]	**38e**	86

[a] NaOH(aq) (100 mol %) used as base and toluene used as solvent.

Scheme 1.26



Scheme 1.27

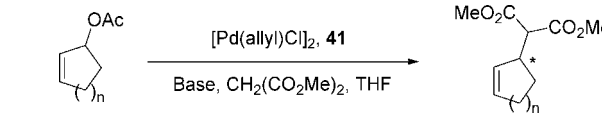


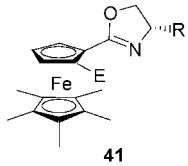
Table 1.23. Enantioselective Allylic Alkylation of Cyclic Substrates Using Ligand 41

entry	ligand	*n*	base	time (h)	conv (%)	yield (h)	ee (%)
1	**41a**[d]	2	NaH	1.5	>99	n.d.	73 (*R*)
2	**41b**[e]	2	NaH	2	>99	94	81 (*R*)
3	**41c**[d]	2	NaH	4	92	n.d.	66 (*R*)
4	**41d**[d]	2	BSA	5	97	n.d.	15 (*R*)
5	**41e**[e]	2	BSA	16	<5	n.d.	n.d.
6	**41b**[d]	3	BSA	3	>99	93	94 (*R*)
7[a]	**41b**[e]	1	BSA	4	>99	97	91 (*R*)
8[b]	**41b**[e]	1	BSA	16	>99	96	92 (*R*)
9[b,c]	**41b**[e]	1	NaH	48	>99	97	92 (*R*)

[a] Reaction carried out at −20 °C. [b] Reaction carried out at −30 °C. [c] DMF used as solvent. [d] 4.4 mol % ligand. [e] 1.1 mol % ligand.

Applying ligand **41b** to a range of substrates ($n = 1, 3$) resulted in an increase in enantiomeric excess (Table 1.23, entries 6−9). The best result of 94% ee was obtained using the BSA method any cyclic substrates ($n = 3$).

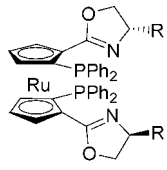
The preparation of novel air-stable tetrasubstituted ruthenocene-based ligands **42** and their application in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 1.6) has



41

a: R = *i*-Pr, E = PPh_2
b: R = *t*-Bu, E = PPh_2
c: R = Bn, E = PPh_2
d: R^1 = *t*-Bu, E= P(*t*-Bu)$_2$
e: R^1 = *t*-Bu, E= SPh

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

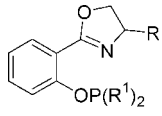


42

a: R = *i*-Pr
b: R = *t*-Bu

2.4. Oxazoline-Phosphonite Ligands

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

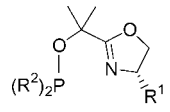


43

a: R = Et, R^1 = Ph
b: R = *i*-Pr, R^1 = Ph
c: R = Et, R^1 = Cy
d: R = *i*-Pr, R^1 = Cy

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

Oxazolinyl 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 PCy_2 groups were more active but less selective (Table 1.24, entries 3, 4).



44

a: R^1 = *t*-Bu, R^2 = Ph
b: R^1 = *t*-Bu, R^2 = *o*-Tol
c: R^1 = *i*-Pr, R^2 = Ph
d: R^1 = *i*-Pr, R^2 = *o*-Tol

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 H_2 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 (*R*)
2	**43b**	1.5	82 (*S*)
3	**43c**	0.5	44 (*R*)
4	**43d**	0.5	69 (*S*)

Scheme 1.28

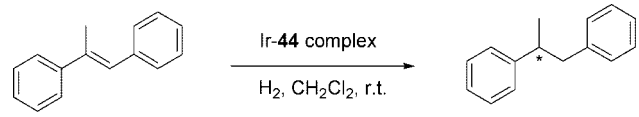


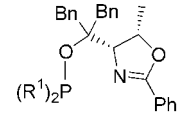
Table 1.25. Enantioselective Hydrogenation of Trisubstituted, Unfunctionalized Olefins with Ir Catalysts Derived from Ligand Class 44

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

Table 1.26. Enantioselective Hydrogenation of Substrates 46a−g (1 bar H_2)

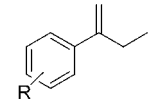
entry	substrate	temp (°C)	time (min)	conv (%)	ee (%)
		(a) Using Ligand **45a**			
1	**46a**	25	30	>99	94
2	**46b**	25	30	>99	91
3	**46c**	25	30	>99	88
4	**46d**	25	30	>99	89
5	**46e**	0	30	>99	90
6	**46f**	25	30	>99	92
7	**46g**	25	30	>99	94
		(b) Using Ligand **45b**			
1	**45a**	25	30	>99	90
2	**45b**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



45

a: R' = Cy
b: R^1 = Ph



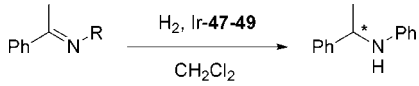
46

a: R = 4-OCH_3
b:R = 4-CH_3
c: R = 4-CF_3
d: R = 4-Cl
e: R = 4-Br
f: R = 3-Cl
g:R = 3-Br

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



50

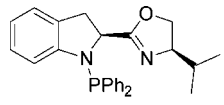
a: R = Ph
b: R = Bn

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

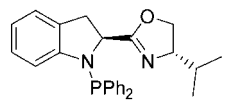
entry	ligand	substrate	P_{H_2} (bar)	temp (°C)	S/Ir	conv (%)	ee (%) (conf)
1	**47a**	**50a**	50	25	50	98	80 (*S*)
2	**47b**	**50a**	50	25	80	83	14 (*R*)
3	**48**	**50a**	50	25	50	100	72 (*S*)
4	**49**	**50a**	50	25	50	94	68 (*S*)
5[a]	**47a**	**50a**	50	0	50	100	84 (*S*)
6	**48**	**50a**	50	0	30	82	85 (*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.

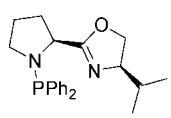
Generally, high conversions and moderate to high enantiomeric excesses (over 68%) were obtained under 50 bar H_2 at room temperature for 12 h. Using the complex bearing ligand **47a** with (*R*)-configuration on the oxazoline ring and (*S*)-configuration on the aminophosphine residue induced an enantiomeric 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).



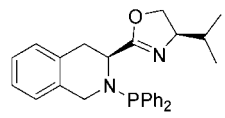
47a



47b

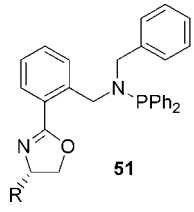


48



49

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]



51

a: R = Me
b: R = *i*-Pr
c: R = Bn

Scheme 1.30

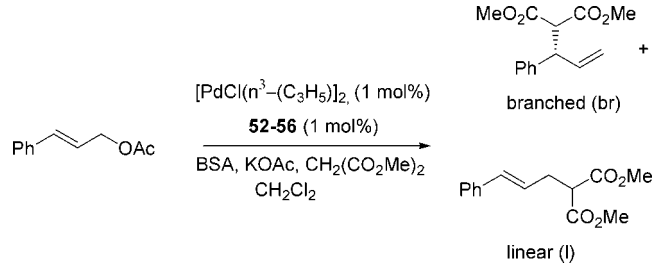


Table 1.28. Enantioselective Pd-Catalyzed Allylic Alkylation Using Ligands 52−56

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

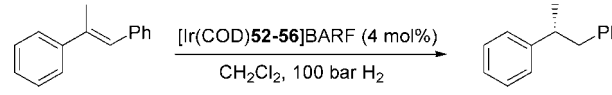


Table 1.29. Enantioselective Ir-Catalyzed Hydrogenation Using Ligands 52−56

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*)

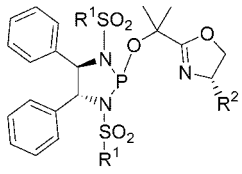
The best enantioselectivity of 38% (*R*) was obtained using *i*-Pr-substituted oxazoline ligand **51b**, with the conversions varying greatly with the base. For example, ligand **51b** led to a conversion of 11% using KOAc, but changing to Cs_2CO_3 resulted in an increase in conversion to 64%.

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 enantiocontrol, 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: R^1 = 4-tolyl, R^2 = *t*-Bu

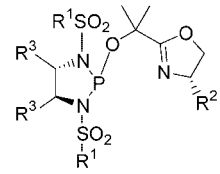
b: R^1 = 4-tolyl, R^2 = Ph

c: R^1 = CF_3, R^2 = *t*-Bu

d: R^1 = mesityl, R^2 = *t*-Bu

e: R^1 = 1-naphthyl, R^2 = *t*-Bu

f: R^1 = 2-naphthyl, R^2 = *t*-Bu

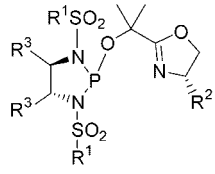


53

a: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = Ph

b: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = $(CH_2)_4$

c: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = Cy

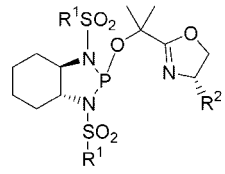


54

a: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = Cy

b: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = $(CH_2)_4$

c: R^1 = 4-tolyl, R^2 = *t*-Bu, R^3 = 3,5-xylyl

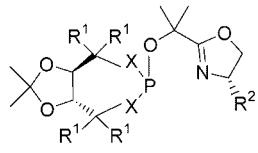


55

a: R^1 = 4-tolyl, R^2 = *t*-Bu

b: R^1 = 1-naphthyl, R^2 = *t*-Bu

c: R^1 = 2-naphthyl, R^2 = *t*-Bu



56

a: R^1 = Ph, R^2 = *t*-Bu, X = O

b: R^1 = Ph, R^2 = Ph, X = O

c: R^1 = 2-naphthyl, R^2 = *t*-Bu, X = O

d: R^1 = Ph, R^2 = *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)phenylpropene 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 (*S*)
2	**57b**	89	84 (*S*)
3	**57c**	57	86 (*S*)
4	**57d**	95	86 (*S*)
5	**57e**	91	86 (*S*)
6	**57f**	67	45 (*S*)
7	**57g**	100	85 (*S*)
8[a]	**57a**	54	95 (*S*)
9[a,b]	**57a**	100	99 (*S*)

[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 (*R*)	90 (*R*)
2	**57a**	benzene	77 (84:16)	95 (*R*)	60 (*R*)
3	**57a**	DMF	15 (71:29)	87 (*R*)	nd
4	**57a**	THF	98 (87:13)	97 (*R*)	88 (*R*)
5[a]	**57a**	THF	100 (80:20)	93 (*R*)	87 (*R*)
6[b]	**57a**	THF	28 (88:12)	98 (*R*)	88 (*R*)
7	**57b**	THF	86 (85:15)	97 (*R*)	89 (*R*)
8	**57c**	THF	45 (60:40)	80 (*R*)	69 (*R*)
9	**57d**	THF	100 (97:3)	99 (*R*)	nd
10	**57e**	THF	80 (71:29)	84 (*R*)	90 (*R*)
11	**57f**	THF	12 (65:35)	83 (*R*)	23 (*R*)

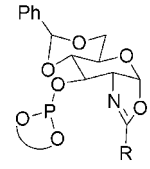
[a] Reaction carried out at 75 °C. [b] Reaction carried out at 25 °C.

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, R^1 = R^2 = *t*-Bu

b: R = Ph, R^1 = *t*-Bu, R^2 = OMe

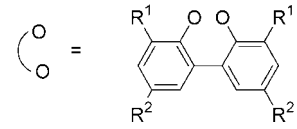
c: R = Ph, R^1 = R^2 = H

d: R = Ph, R^1 = $SiMe_3$, R^2 = H

e: R = *i*-Pr, R^1 = R^2 = *t*-Bu

f: R = *t*-Bu, R^1 = R^2 = *t*-Bu

g: R = Me, R^1 = R^2 = *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

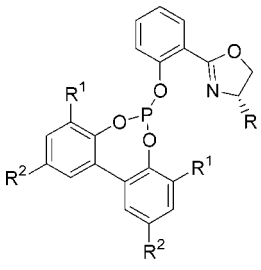
entry	ligand	conv (%)	ee (%)
1	**58a**	71	>99 (*S*)
2	**58b**	100	>99 (*S*)
3	**58c**	84	>99 (*S*)
4	**58d**	95	>99 (*S*)
5	**58e**	100	42 (*S*)
6	**58f**	100	95 (*S*)
7	**58g**	100	99 (*S*)
8	**59a**	100	99 (*R*)

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]

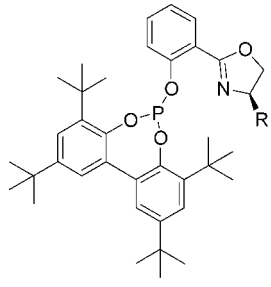
Ligand **57d** was applied in the copper-catalyzed 1,4-addition of 2-cyclohexenone and gave an enantiomeric excess of 64% and yield of 50% after 2 h at −30 °C. Changing the copper precursor from $Cu(OAc)_2$ to $[Cu(MeCN)_4]BF_4$ led to an increase in ee to 78% with no improvement in yield after 2 h at −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, R^1 = R^2 = *t*-Bu
b: R = Ph, R^1 = R^2 = *t*-Bu
c: R = *i*-Pr, R^1 = R^2 = *t*-Bu
d: R = Et, R^1 = R^2 = *t*-Bu
e: R = Et, R^1 = R^2 = H
f: R = Et, R^1 = *t*-Bu, R^2 = OMe
g: R = *i*-Pr, R^1 = *t*-Bu, R^2 = 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 of the biphenyl phosphite unit shown to be necessary for high enantioselection (Table 1.32, entries 4, 6).

Scheme 1.32

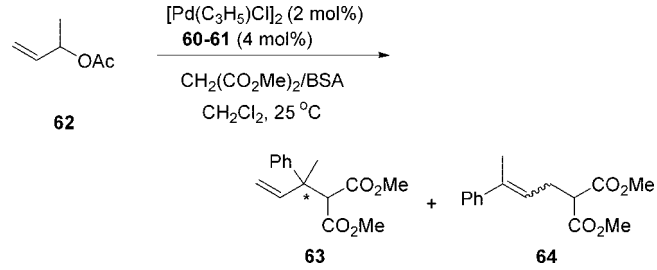


Table 1.33. Pd-Catalyzed Regio- and Enantioselective Allylic Alkylation of 62 Using Ligands 60 and 61

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

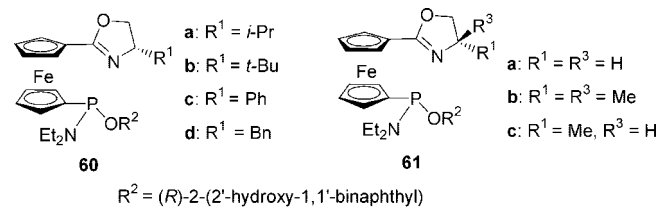
The application of ligands **58e**−**g** and **59a**−**e** in the hydrosilylation of acetophenone (Scheme 1.4) was subsequently reported. The ligands gave moderate to good conversions (48−85%), with the highest enantioselectivity of 45% being obtained using rhodium complexes of **58c**. Other ketones 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

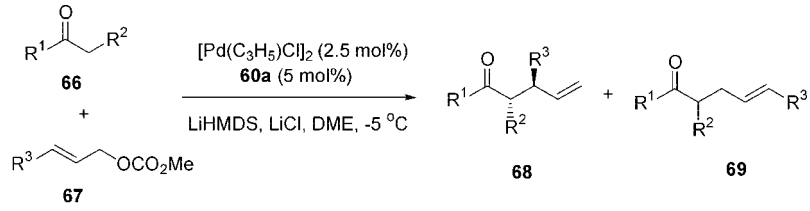
Hou has developed a range of *P*,*N*-ferrocene/oxazoline containing ligands **60** and **61**.[47]

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



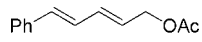
66a: R^1 = Ph, R^2 = Me
66b: R^1 = Ph, R^2 = Et
66c: R^1 = Ph, R^2 = *n*-Pr
66d: R^1 = 4-MeOC$_6$H$_4$, R^2 = Me
66e: R^1 = 1-Naphthyl, R^2 = Me
66f: R^1 = Cy, R^2 = Me

67a: R^3 = Ph
67a: R^3 = 4-CF$_3$C$_6$H$_4$
67a: R^3 = 4-MeC$_6$H$_4$
67a: R^3 = 3-BrC$_6$H$_4$
67a: R^3 = 4-MeOC$_6$H$_4$
67a: R^3 = 1-Naphthyl

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]

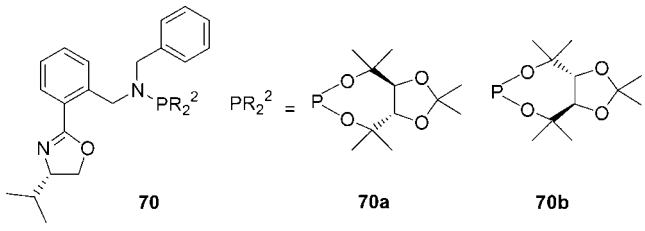


65

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).

