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Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis

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