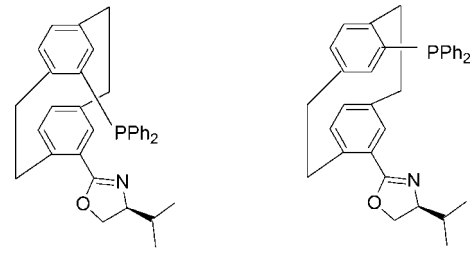
Guiry has reported the synthesis and application of novel phosphoramidite-oxazoline ligand **70** in the palladium-catalyzed enantioselective Suzuki coupling, an asymmetric transformation which has received limited attention to date (Scheme 1.34, Table 1.35).[39]



70 **70a** **70b**

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 Cs_2CO_3 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).

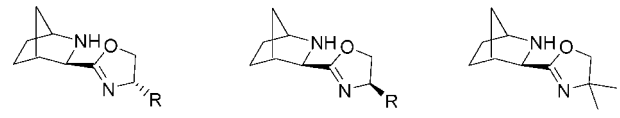
Bolm has developed new aromatic-substituted phosphinyl-oxazolinyl[2.2]paracyclophanes of type **71** and applied them in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (Scheme 1.6), with **71a** resulting in an ee of 56%, and **71b** resulting in 82% ee.[50]



71a **71b**

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]



72a-e **73a-e** **74**

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

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

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

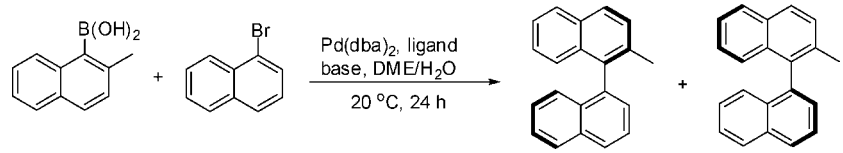


Table 1.35. Pd-Catalyzed Enantioselective Suzuki Coupling Using Ligand 70

entry	ligand	base	yield (%)	ee (%) (conf)
1	**70a**	KOH	30	38 (*R*)
2	**70a**	NaOH	25	36 (*R*)
3	**70a**	CsOH	16	37 (*R*)
4	**70a**	CsF	19	40 (*R*)
5	**70a**	Cs_2CO_3	54	46 (*R*)
6	**70a**	$Ba(OH)_2$	31	43 (*R*)
7	**70b**	KOH	45	35 (*R*)
8	**70b**	NaOH	43	34 (*R*)
9	**70b**	CsOH	61	33 (*R*)
10	**70b**	Cs_2CO_3	49	0 (*R*)
11	**70b**	$Ba(OH)_2$	25	18 (*R*)

Scheme 1.35

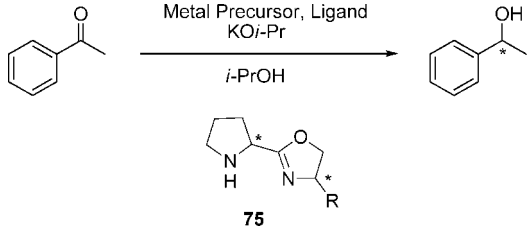


Table 1.36. Asymmetric Transfer Hydrogenation of Acetophenone Using Ruthenium Complexes of Ligands 75

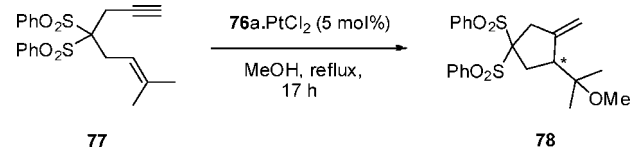
			conv (%)		ee (%)		
entry	ligand	R	1 h	15 h	1 h	15 h	conf
1	**75a**	H	6	8	7	4	*R*
2	**75b**	*i*-Pr	8	76	52	51	*R*
3	**75c**	*i*-Pr	8	73	63	61	*S*
4	**75d**	Ph	3	30	14	15	*R*
5	**75e**	Ph	1	24	10	14	*S*
6	**75f**	*t*-Bu	5	43	25	20	*R*
7	**75g**	*t*-Bu	5	37	34	25	*R*
8	**75h**	Me	2	51	14	16	*R*
9	**75i**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

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). $[Ru(p\text{-cymene})Cl_2]_2$ 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.

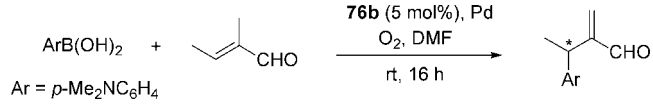
Echavarren has applied the platinum complex of *i*-Pr-pyrox **76a** in the alkoxycyclization of enyne **77** to **78** (Scheme 1.36), and although this afforded the cyclized product **78** in 97% yield, the enantiomeric excess obtained was only 10%.[53]

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

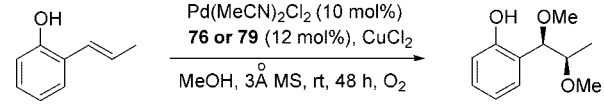
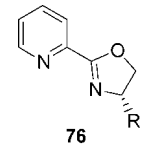


Table 1.37. Enantioselective Aerobic Dialkoxylation of 2-Propenyl Phenols Using Palladium Complexes of 76 and 79

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

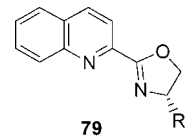
(Scheme 1.37). Yields of 67−79% and enantiomeric excesses of 68−75% were reported for the reaction of *trans*-2-methyl-2-butanal with a range of boronic acids.[54]



76

a: R = *i*-Pr
b: R = *t*-Bu

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]



79

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

Scheme 1.39

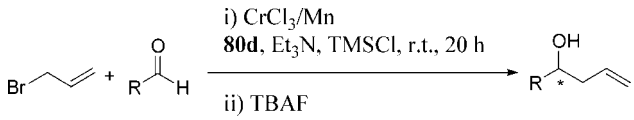


Table 1.38. Nozaki−Hiyama−Kishi Allylation of a Range of Aldehydes Using 80d

entry	R	yield (%)	ee (%)
1	C_6H_5	89	94
2	4-BrC_6H_4	73	90
3	4-$MeOC_6H_4$	98	89
4	2-Furyl	61	92
5	$PhCH_2CH_2$	98	48
6	C_6H_{11}	64	87

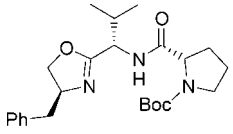
Good enantioselectivities were observed using quinoline-derived oxazoline ligands **79a−c** (Table 1.37, entries 2−4). Ligand **79b** gave a yield of 85% and an enantiomeric excess of 84% (Table 1.37, entry 2). Interestingly, increasing the amount of copper led to a significant decrease in enantioselectivity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

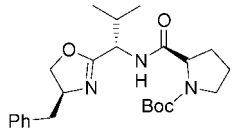
These ligands were applied in the Nozaki−Hiyama−Kishi allylation of benzaldehyde (Scheme 1.39),[56] with ligand **80d** affording the highest enantiomeric excess of 92% (*R*). This ligand was then applied in the allylation of a range of aldehydes (Table 1.38), with excellent yields and enantioselectivities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

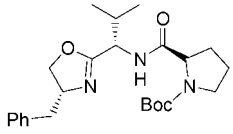
To further explore substrate scope, methallyl bromide and *trans*-crotyl bromide were used as reagent reactions with benzaldehyde. Crotylation yielded an *anti*/*syn* ratio of 2.3:1, with both *anti*- and *syn*-diastereomers having a high enantiomeric excess of 91% and 95%, respectively. Methallylation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



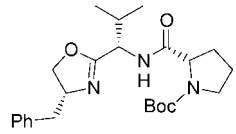
80a



80b



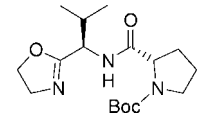
80c



80d

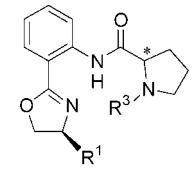
More recently, Sigman has reported the application of the structurally related ligand **81** in the first enantioselective allylation of ketones (Scheme 1.40, Table 1.39).[58]

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]

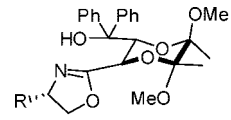


R^1, R^2 = *i*-Pr, Ph, *t*-Bu, Bn
R^3 = Cbz, Boc

82

4. Mono(oxazoline) N,O-Ligands

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

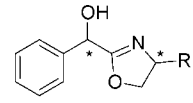


a: R = Ph
b: R = *i*-Pr
c: R = Me

83a-c

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.



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

84a-c

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

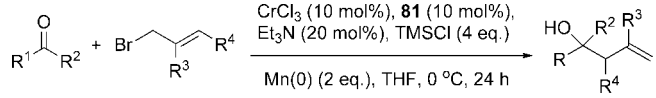
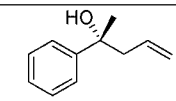
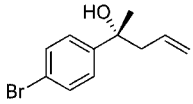
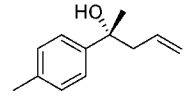
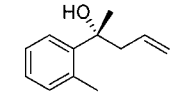
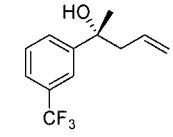
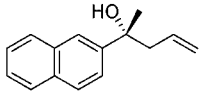
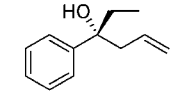
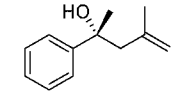
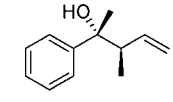
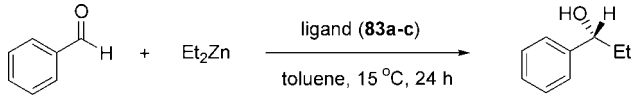


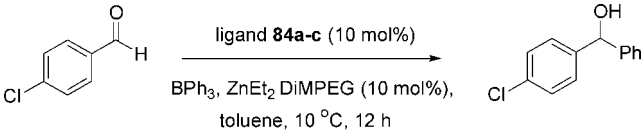
Table 1.39. NHK Allylation of a Range of Ketones Using 81

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 (*anti*) 70 (*syn*)

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

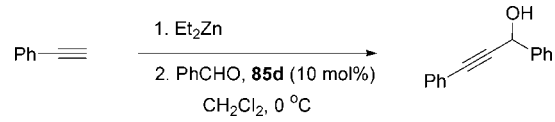
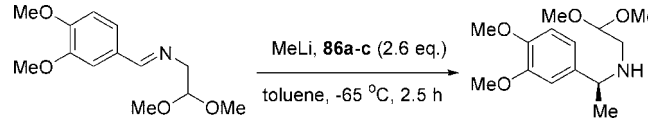


Table 1.40. Application of Ligand 85d in the Enantioselective Alkynylation of Aldehydes

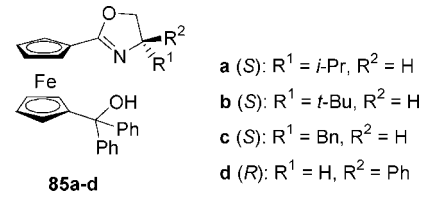
entry	aldehyde	yield (%)	ee (%)	conf
1	4-BrC_6H_4CHO	86	86	(−)
2	2-ClC_6H_4CHO	72	67	(−)
3[a]	2-ClC_6H_4CHO	82	89	(−)
4	3-$NO_2C_6H_4CHO$	87	82	(−)
5	4-$MeOC_6H_4CHO$	82	90	(−)
6	1-naphthaldehyde	84	88	(−)
7[a]	1-naphthaldehyde	86	93	(−)
8[a]	α-furan-CHO	85	82	(−)
9[a]	$C_6H_{11}CHO$	74	81	(−)-(*R*)
10[a]	$PhCH_2CHO$	72	65	(−)
11[a]	Me_2CHCHO	88	83	(−)
12[a]	Me_3CCHO	88	75	(−)
13	PhCH=CHCHO	88	54	(−)
14[a]	MeCH=CHCHO	82	59	(−)

[a] 20 mol % of **85d** used.

Scheme 1.44



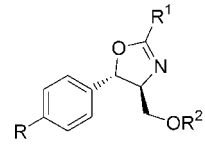
Rozwadowska has synthesized a range of ligands of type **86** and applied them in the enantioselective addition of methyllithium to a prochiral imine (Scheme 1.44).[63]



85a-d

a (*S*): R^1 = *i*-Pr, R^2 = H
b (*S*): R^1 = *t*-Bu, R^2 = H
c (*S*): R^1 = Bn, R^2 = H
d (*R*): R^1 = H, R^2 = Ph

Ligands **86a**−**c** gave yields of up 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.

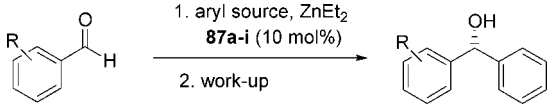


86a-c

a: R = SCH_3, R^1 = Me, R^2 = OMe
b: R = SCH_3, R^1 = Et, R^2 = OMe
c: R = H, R^1 = CH_3, R^2 = CH_3

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

Scheme 1.45



88a-d

a: R = 4-Cl

b: R = 4-MeO

c: R = 2-Br

d: R = 4-Me

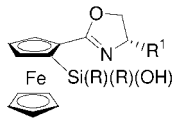
Table 1.41. Asymmetric Phenyl Transfer Reaction to Substituted Benzaldehydes 88 Using Ligands 87a−d

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: Ph_2Zn (0.65 equiv) and Et_2Zn (1.3 equiv) in toluene at 10 °C for 12 h. Method B: BPh_3 (1.0 equiv) and Et_2Zn (3.0 equiv) at 10 °C for 12 h. Method C: $PhB(OH)_2$ (2.4 equiv), Et_2Zn (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).

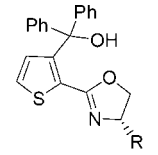


87a-i

Ligand	R	R^1
87a	Me	*t*-Bu
87b	*i*-Pr	*t*-Bu
87c	Ph	*t*-Bu
87d	*i*-Pr	Ph
87e	Ph	Ph
87f	*i*-Pr	*i*-Pr
87g	Ph	*i*-Pr
87h	*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 **89e**, 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%.



89a-g

a: R = Ph

b: R = *i*-Pr

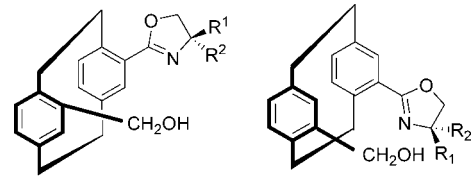
c: R = Bn

d: R = *t*-Bu

e: R = CH_2SMe

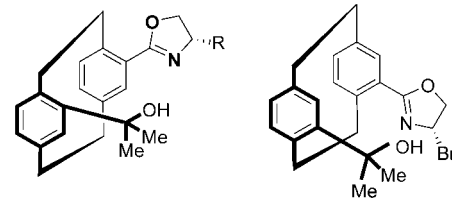
f: R = CH_2SBn

g: R = $(CH_2)_2SMe$



(*S*, 4*S*p, 13*R*p)-**90a-c** (*S*, 4*R*p, 13*S*p)-**91a-c**

a: R^1 = H, R^2 = *i*-Pr
b: R^1 = H, R^2 = *t*-Bu
c: R^1 = H, R^2 = Bn



(*S*, 4*S*p, 13*R*p)-**92,** R = *t*-Bu
(*S*, 4*S*p, 13*R*p)-**93**, R = Bn

(*S*, 4*R*p, 13*S*p)-**94**

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

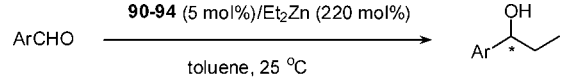
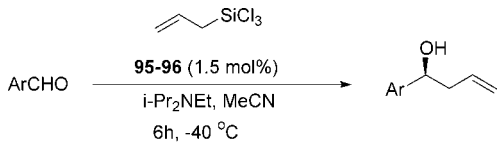


Table 1.42. Enantioselective Addition of Diethylzinc to Aldehydes Using Ligands 90−94

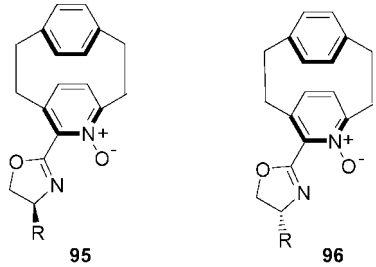
entry	Ar	ligand	time (h)	yield (%)	ee (%) (conf)
1	Ph	**90a**	5	94	91 (*R*)
2	Ph	**91a**	24	49	25 (*S*)
3	Ph	**90b**	7	93	94 (*R*)
4	Ph	**91b**	24	46	36 (*S*)
5	Ph	**90c**	5	94	91 (*R*)
6	Ph	**91c**	24	51	45 (*S*)
7	Ph	**92**	3.5	93	97 (*R*)
8	Ph	**93**	1.5	95	98 (*R*)
9	Ph	**94**	48	<5	
10	4-ClC_6H_4	**93**	2	96	97 (*R*)
11	4-BrC_6H_4	**93**	2	95	96 (*R*)
12	4-$MeOC_6H_4$	**93**	3.5	94	96 (*R*)
13	2-$MeOC_6H_4$	**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**.



95
95a: R = *t*-Bu
95b: R = Bn

96
96a: R = *t*-Bu
96b: R = Bn

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-FC_6H_4CHO.[67]

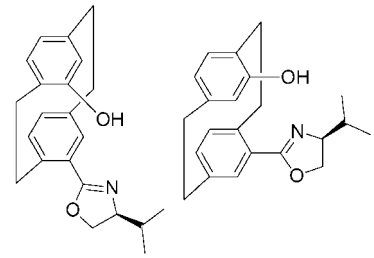
Bolm has reported the synthesis and application of hydroxyoxazolinyl paracyclophanes **97**−**100** in the asymmetric addition of diethylzinc to benzaldehyde (Scheme 1.41, Table 1.43).[68]

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).

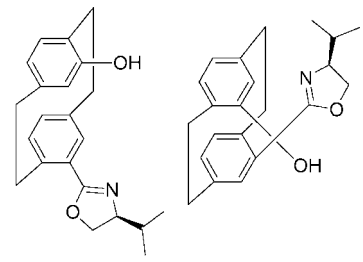
Wu and Zhang have reported the synthesis of ligand class **101** and their application in the enantioselective diethylzinc addition to *N*-diphenylphosphinoylimine (Scheme 1.48, Table 1.44).[69]

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

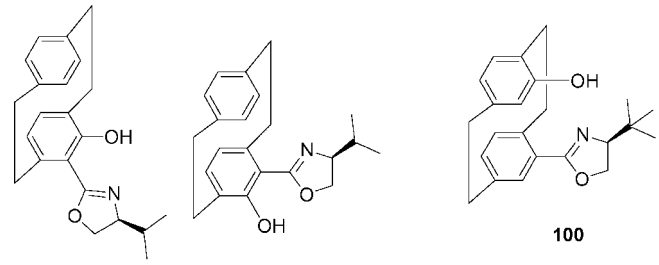
entry	substitution pattern	ligand	time (h)	yield (%)	ee (%) (conf)
1	*pseudo-geminal*	**97a**	24	93	11 (*S*)
2	*pseudo-geminal*	**97b**	2	78	78 (*R*)
3	*pseudo-ortho*	**98a**	24	74	35 (*S*)
4	*pseudo-ortho*	**98b**	4	96	51 (*S*)
5	*ortho*	**99a**	24	79	62 (*S*)
6	*ortho*	**99b**	48	72	44 (*R*)
7	*pseudo-geminal*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



97a **97b**
pseudo-geminal

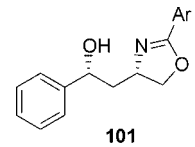


98a **98b**
pseudo-ortho



99a **99b** **100**
ortho *pseudo-geminal*

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).



101

a: Ar = Ph
b: Ar = *p*-FC_6H_4
c: Ar = *p*-ClC_6H_4
d: Ar = *p*-BrC_6H_4
e: Ar = Np

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

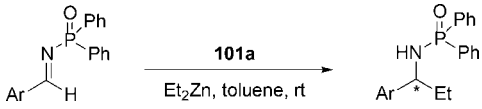
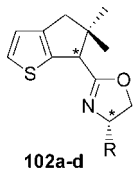


Table 1.44. Enantioselective Diethylzinc Addition of Aromatic Imines in the Presence of Ligand 101

entry	Ar	yield (%)	ee (%)
1	Ph	80	91
2	4-ClC_6H_4	76	88
3	4-BrC_6H_4	85	94
4	4-$MeOC_6H_4$	78	94
5	4-BnC_6H_4	81	95
6	piperonyl	83	92
7	β-naphthyl	84	86
8	4-FC_6H_4	trace	

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



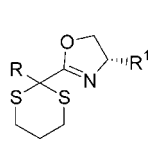
102a-d

a: (*R*), R = *i*-Pr
b: (*S*), R = *i*-Pr
c: (*R*), R = Bn
d: (*S*), R = Bn

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).

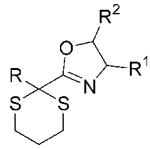
Ligands **103a**−**e** promoted good levels of enantioselectivities, with diethyl ether as solvent, resulting in slightly enhanced enantioselectivities compared to the case of toluene (Table 1.46, entries 2, 6, 8). Substituents on the aryl ring had a negligible effect on the stereochemical outcome of 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 Et_2Zn to enones (Scheme 1.49).[72]



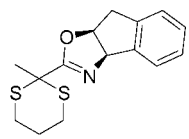
104a-d

a: R = H, R^1 = Bn
b: R = Me, R^1 = Bn
c: R = Me, R^1 = *i*-Pr
d: R =Me, R^1 = *t*-Bu



105a-b

a: R^1 = Me, R^2 = Ph
b: R^1 = Ph, R^2 = Ph



106

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

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

entry	ligand	solvent	time (h)	yield (%)	ee (%) (conf)
1	**102b**	CH_2Cl_2	70	91	70 (*S*)
2	**102d**	CH_2Cl_2	30	93	73 (*S*)
3[a]	**102d**	CH_2Cl_2	60	94	74 (*S*)

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

Scheme 1.49

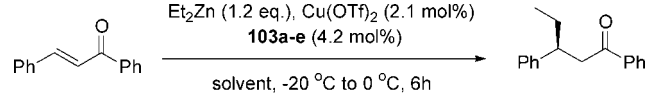
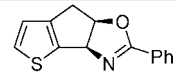
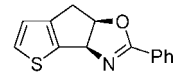
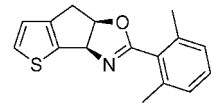
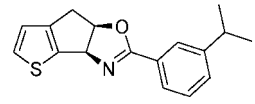
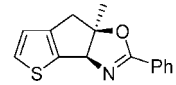
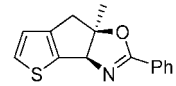
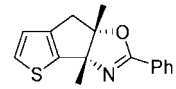
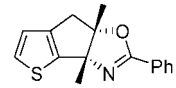
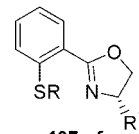


Table 1.46. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et_2Zn to Chalcone Using Ligands 103a−e

Entry	Ligand	Solvent	Yield (%)	ee (%) (Conf.)
1	 **103a**	toluene	61	51 (*S*)
2	 **103a**	Et_2O	51	53 (*S*)
3	 **103b**	toluene	58	47 (*S*)
4	 **103c**	toluene	55	43 (*S*)
5	 **103d**	toluene	58	70 (*R*)
6	 **103d**	Et_2O	49	79 (*R*)
7	 **103e**	toluene	58	58 (*R*)
8	 **103e**	Et_2O	40	65 (*R*)

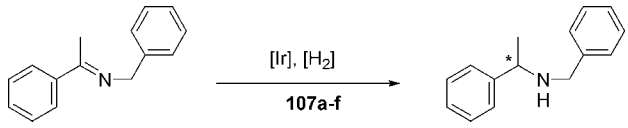
Claver has reported the facile two-step synthesis of oxazoline-thioether ligands **107**, from 2-fluorobenzonitrile.[73]



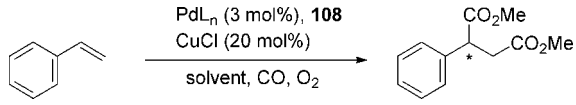
107a-f

a: R = Me, R^1 = Ph
b: R = Me, R^1 = *i*-Pr
c: R = Ph, R^1 = Ph
d: R = Ph, R^1 = *i*-Pr
e: R = *t*-Bu, R^1 = Ph
f: R = *t*-Bu, R^1 = *i*-Pr

Scheme 1.50

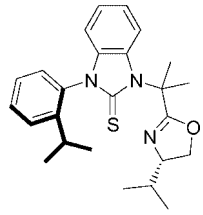


Scheme 1.51



The ligands were applied in the hydrogenation of *N*-(α-methyl)benzylidenbenzylamine (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]

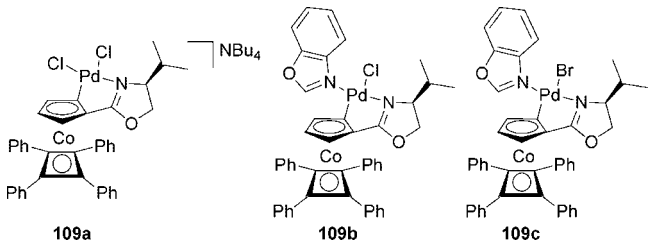


108

$[PdCl(C_3H_5)]_2$ 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

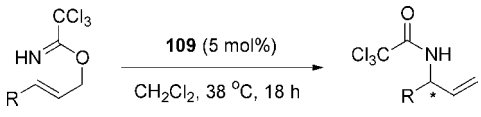
Overman has carried out extensive work on the asymmetric rearrangement of allylic trichloroacetimidates (Scheme 1.52, Table 1.48) using palladium(II) complexes of the COP family, for example **109a**−**c**. Each complex led to excellent enantiomeric excesses (>95%) for both substrates shown, with other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



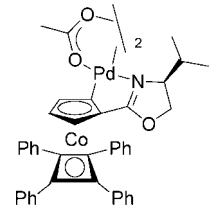
109a **109b** **109c**

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

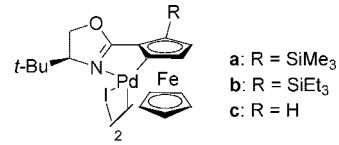


A range of ferrocenyloxazoline palladacycle catalysts **110** have been applied by Overman in the rearrangement of *N*-(4-trifluoromethylphenyl)benzimidates (Scheme 1.54, Table 1.49).[77]



109d

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).



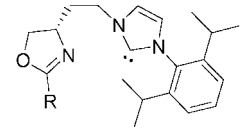
a: R = $SiMe_3$
b: R = $SiEt_3$
c: R = H

110

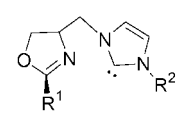
Mixed oxazoline−carbene ligands have been reported by the groups of Gade, Bellemin-Laponnaz, and Pfaltz.[78−80]

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).

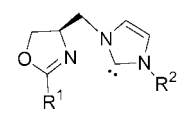


112a
R = Adamantyl



112

b: R^1 = *t*-Bu, R^2 = Me
c: R^1 = *t*-Bu, R^2 = *i*-Pr
d: R^1 = *t*-Bu, R^2 = Neopentyl
e: R^1 = *t*-Bu, R^2 = Isobutyl



112

f: R^1 = *t*-Bu, R^2 = Me
g: R^1 = *t*-Bu, R^2 = *i*-Pr
h: R^1 = *t*-Bu, R^2 = Neopentyl
i: R^1 = *t*-Bu, R^2 = Isobutyl

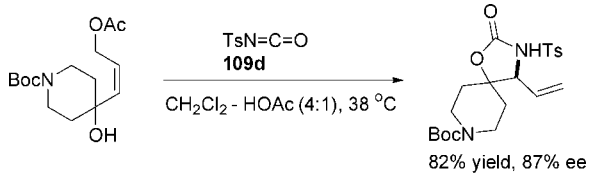
Table 1.47. Pd-Catalyzed Carbonylation of Styrene Using Thiourea Ligand 108

entry	PdL_n	Pd/**108**	solvent	temp (deg)	time (h)	yield (%)	ee (%)
1	$Pd(OAc)_2$	1:1	MeOH	50	24	77	60
2	$[PdCl(C_3H_5)]_2$	1:1	MeOH	20	52	84	67
3	$[PdCl(C_3H_5)]_2$	1:2	MeOH	20	52	95	75
4	$[PdCl(C_3H_5)]_2$	1:2	MeOH/THF	20	52	94	66

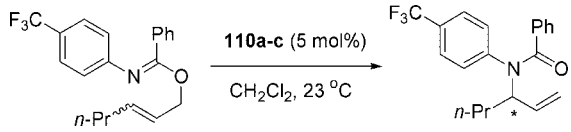
Table 1.48. Asymmetric Allylic Trichloroacetimidate Rearrangement Using 109a−c

entry	R (imidate)	catalyst	ee (%)
1	CH_2CH_2Ph	**109b**	97
2	CH_2CH_2Ph	**109a**	97
3	CH_2CH_2Ph	**109c**	96
4	Me	**109b**	95
5	Me	**109a**	95

Scheme 1.53



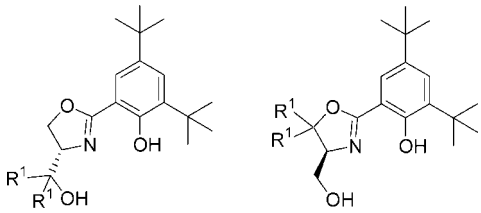
Scheme 1.54



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]



114
a: R^1 = Me
b: R^1 = Et
c: R^1 = Ph

114
d: R^1 = Me
e: R^1 = Et
f: R^1 = Ph

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 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.

Table 1.49. Enantioselective Imidate Rearrangement Using Palladacycle 110

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

Scheme 1.55

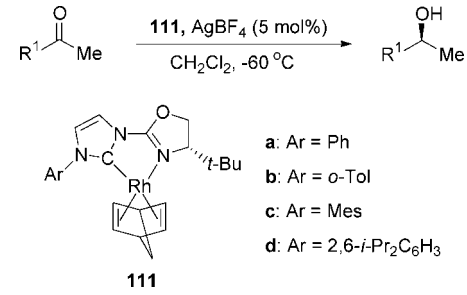
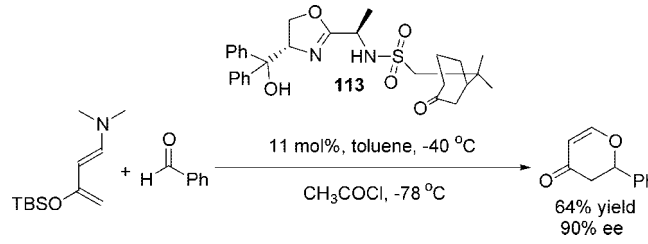


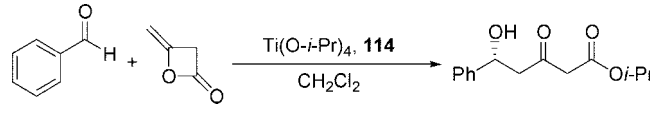
Table 1.50. Asymmetric Hydrosilylation of Ketones Using Catalyst 111c

entry	R^1	yield (%)	ee (%)
1	Ph	92	90
2	naphthyl	99	91
3	$4\text{-}MeOC_6H_4$	92	88
4	$4\text{-}FC_6H_4$	90	91
5	$H_3C(CH_2)_5$	95	79
6	*t*-Bu	70	95
7	adamantyl	96	89

Scheme 1.56



Scheme 1.57

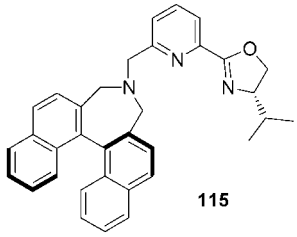


Iwasa has applied ligand **115**, which contains both axial chirality and carbon-centered chirality in the asymmetric fluorination of the β-keto ester 2-*tert*-butoxycarbonyl-1-indanone (Scheme 1.58), and achieved an enantiomeric

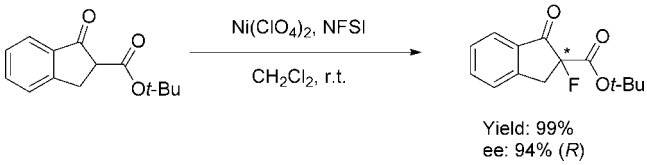
Table 1.51. Enantioselective Addition of Diketene to Benzaldehyde Using 114a−f

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



115



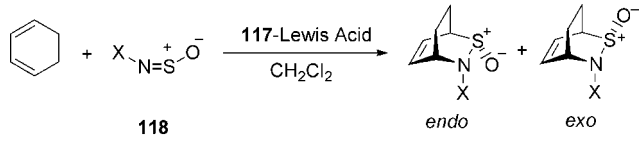
Yield: 99%
ee: 94% (*R*)

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

entry	ligand	R^1	R^2	yield (%)	ee (%) (*R*)
1	**116a**	Ph	Ph	99	85
2[a]	**116a**	Ph	Ph	99	91
3	**116b**	Bn	Ph	93	79
4	**116c**	4-ClC_6H_4	Ph	85	63
5	**116d**	4-$MeOC_6H_4$	Ph	81	75
6	**116e**	2,4,6-$Me_3C_6H_2$	Ph	95	87
7	**116f**	3-$CF_3C_6H_4$	Ph	83	54
8	**116g**	*t*-Bu	Ph	91	37

[a] Cs_2CO_3/CH_2Cl_2 used as the base/solvent system.

Scheme 1.59

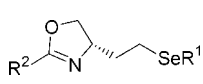


118

a: X = Cbz
b: X = Ts

excess of 94% when $Ni(ClO_4)_2$ 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]



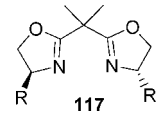
116a-j

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 C_2-symmetric bis(oxazoline) ligands by Desimoni and Jørgensen, only applications of these ligands reported from 2006 onward will be described here.[85]



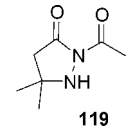
117

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

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]



119

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).

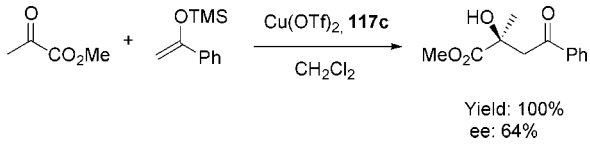
Zhou has achieved enantiomeric excesses of up to 90% in the asymmetric Friedel−Crafts alkylation of indole with nitroalkenes employing $Zn(OTf)_2$ complexes of **117c**.[91]

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]

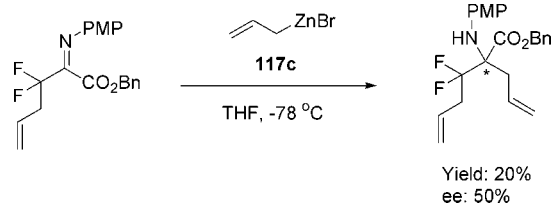
Table 1.53. Enantioselective Hetero-Diels−Alder Reaction Using Ligand 113c

entry	*N*-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

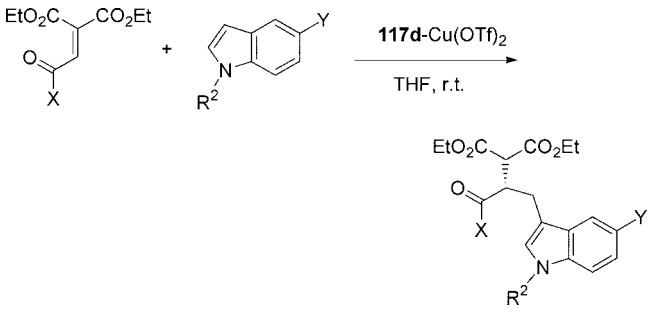


Table 1.54. Enantioselective Addition of Indoles Using Ligand 117d

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

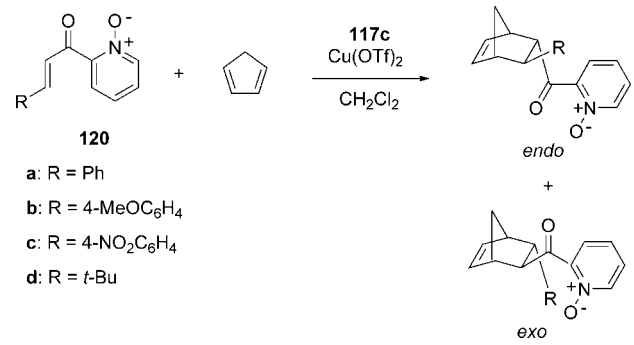


Table 1.55. Enantioselective Diels−Alder Reaction Using Cu(OTf)$_2$−117c

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]

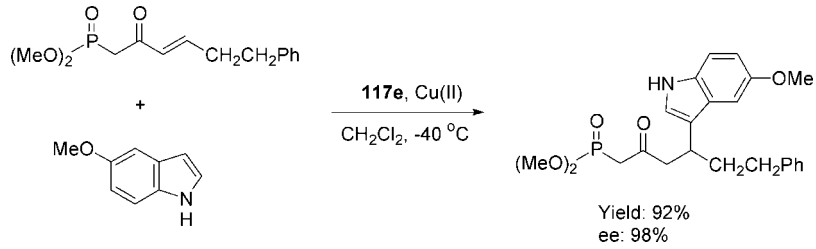
Nakamura and Toru have applied ligands **117c** and **117e** in the enantioselective Mannich-type reaction of imines in the presence of Lewis acids (Scheme 1.66).[96] The nature of the aromatic substitution on the imine group proved crucial, with only 2-pyridylimines giving satisfactory enantioselectivities. Phenyl-subsituted 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.

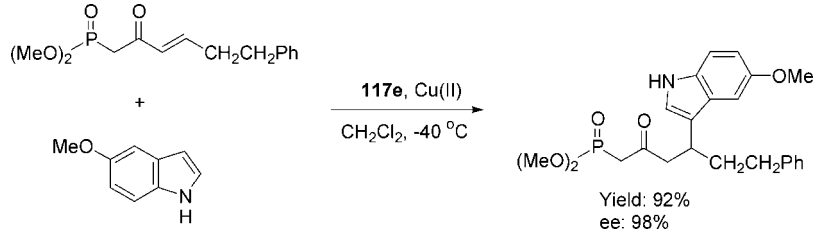
(*R*,*R*)-**117c** has been applied by Gade and Bellemin-Laponnaz in the copper-catalyzed α-amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate, and they obtained a yield of 93% and an enantiomeric excess of 98% (Scheme 1.68).[98]

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.

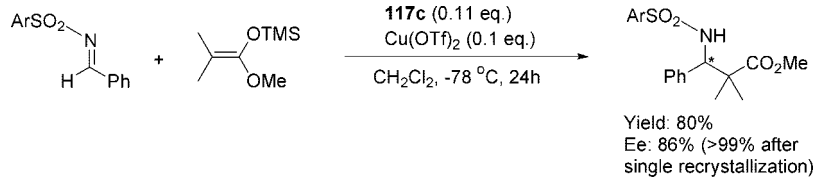
Scheme 1.64



Scheme 1.65



Scheme 1.66



Scheme 1.67

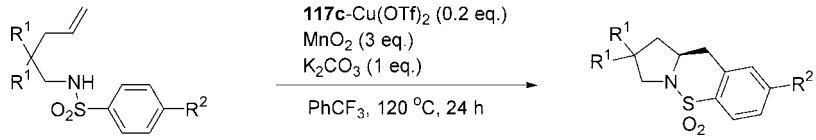
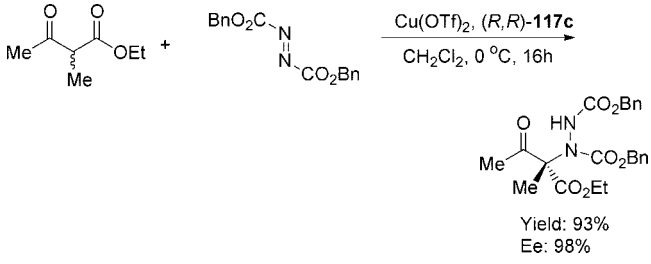


Table 1.56. Cu-Catalyzed Enantioselective Carboamination Using Ligand 117c

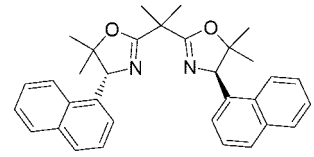
entry	substrate	yield (%)	ee (%)
1	R^1 = Me, R^2 = Me	85	92
2	R^1 = Me, R^2 = H	73	92
3	R^1 = Me, R^2 = Cl	45	92
4	R^1 = Me, R^2 = OMe	75	94
5	R^1 = Ph, R^2 = Me	78	94
6	R^1 = $CH_2(CH_2)_2CH_2$, R^2 = Me	83	92
7	R^1 = $CH_2(CH_2)_3CH_2$, R^2 = Me	68	92

Scheme 1.68



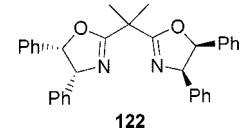
Itagaki has prepared and applied ligand **121** in the copper-catalyzed asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) (Scheme 1.69, Table 1.57).[99]

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/Ph_3CPF_6/**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 %.



121

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]



122

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

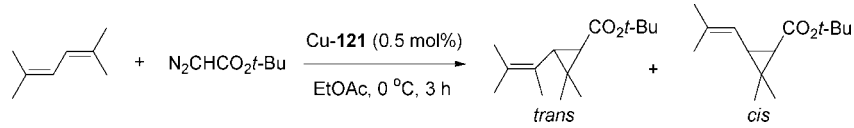
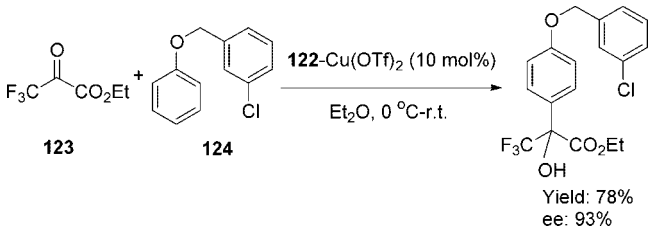


Table 1.57. Asymmetric Cyclopropanation of DMHD Using Cu(1) Complexes of 121

entry	catalyst system	yield (%)	*trans*/*cis*	ee (*trans*) (%)	ee (*cis*) (%)
1	Cu(OTf)/**121**	83	87:13	96	71
2	$Cu(CH_3CN)_4PF_6$/**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	$CuCl/Ph_3CPF_6$/**121**	91	88:12	96	74
6[a]	$CuCl/Ph_3CPF_6$/**121**	92	88:12	96	71

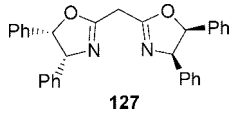
[a] 0.2 mol % of catalyst utilized.

Scheme 1.70



acids and solvents resulted in an optimum enantiomeric excess of 93% using $Cu(OTf)_2$ and toluene/CH_2Cl_2 (4:1).

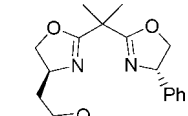
These reaction conditions were then applied to the addition of diene **125** to a range of aldehyde substrates, with the most successful substrate being 6-phenyl-*N*-oxypyridine-2-carbaldehyde, which gave the desired product in 49% yield and with an enantiomeric excess of 95%.



127

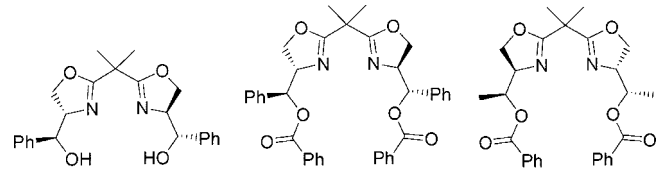
Ligand **127** is structurally related to **122** and has been applied by Singh in the enantioselective Friedel−Crafts alkylation of indoles with nitroalkenes to afford enantiomeric excess of 57−86% for the alkylation of a range of indoles using various nitroolefins.[101]

The C_1-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]

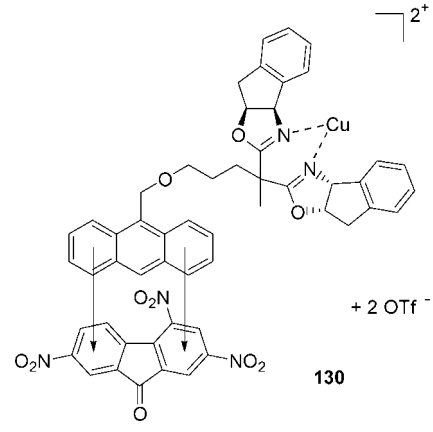


128

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.

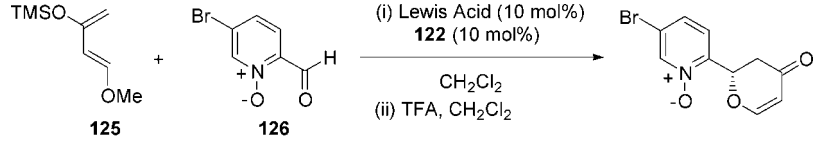


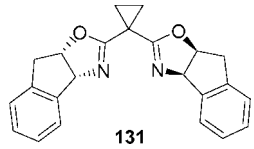
The charge-transfer complex **130** has been applied by Schulz in the copper-catalyzed Diels−Alder reaction between cyclopentadiene and 3-acryloyloxazolidin-2-one with a diastereoselectivity of up to 97% and an enantiomeric excess up to 94%.[105] No loss of activity or stereoselectivity was observed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





131

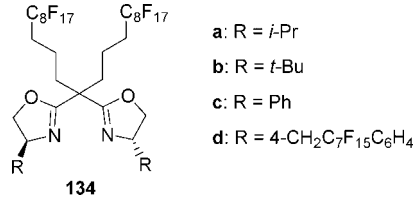
Lautens has applied ligand **131** in the enantioselective catalytic ring expansion of methylenecyclopropane carboxamides, with the highest enantioselectivity of 86% reported for the reaction of cyclopropane **132** with *N*-tosylaldimine **133**, using a 1.5:1 ratio of 10:MgI_2 (Scheme 1.72).[106]

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 PDE_4 inhibitors.[108]

The C_2-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]

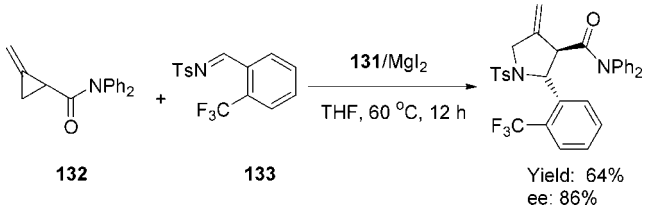
In an extension to this work, Sinou has also reported the application of **134c** in the copper-catalyzed glyoxylate-ene reaction and using a solid/liquid extraction methodology for recycling the catalyst.[110] These catalysts gave moderate to high enantioselectivities and were successfully reused. The 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).



134

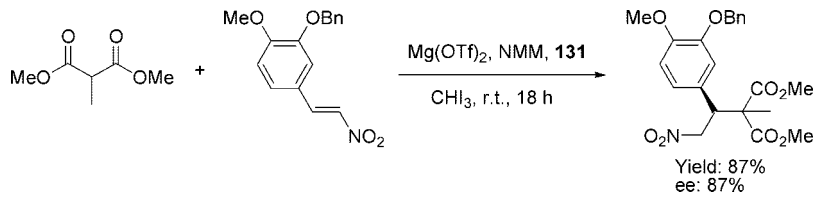
Ligand **134d** was applied in the palladium-catalyzed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate with quantitative yield and an enantiomeric excess of 92%. The enantioselective allylic oxdidation of cyclohexene utilizing Cu-**134d** led to a yield of 43% and ee of 50%.[111]

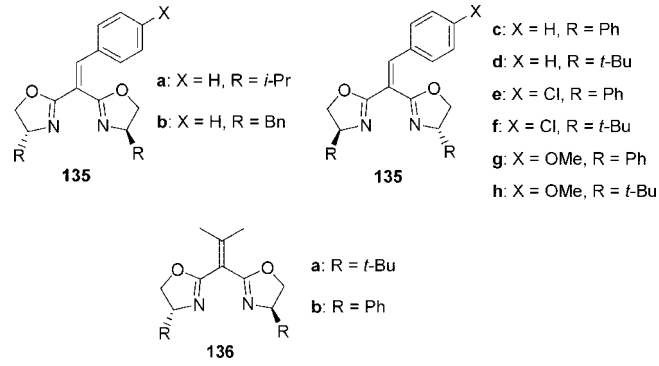
Scheme 1.72



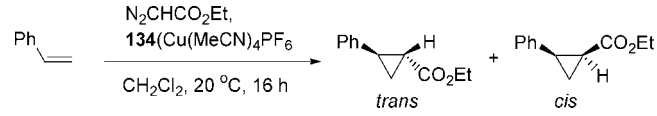
132 133

Scheme 1.73

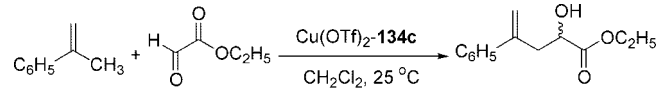




Scheme 1.74



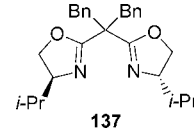
Scheme 1.75



Run	Time(h)	Yield(%)	Ee(%)
1	34	78	87
2	24	76	84
3	24	76	84
4	24	75	87
5	48	78	88

Burke has developed arylid-Box **135**, a new family of chiral bis(oxazolines) containing an arylidene bridging unit. The ligands have been successfully applied in the Cu(1)-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 cylcopropanation 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]

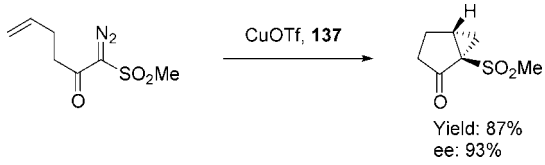


137

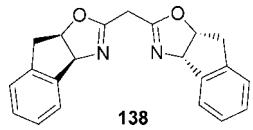
Ligand **137** was applied by Nakada in the intramolecular enantioselective cyclopropanation of 2-diazo-3-oxo-6-hepenoic mesityl ester with an isolated yield of 87% and an enantiomeric excess of 93% (Scheme 1.76).[114]

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

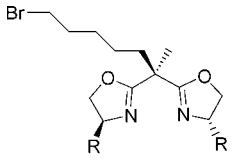


oselectivity of 95% with a good yield of 74% (Table 1.58, entry 1). Increasing the size of the propiolate to benzyl propiolate gave a significantly lower ee of 86% (Table 1.58, entry 2). A similar trend was observed using ynones, with the smaller 1-pentyn-3-one giving the highest ee of 99% (Table 1.58,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

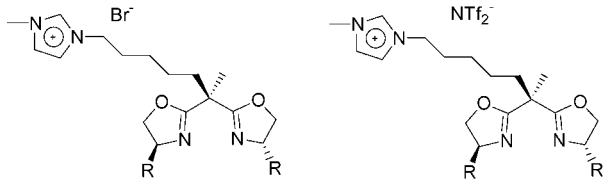


138

This IndaBOX ligand **138** has also been utilized by Kim in the copper-catalyzed Diels−Alder reaction in ionic liquids.[116] Using [Bmim]SbF_6 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]



139
a: R = *i*-Pr
b: R = *t*-Bu

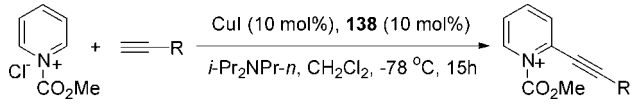


140
a: R = *i*-Pr
b: R = *t*-Bu

140
c: R = *t*-Bu

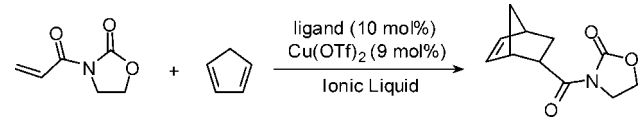
A range of new bis(oxazolines) **139** and **140** have been applied in the enantioselective Cu-catalyzed Diels−Alder reaction (Scheme 1.77). The optimum results were obtained

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



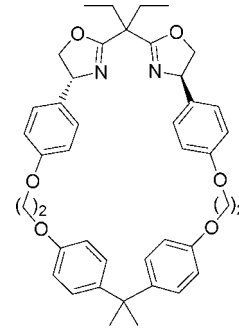
entry	R	yield (%)	ee (%)
1	CO_2CH_3	74	95
2	CO_2Bn	81	85
3	$COCH_3$	69	93
4	$COCH_2CH_3$	65	99
5	$CO(CH_2)_3CH_3$	70	91
6	$CO(CH_2)_4CH_3$	68	90

Scheme 1.77



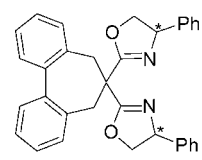
using ligands **139b** and **140c**, which both gave 100% conversion and enantioselectivities (*endo*) of 93% and 84%, respectively.[118]

A range of chiral macrocylic 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]

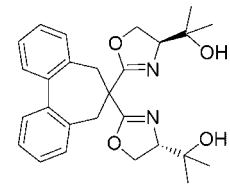


141

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).



142



143

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-chlorobenzaldehdye 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]

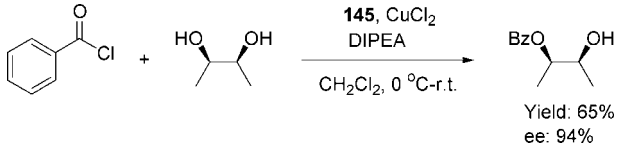
These ligands have been applied in the enantioselective cyclopropanation of styrene (Scheme 1.74, Table 1.59).

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

Table 1.59. Application of Borabox 144 in the Enantioselective Cyclopropanation of Styrene

entry	ligand	yield (%)	*cis*:*trans*	ee (*cis*) (%)	ee (*trans*) (%)
1	**144a**	77	29:71	58	65
2	**144b**	84	30:70	66	70
3	**144c**	68	32:68	24	33
4	**144d**	75	28:72	59	72
5	**144e**	79	28:72	78	66
6	**144f**	89	32:68	68	77

Scheme 1.78



Scheme 1.79

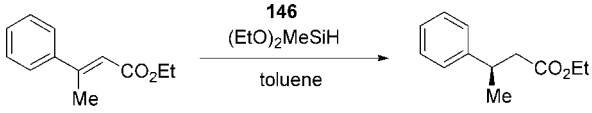
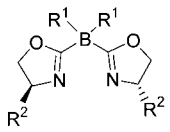


Table 1.60. Enantioselective Conjugate Reduction Using 146

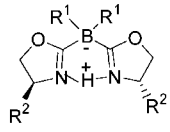
entry	complex	temp (°C)	time (h)	yield (%)	ee (%)
1	**146a**	60	1	96	96
2	**146a**	30	1	96	97
3	**146b**	60	5	97	95
4	**146b**	40	24	99	95
5[a]	**146b**	60	2	97	95
6	**146c**	60	2	96	73

[a] $AgBF_4$ (0.02 mmol) added to reaction.

higher enantioselectivities (Table 1.59, entries 2, 4, 6), but this effect was less pronounced than in the original BOX ligands. The *cis*:*trans* ratios were moderate, with ligands **144d** and **144e** giving the highest *trans* preference (Table 1.59, entries 4, 5).



144



145

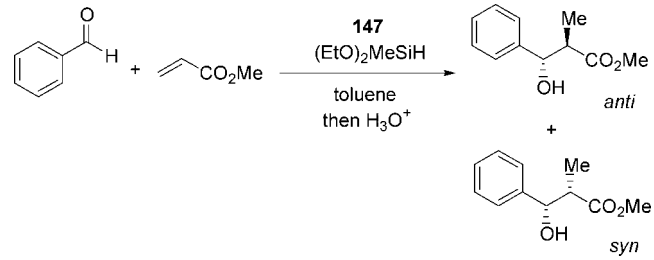
a: R^1 = Ph, R^2 = *i*-Pr
b: R^1 = Ph, R^2 = *t*-Bu
c: R^1 = Cy, R^2 = *i*-Pr
d: R^1 = Et, R^2 = *t*-Bu
e: R^1 = Cy, R^2 = *t*-Bu
f: R^1 = Ar, R^2 = *t*-Bu
g: R^1 = Bn, R^2 = Bn
h: R^1 = Ar, R^2 = Bn
Ar = 3,5-bis(trifluoromethyl)phenyl

The protonated derivatives **145** have also been described by Pfaltz and applied in the enantioselective monobenzoylation of *meso* 1,2-diols, with **145h** being the optimum ligand for this process (Scheme 1.78). This work has been applied

Table 1.61. Enantioselective Reductive Aldol Reaction Using 147

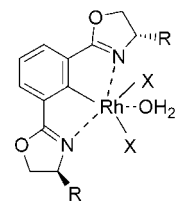
entry	complex	yield (%)	*anti*:*syn*	ee (*anti*) (%)	ee (*syn*) (%)
1	**147a**	93	88:12	87	1
2	**147b**	97	87:13	83	2
3	**147c**	95	85:15	77	32
4	**147d**	95	85:15	77	28
5	**147e**	95	87:13	86	1

Scheme 1.80



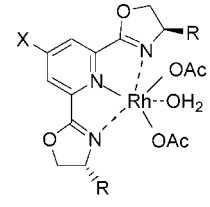
in the kinetic resolution of diols and pyridyl alcohols, with ligand **145h** again proving particularly effective.

Rhodium complexes **146** bearing two oxazoline rings linked by a phenyl moiety have been applied by Nishiyama in the asymmetric conjugate reduction of α,β-unsaturated esters using diethoxymethylsilane as the hydrogen donor (Scheme 1.79, Table 1.60).[123]



146

a: R = *i*-Pr, X = OAc
b: R = *i*-Pr, X = Cl
c: R = Bn, X = Cl



147

a: R = *i*-Pr, X = NO_2
b: R = *i*-Pr, X = H
c: R = *i*-Pr, X = Me
d: R = *i*-Pr, X = OMe
e: R = Bn, X = NO_2

The reduction of the ester to the desired chiral product was carried out using acetate complex **146a** in 96% yield and 96% ee (*R*) (Table 1.60, entry 1). At 30 °C the enantioselectivity increased slightly to 97% (Table 1.60, entry 2). The chloride complex **146b** exhibited a slightly lower catalytic activity but gave similar levels of enantioselectivity (Table 1.60, entries 3, 4). The addition of $AgBF_4$ led to a much faster reaction time while maintaining the stereoselectivity (Table 1.60, entry 5). Replacing the *i*-Pr groups on the oxazolines with Bn groups (**146c**) led to a significant decrease in enantioselectivity to 73% (Table 1.60, entry 6). Catalyst **146a** was applied in the reduction of a range of α,β-unsaturated esters, with enantioselectivities of up to 98% reported.

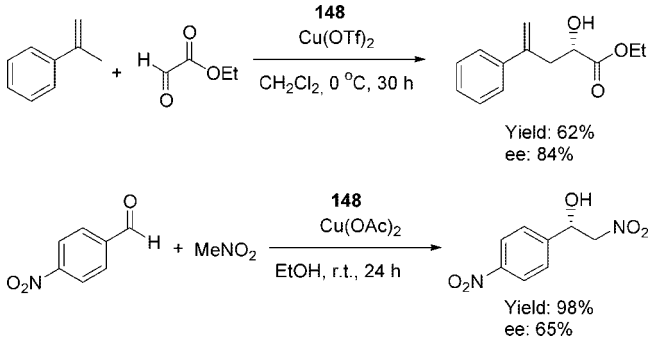
This work was later extended to include the enantioselective reduction of α,β-unsaturated aldehydes, with Rh complex **146a** reducing (*E*)-β-methylcinnamaldehyde with an enantioselectivity of 91%.[124]

Nishiyama has also prepared the analogous pyridine complexes **147** and applied them in the enantioselective reductive aldol reaction (Scheme 1.80, Table 1.61).[125]

The reactions were complete within 30 min in all cases to give the aldol product in high yield (93−97%). There were little differences in the *anti*:*syn* ratios obtained (85:15 to 88:12). Catalysts **147a** and **147e** gave higher enantiomeric excesses of the *anti* product, 87% and 86%, respectively (Table 1.61, entries 1, 5). The ee's of the *syn* product were poor in all cases.

The novel chiral spiro ligand **148** has been developed by Sasai and applied in a range of asymmetric reactions (Scheme 1.81).[126]

Scheme 1.81



Scheme 1.82

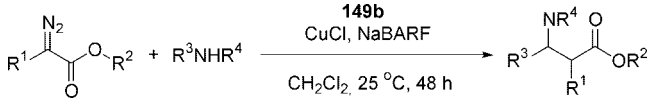
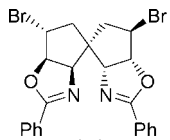


Table 1.62. Catalytic Asymmetric NH Insertion Using Cu Complexes of 149b

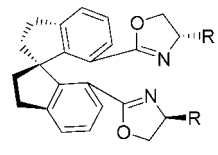
entry	R^1	R^2	R^3	R^4	yield (%)	ee (%)
1	Me	Et	Ph	H	94	98
2	Me	Et	4-ClC_6H_4	H	92	98
3	Me	Et	4-BrC_6H_4	H	95	98
4	Me	Et	3-BrC_6H_4	H	96	98
5	Me	Et	2-$MeOC_6H_4$	H	86	98
6	Me	Et	1-naphthylC_6H_4	H	89	98
7	Me	Et	2-naphthylC_6H_4	H	91	98

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]



148

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.



149

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

The application of the Spirobox ligand (S_a,*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

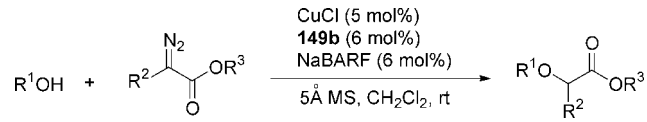


Table 1.63. Asymmetric Catalytic Carbenoid Insertion into O−H Bonds of Phenols Using Ligand 149b

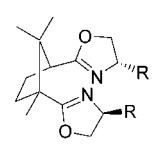
entry	R^1	R^2	R^3	yield (%)	ee (%)
1	Ph	Me	Et	87	99
2	2-MeC_6H_4	Me	Et	71	98
3	2-$MeOC_6H_4$	Me	Et	68	95
4	2-PhC_6H_4	Me	Et	83	99.2
5	3-MeC_6H_4	Me	Et	79	99.3
6	3-$MeOC_6H_4$	Me	Et	71	99
7	3-BrC_6H_4	Me	Et	78	99
8	3-PhC_6H_4	Me	Et	82	99
9	4-MeC_6H_4	Me	Et	88	99
10	4-$MeOC_6H_4$	Me	Et	78	99
11	4-*t*-BuC_6H_4	Me	Et	70	98
12	4-ClC_6H_4	Me	Et	83	99.1
13	4-BrC_6H_4	Me	Et	85	99.6
14	4-$MeO_2CC_6H_4$	Me	Et	62	99
15	2,4-$Me_2C_6H_3$	Me	Et	80	99
16	3,5-$Ph_2C_6H_3$	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	*t*-Bu	80	99

the corresponding α-aryloxypropionates in good yields and excellent enantioselectivities of ≥95% regardless of the nature or position of the subsituents (Table 1.63, entries 1−18). Aliphatic alcohols also underwent O−H insertion, although with lower enantioselectivities (Table 1.63, entries 19, 20). Changing R^2 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 sensititve to the size of the R^3 group of the α-diazoester, with similar results obtained with both ethyl and *tert*-butyl groups.

The cyclohexane-linked bis(oxazoline) ligand **150** (cHBOX) 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 cylopropanation 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]

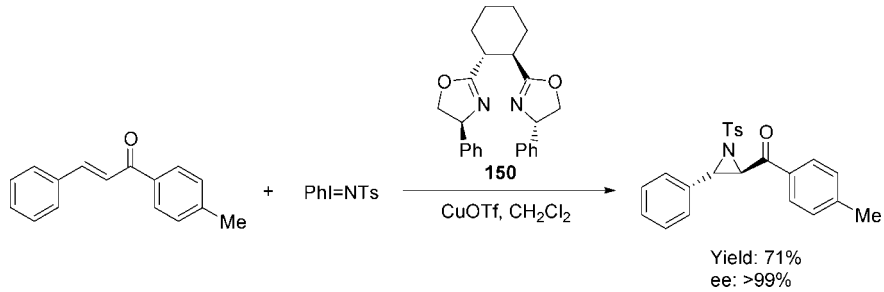


151

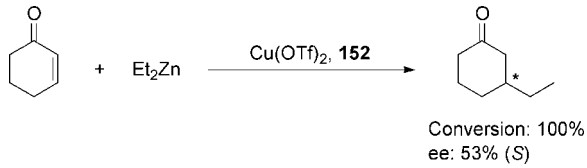
a: R = *i*-Pr
b: R = Ph
c: R = Bn

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]

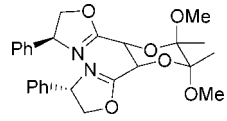
Scheme 1.84



Scheme 1.85



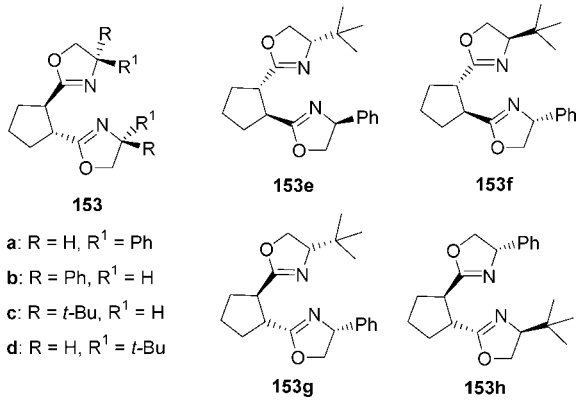
Bolm has developed a range of C_2-symmetric and C_1-symmetric bis(oxazoline) containing ligands **153** for application in a range of asymmetric metal-catalyzed transformations. There are relatively few examples of C_1-symmetric bis(oxazoline)-containing ligands reported.[56]



152

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).



153

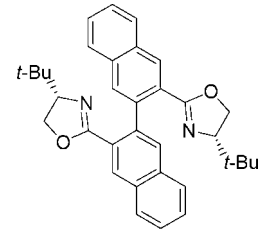
a: R = H, R^1 = Ph
b: R = Ph, R^1 = H
c: R = *t*-Bu, R^1 = H
d: R = H, R^1 = *t*-Bu

153e **153f** **153g** **153h**

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]

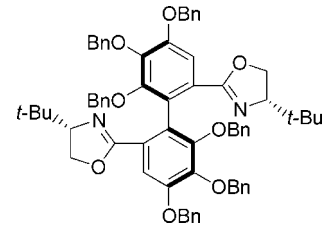
Bis(oxazoline) ligands containing a biaryl backbone have recently been developed and applied with some success in asymmetric catalysis.

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]



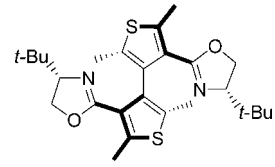
154

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]



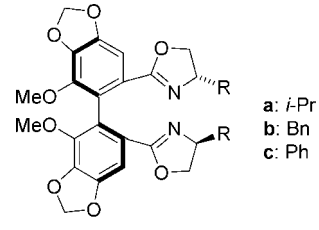
155

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]



156

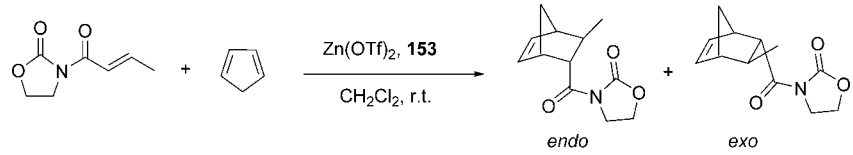
Ligand class **157** has been applied in the asymmetric pinacol coupling reaction. Ligand **157a**, with *i*-Pr-substituted oxazoline rings, afforded the highest enantiomeric excess of 81% for the pinacol coupling of benzaldehyde and was subsequently applied to the pinacol coupling of a range of aromatic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



a: *i*-Pr
b: Bn
c: Ph

157

Scheme 1.86



153b: Yield: 99%
endo:*exo* 85:15
ee: 71%

Scheme 1.87

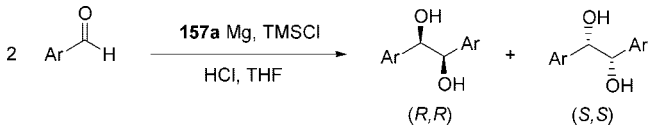
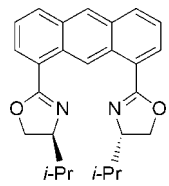


Table 1.64. Asymmetric Pinacol Coupling of Aromatic Aldehydes Using 157a

entry	aldehyde	yield (%)	ee (%)
1	C_6H_5CHO	81	81 (*R*,*R*)
2	4-MeC_6H_4CHO	84	83 (*R*,*R*)
3	4-$MeOC_6H_4CHO$	86	79 (*R*,*R*)
4	1-naphthaldehyde	86	78 (*R*,*R*)

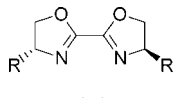
The asymmetric pinacol couplings proceeded with excellent yield and very good enantioselectivity. The best substrate was *p*-tolualdehyde, which gave the desired pinacol product in 84% yield and 83% enantiomeric excess, with no *meso* product detected (Table 1.64, entry 2).

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]



158

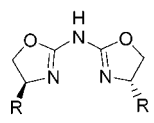
Bis(oxazoline) ligands **159**, in which the oxazoline rings are joined directly to each other, have been applied in the [2,3]-Wittig rearrangement (Scheme 1.89) and cycloisomerization of 1,6-enynes (Scheme 1.90).[138]



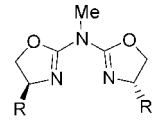
159

a: R = *i*-Pr
b: R = Ph

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



160



161

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

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]

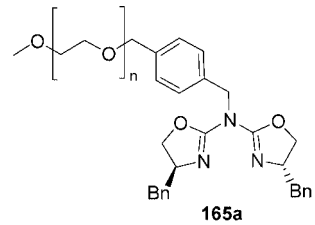
Ligand **161c** was found to be slightly more active than **161b**, while maintaining the same level of enantioselection (Table 1.65, entries 1, 2), and was thus investigated in the conjugate reduction of a range of aromatic and aliphatic aldehydes. Excellent yields and enantioselectivities were obtained 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]

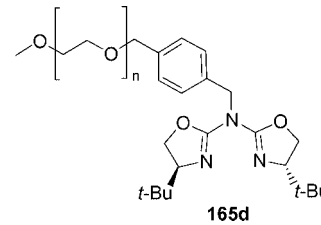
Ligand classes **160** and **161** were applied by Reiser in the Cu(II)-catalyzed benzoylation of (*rac*)-**163** to monobenzylated product **164** (Scheme 1.94, Table 1.66).[142]

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 $CuCl_2$ and ligand.

Subsequent immobilization of **160a** onto $MeOPEG_{5000}$ afforded **165a**, which was repeatedly applied in the asymmetric benzoylation of **163** and afforded a yield of 41% and an enantiomeric excess of 98% after 5 cycles.



165a

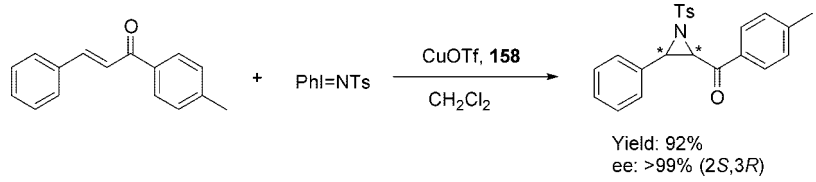


165d

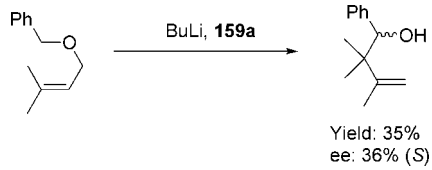
Application of ligand **165d** in the cyclopropanation of styrene has been reported to give enantiomeric excesses of up to 91%.[143]

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

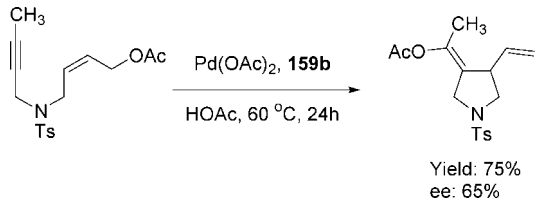
Scheme 1.88



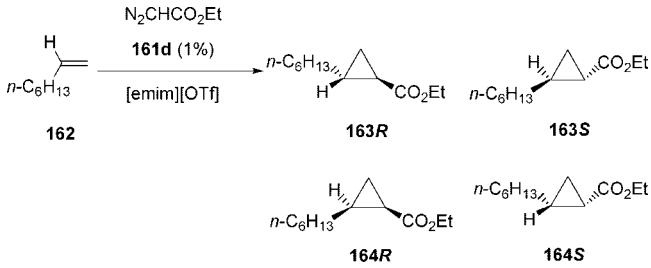
Scheme 1.89



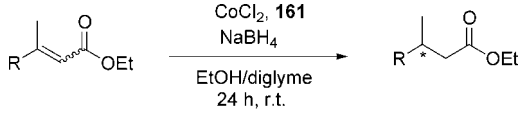
Scheme 1.90



Scheme 1.91



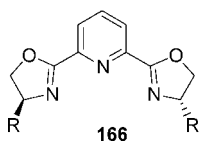
Scheme 1.92



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, R^1 = H]. Using these optimal conditions, **160b** was applied to the addition of a range of malonates to a series of indoles, with [R = *p*-ClC_6H_4, R^1 = 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]

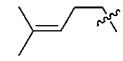
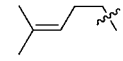
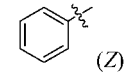
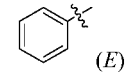
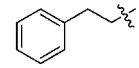
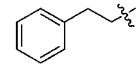
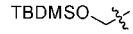
The application of **166** in the enantioselective Diels−Alder reaction of **167** and diene **168** has been described by Shibasaki and Kanai (Scheme 1.96, Table 1.67).[146]



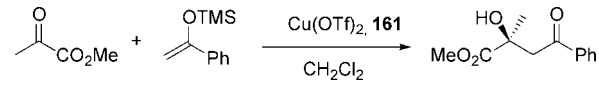
a: R = Bn
b: R = *i*-Pr
c: R = Ph
d: R = *t*-Bu
e: R = adamantyl
f: R = indene

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

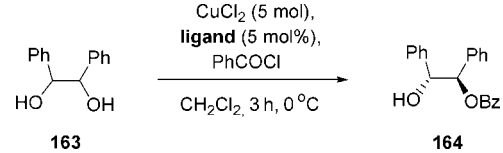
Table 1.65. Enantioselective Conjugate Reduction of α,β-Unsaturated Esters Using 161b and 161c

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

Scheme 1.93



Scheme 1.94



A high enantioselectivity was obtained when the catalyst was prepared from $FeBr_3$ and $AgSbF_6$ in a 1:2 ratio (Table 1.67, entry 4). The best result was obtained when the reaction was carried out using $FeBr_3$ and $AgSbF_6$ at −50 °C, which gave an ee of 92%, with a chemical yield of 75% (Table 1.67, entry 6).

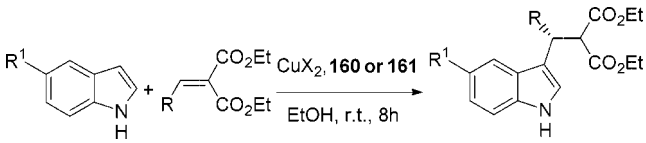
Pybox-*i*-Pr (**166b**) has been applied by Suga in the asymmetric cycloaddition of 2-benzopyryrium-r-olate **169**

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	*R,R*	160
2	**160b**	38	68	*R,R*	7.8
3	(*ent*)-**160c**	48	87	*S,S*	35
4	**160d**	49	33	*R,R*	2.6
5	**161a**	45	99	*R,R*	501
6[a]	**161a**	49	99	*R,R*	751
7	(*ent*)-**161c**	46	93	*S,S*	66

[a] Reaction performed with 0.5 mol % $CuCl_2$ and 0.5 mol % **161c**.

Scheme 1.95



Scheme 1.96

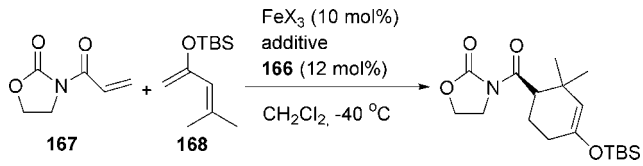
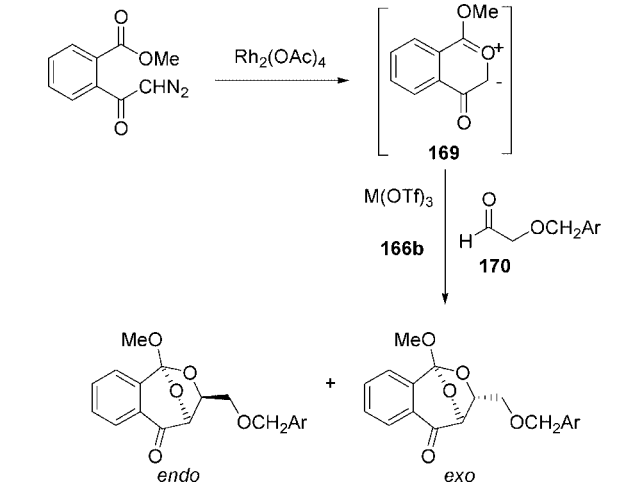


Table 1.67. Enantioselective Diels−Alder Reaction Using 166

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



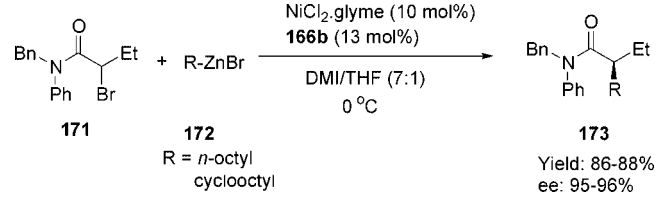
with benzyloxacetaldehyde derivatives **170** (Scheme 1.97, Table 1.68).[147]

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

					ee (%)	
entry	Ar	temp (°C)	yield (%)	*endo*:*exo*	*endo*	*exo*
1	Ph	−10	96	88:12	91	18
2	2-$MeOC_6H_4$	−10	82	85:15	82	15
3	4-$MeOC_6H_4$	−10	53	91:9	89	12
4	4-FC_6H_4	−10	97	82:18	93	22
5	4-ClC_6H_4	−25	84	73:27	86	10
6	4-BrC_6H_4	−25	77	67:33	83	5

Scheme 1.98



Scheme 1.99

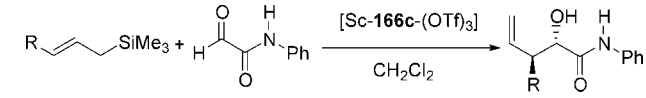
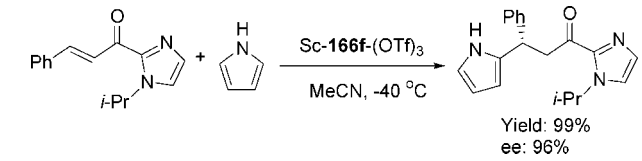


Table 1.69. Enantioselective Sakurai−Hosomi Additions Using a Scandium Complex of Ligand 166c

entry	R	cat. loading	temp (°C)	*anti*:*syn*	yield (%)	ee (%)
1	Me	10	−20	26:1	89	95
2	(*Z*)-Me	10	−20	1:4	76	94
3	Et	10	−20	32:2	76	91
4	*n*-Pr	10	−20	29:1	71	93
5	Ph	15	r.t.	99:1	67	99
6	4-MeC_6H_4	15	r.t.	99:1	75	99
7	4-$MeOC_6H_4$	15	r.t.	99:1	64	97
8	4-FC_6H_4	15	r.t.	99:1	73	99
9	2-MeC_6H_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

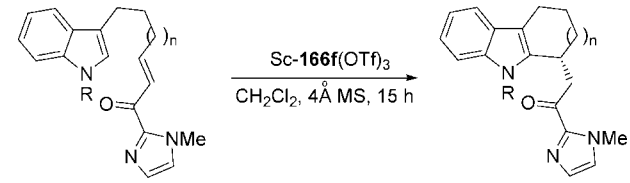
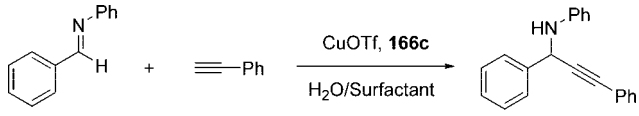


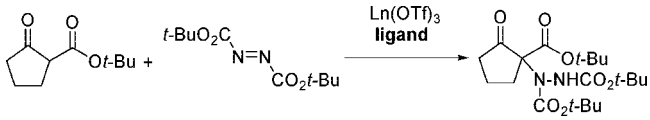
Table 1.70. Intramolecular Alkylations of Tethered Indoles Using Scandium-Triflate Complexes of 166f

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]

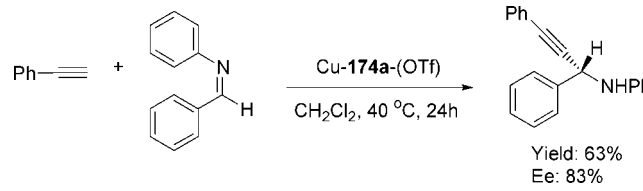
Scandium complexes of ligand **166f** has also been applied by Evans in a wide range of enantioselective Friedel−Crafts alkylations utilizing a variety of indoles and various β-substituted α,β-unsaturated phosphonates and α,β-unsaturated 2-acyl imidazoles.[151] The ligand was also applied in the more 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.

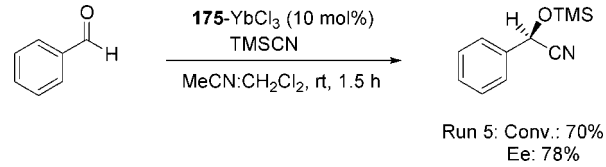
Ligand **166c** was applied by Li and Chan in the asymmetric addition of alkynes to imines in water (Scheme 1.102). In the absence of surfactant, an enantioselectivity of 80% and yield of 77% were obtained. However, adding stearic acid led to an increase in both yield and enantioselectivity to 86% and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

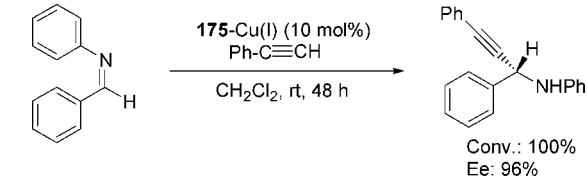
Scheme 1.104



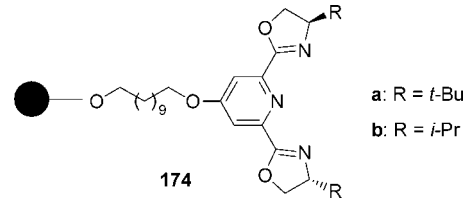
Scheme 1.105



Scheme 1.106



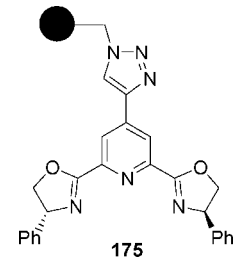
Polymer-bound versions of type **174** derived from the Pybox ligand class **166** have also been applied in asymmetric catalysis. Portnoy has applied **174a** in the reaction of phenyl acetylene and benzilideneaniline (Scheme 1.104) and obtained an enantiomeric excess of 83%.[154]



174

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]



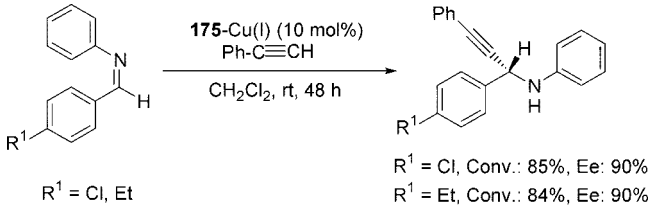
175

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

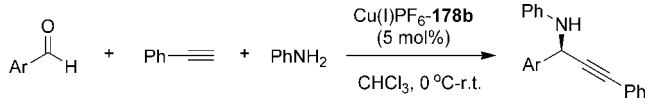
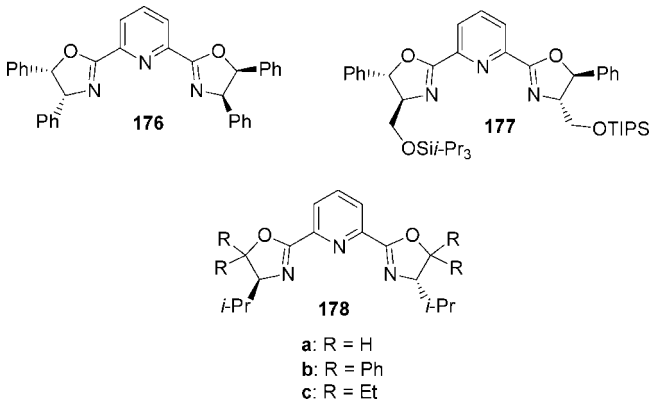


Table 1.71. Enantioselective Propargylamine Synthesis Using Ligand 178b

entry	Ar	time (h)	yield (%)	ee (%) (conf)
1	4-*i*-PrC_6H_4	20	89	95 (*R*)
2	4-$NO_2C_6H_4$	28	82	94 (*R*)
3	3-MeC_6H_4	12	91	96 (*R*)
4	4-ClC_6H_4	24	94	96 (*R*)
5	3-FC_6H_4	28	85	93 (*R*)
6	3-BrC_6H_4	26	92	91 (*R*)
7	3,5-$(Me)_2C_6H_3$	12	98	95 (*R*)
8	3-Cl-4-FC_6H_3	26	97	91 (*R*)
9	2-ClC_6H_4	12	93	98 (*S*)

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

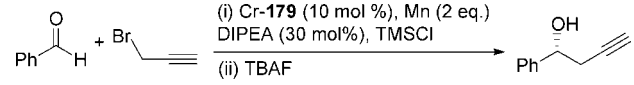
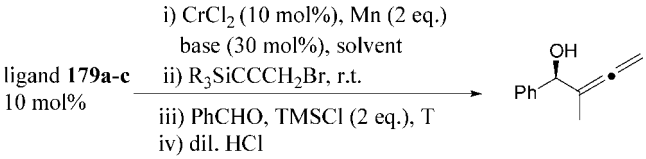


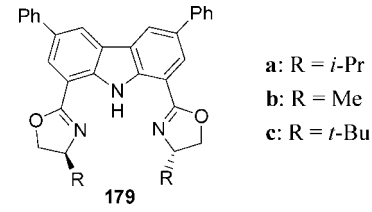
Table 1.72. Asymmetric NHK Propargylation using Ligands 179a−c

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

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-ClC_6H_4CHO.

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_3Si	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_2Cl_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_2CO_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

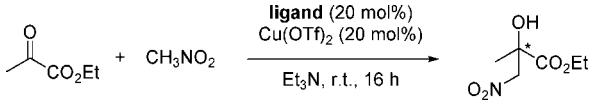
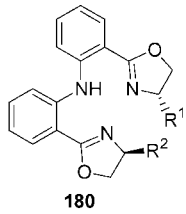


Table 1.74. Enantioselective Henry Reaction Using Ligands 180b and 180d

entry	ligand	solvent	yield (%)	ee (%) (*S*)
1	**180b**	$ClCH_2CH_2Cl$	32	76
2	**180b**	CH_2Cl_2	43	80
3[a]	**180b**	CH_2Cl_2	29	82
4	**180d**	$ClCH_2CH_2Cl$	32	19
5	**180d**	CH_2Cl_2	23	32

[a] Reaction was performed at −20 °C.

step in the synthesis involved an aryl amination which allowed the preparation of both C_2-symmetric (**180a**−**d**) and C_1-symmetric (**180e**−**j**) ligands.[162]



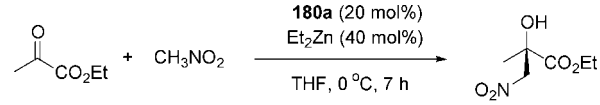
180

180a R^1 = Bn, R^2 = Bn
180b R^1 = *i*-Pr, R^2 = *i*-Pr
180c R^1 = Ph, R^2 = Ph
180d R^1 = *t*-Bu, R^2 = *t*-Bu
180e R^1 = Ph, R^2 = Bn
180f R^1 = *t*-Bu R^2 = Bn
180g R^1 = *t*-Bu, R^2 = *i*-Pr
180h R^1 = *i*-Pr R^2 = Ph
180i R^1 = *t*-Bu, R^2 = Ph
180j R^1 = Bn, R^2 = *i*-Pr

Da and Xu have applied two examples of Guiry's bis(oxazoline) C_2-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



Yield: 76%
ee: 79% (*R*)

Scheme 1.113

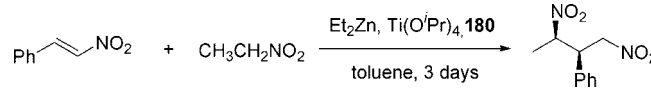


Table 1.75. Asymmetric Michael Addition of Nitroethane to β-Nitrostyrene Using Ligands 180a−d

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

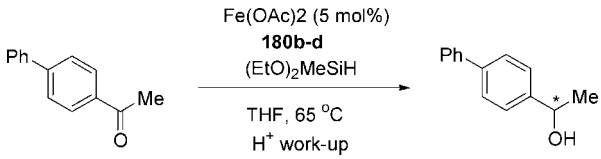
These ligands were subsequently more successfully applied in a zinc-catalyzed enantioselective Henry reaction (Scheme 1.112), with benzyl-substituted **180a** affording the highest enantioselectivity of 79%.[164]

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 substiuents on the oxazoline rings, with small changes in structure translating into large variations in enantiodiscrimination.

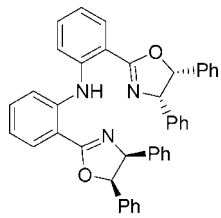
The optimal ligand **180f** was then used in the allylation of a range of aliphatic and aromatic aldehydes, with enantiomeric excesses of 87−91% reported and with the best aldehyde substrate being the linear aliphatic heptaldehyde.

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]

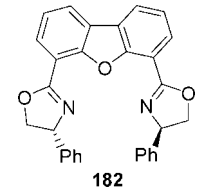


181

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 optimium 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]



182

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.

Funtionalized 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.

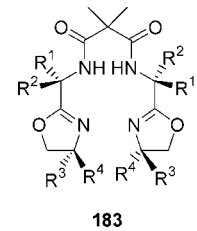
This bis(phenyl)-substituted ligand **182** was also applied to the enantioselective addition of nitrones to activated cyclopropanes (Scheme 1.119).[172]

Good to excellent enantioselectivities (71−99%) were obtained using a range of substituted cylcopropanes and various nitrones. The optimum selectivity and enantioselectivity were obtained with the substrate where R^1 and $R^2 = (CH_2)_5$, 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).

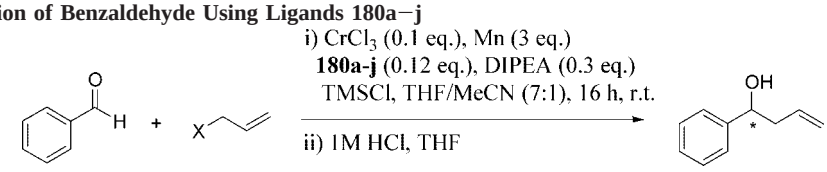


183

a: R^1 = *i*-Pr, R^2 = H, R^3 = H, R^4 = *i*-Pr
b: R^1 = *i*-Pr, R^2 = H, R^3 = Ph, R^4 = *i*-Pr
c: R^1 = H, R^2 = Ph, R^3 = H, R^4 = *i*-Pr
d: R^1 = H, R^2 = *i*-Pr, R^3 = H, R^4 = *i*-Pr
e: R^1 = *i*-Pr, R^2 = H, R^3 = Me, R^4 = Me
f: R^1 = Me, R^2 = Me, R^3 = H, R^4 = *i*-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

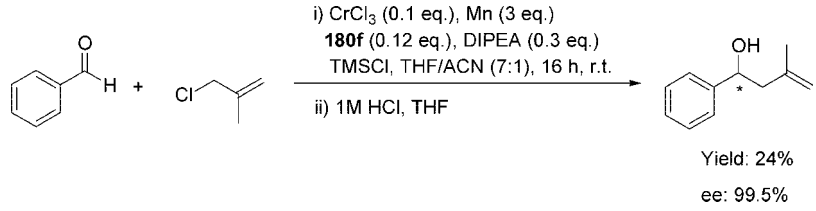


entry	ligand	R^1	R^2	X	yield (conv) (%)	ee (%) (conf)
1	**180b**	*i*-Pr	*i*-Pr	Br	78 (96)	69 (*S*)
2	**180c**	Ph	Ph	Br	60 (99)	44 (*S*)
3	**180f**	*t*-Bu	Bn	Br	87 (100)	87 (*R*)
4	**180f**	*t*-Bu	Bn	Cl	10 (19)	74 (*R*)
5	**180f**	*t*-Bu	Bn	I	88 (98)	80 (*R*)
6	**180g**	*t*-Bu	*i*-Pr	Br	97 (100)	71 (*R*)

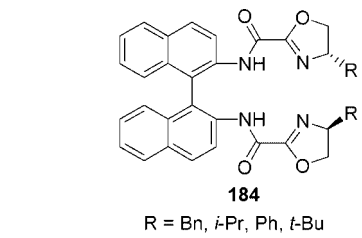
Table 1.77. NHK Crotylation of Benzaldehyde Using Ligands 180

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

Scheme 1.115

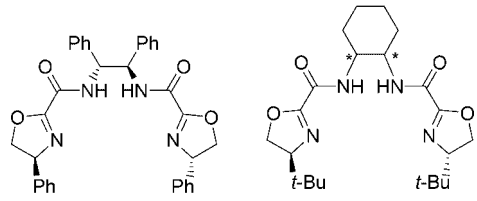


satisfactory enantioselectivities (<45%), ligand **186** resulted in an ee of 98%.[174]



184

R = Bn, *i*-Pr, Ph, *t*-Bu

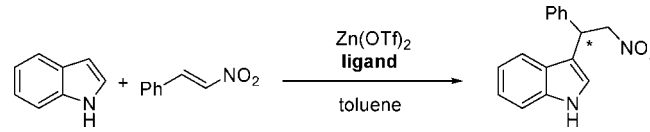


185 **186**

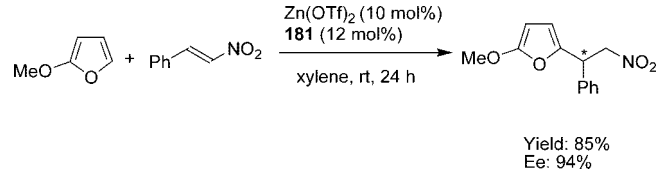
Zhang has developed a new class of *N*,*N*,*O*,*O*-bis(oxazoline) ligands of type **187** and has applied them in the enantioselective addition of diethylzinc to aldehydes (Scheme 1.41). For the addition to benzaldehyde, **187b** afforded the highest enantiomeric excess of 87%, with a yield of 93%. This 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-substituted ligand **188b**, which gave >95% isolated yield and an ee of 98% after 30 min at room temperature.

Scheme 1.116



Scheme 1.117



Scheme 1.118

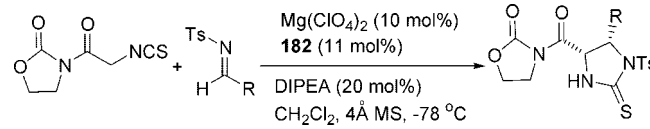
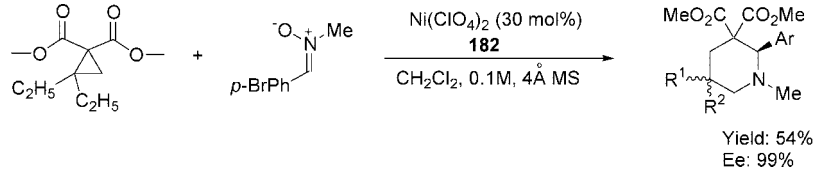


Table 1.78. Enantioselective Addition of Isothiocyanate-Substituted Oxazolidinone to a Range of *N*-Ts Imines Using Ligand 182

entry	R	yield	*syn*/*anti*	ee (%)
1	Ph	94	12:88	96
2	4-MeC_6H_4	96	12:88	99
3	4-BrC_6H_4	86	16:84	98
4	2-*N*-Ts-indolyl	99	10:90	99
5	2-Np	94	7:93	98
6	2-thiophenyl	95	13:87	90

Scheme 1.119



Scheme 1.120

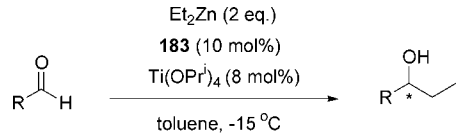
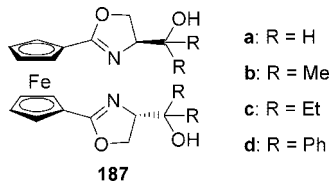


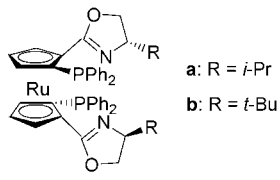
Table 1.79. Enantioselective Addition of Diethylzinc to Aldehydes Using Ligand 183

entry	ligand	R	yield (%)	ee (%) (conf)
1	**183a**	Ph	87	78 (*S*)
2	**183b**	Ph	85	70 (*S*)
3	**183c**	Ph	90	79 (*S*)
4	**183d**	Ph	93	73 (*R*))
5	**183e**	Ph	92	90 (*S*)
6	**183f**	Ph	18	25 (*S*)
7	**183e**	3-MeC_6H_4	95	91 (*S*)
8	**183e**	3-$NO_2C_6H_4$	94	97 (*S*)
9	**183e**	4-$NO_2C_6H_4$	95	94 (*S*)

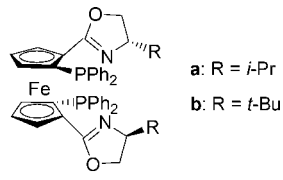


187

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]

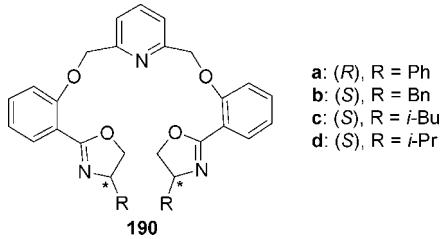


188



189

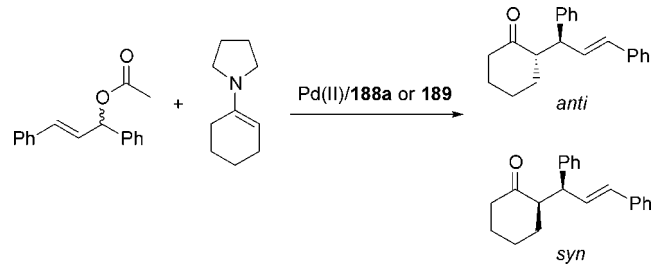
Isolated yields of 60−90% were obtained, with typical *anti*/*syn* ratios of 60:40 and enantioselectivities of up to 99% using **189b**. In general, the enantioselectivity using the ruthenocene-containing ligands was found to be slightly inferior.



190

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

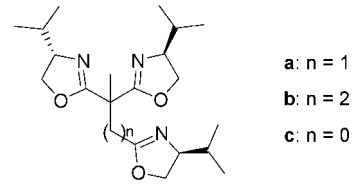


of 80% and a *trans*/*cis* ratio of 82:18, with ee's of 84% and 65%, respectively.

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** (R = 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).



191

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).

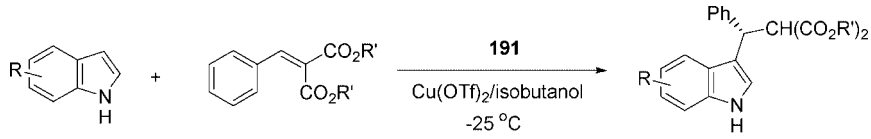
Tang also reported the tolerance of the catalyst system to water, with the enantioselectivity being maintained with a H_2O/catalyst ratio of 50 mmol.[180]

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



192

R = H
R = 2-Me
R = 4-MeO
R = 5-MeO
R = 5-Me
R = 7-Me

193

R′ = Et
R′ = Me
R′ = *t*-Bu
R′ = *i*-Pr

194

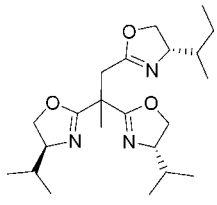
Table 1.80. (a) Effects on Enantioselective Indole Alkylation Using 191a

Effect of Ester Group				
entry	R	R′	conv (%)	ee (%)
1	H	Et	99	94
2	H	Me	93	91
3	H	*t*-Bu	90	98
4	H	*i*-Pr	26	91

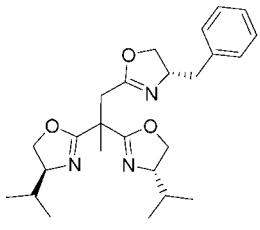
Effect of Indole Substituent				
entry	R	R′	yield (%)	ee (%)
1	2-Me	Et	99	−53
2	4-MeO	Et	90	+98
3	5-MeO	Et	79	+94
4	5-Me	Et	89	+95
5	7-Me	Et	82	+89

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

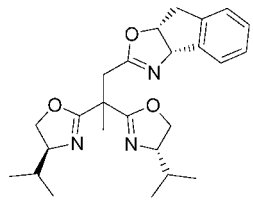
The ester groups of the cyclopropane had a small effect on the enantioselectivity, with the benzyl diester and ethyl diester giving higher ee (up to 97%) then the corresponding methyl diester (90% ee) (Table 1.82, entries 1−3). Both electron-rich and electron-poor α-aryl nitrones proceeded with excellent 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]



191d



191e



191f

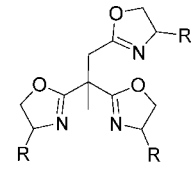
Table 1.81. Application of Tris(oxazoline) 191g in Enantioselective 1,3-Dipolar Cycloaddition between Nitrones 195 and Alkenes 196

entry	R^1/R^2	R^3/R^4	yield (%)	**197**/**198**	ee (%)
1	Ph/Et	4-$CH_3C_6H_4$/Ph	93	>99/1	91
2[a]	Ph/Et	4-BrC_6H_4/Ph	76	>99/1	95
3	Ph/Et	Ph/Ph	94	97/3	95
4	4-$CH_3C_6H_4$/Et	Ph/Ph	95	95/5	92
5	4-$NO_2C_6H_4$/Me	Ph/Ph	93	97/3	94
6	4-BrC_6H_4/Et	Ph/Ph	99	95/5	95
7	Ph/Me	Ph/4-$CF_3C_6H_4$	100	92/8	98
8	Ph/Me	Ph/4-$CH_3OC_6H_4$	94	95/5	96
9	Ph/Me	4-BrC_6H_4/Ph	92	>99/1	98
10	Ph/*i*-Bu	4-BrC_6H_4/Ph	95	>99/1	96
11[a]	Cy/Et	4-BrC_6H_4/Ph	91	90/10	89

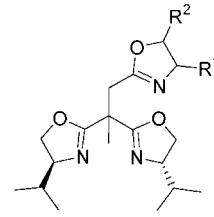
[a] Using 6.7 mol % of **191g**.

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]

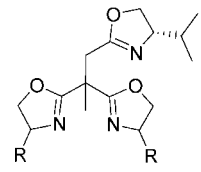
In 2006, Tang reported the application of a range of tris(oxazoline) ligands **199** in the enantioselective synthesis of β-lactams using the Kinugasa reaction (Scheme 1.125, Table 1.82).[185]



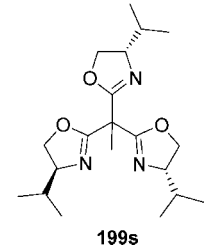
199h: R = (*S*)-*i*-Pr
199i: R = (*S*)-*s*-Bu
199j: R = (*R*)-Ph
199k: R = (*S*)-*t*-Bu



199e: R^1 = (*S*)-Bn; R^2 = H
199l: R^1 = (*S*)-*s*-Bu; R^2 = H
199m: R^1 = (*S*)-*t*-Bu; R^2 = H
199n: R^1 = (*S*)-Ph; R^2 = H
199o: R^1 = (*R*)-Ph; R^2 = H
199p: $R^1 = R^2$ = (*S*, *R*)-$C_6H_5CH_2$-



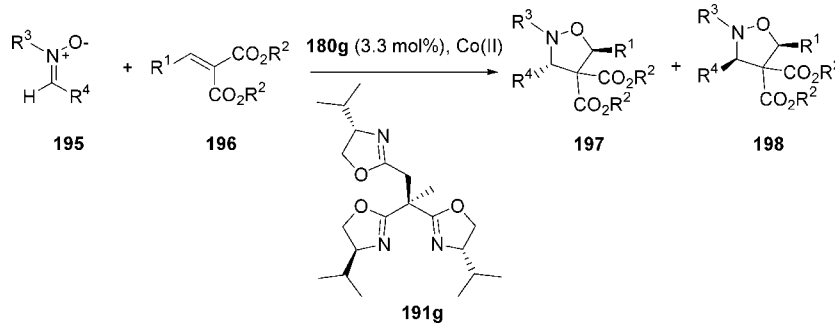
199q: R = (*S*)-Ph
199r: R= (*R*)-Ph;



199s

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

Scheme 1.123



Scheme 1.124

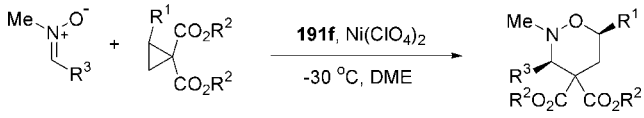


Table 1.82. Asymmetric Cycloaddition of Cyclopropanes with Nitrones Using Ligand 191f

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_6H_4	4	85	12:1	97
5	Ph	Et	4-$MeO_2CC_6H_4$	4	97	11:1	97
6	Ph	Et	4-MeC_6H_4	4	80	12:1	96
7	Ph	Et	4-$MeOC_6H_4$	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

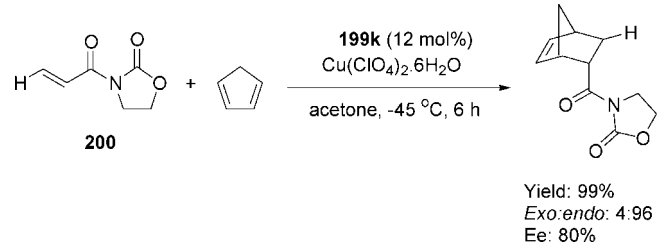
Table 1.83. Application of Ligands 199e and 199h−s in the Asymmetric Kinugasa Reaction

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

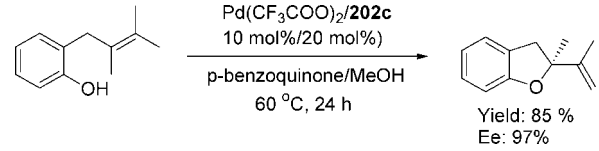
1.83, entries 5−9). For example, **199n** and **199o** with opposite chiral centers gave similar enantioselectivities (Table 1.83, entries 7, 8). Increasing the steric hindrance diminished the reaction rate dramatically, with ligand **199k** not giving any desired lactam product.

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 enantioselectivity of 95% being obtained using *p*-methoxystyrene and ethyl phenyldiazoacetate.[186]

Scheme 1.126

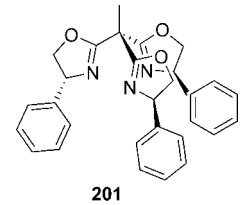


Scheme 1.127



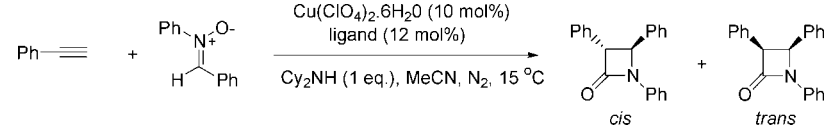
The *tert*-butyl-substituted ligand **199k** has also been utilized by Tang in the copper-catalyzed enantioselective Diels−Alder reaction of cyclopentadiene with acryloyl-2-oxazolidinones or ketoesters. The best results were obtained with the oxazolidinone-type dienophile systems (Scheme 1.126). Although good enantioselectivities (80−82%) and high *exo*/*endo* 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 *exo*/*endo* ratio of 4:96, and an enantiomeric excess of 80%.[187]

Gade amd Bellemin-Laponnaz 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]

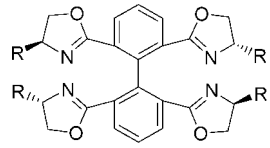


Zhang has developed a new class of tetra(oxazoline) containing ligands **202** and reported their application in the

Scheme 1.125



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 allyphenols, 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.

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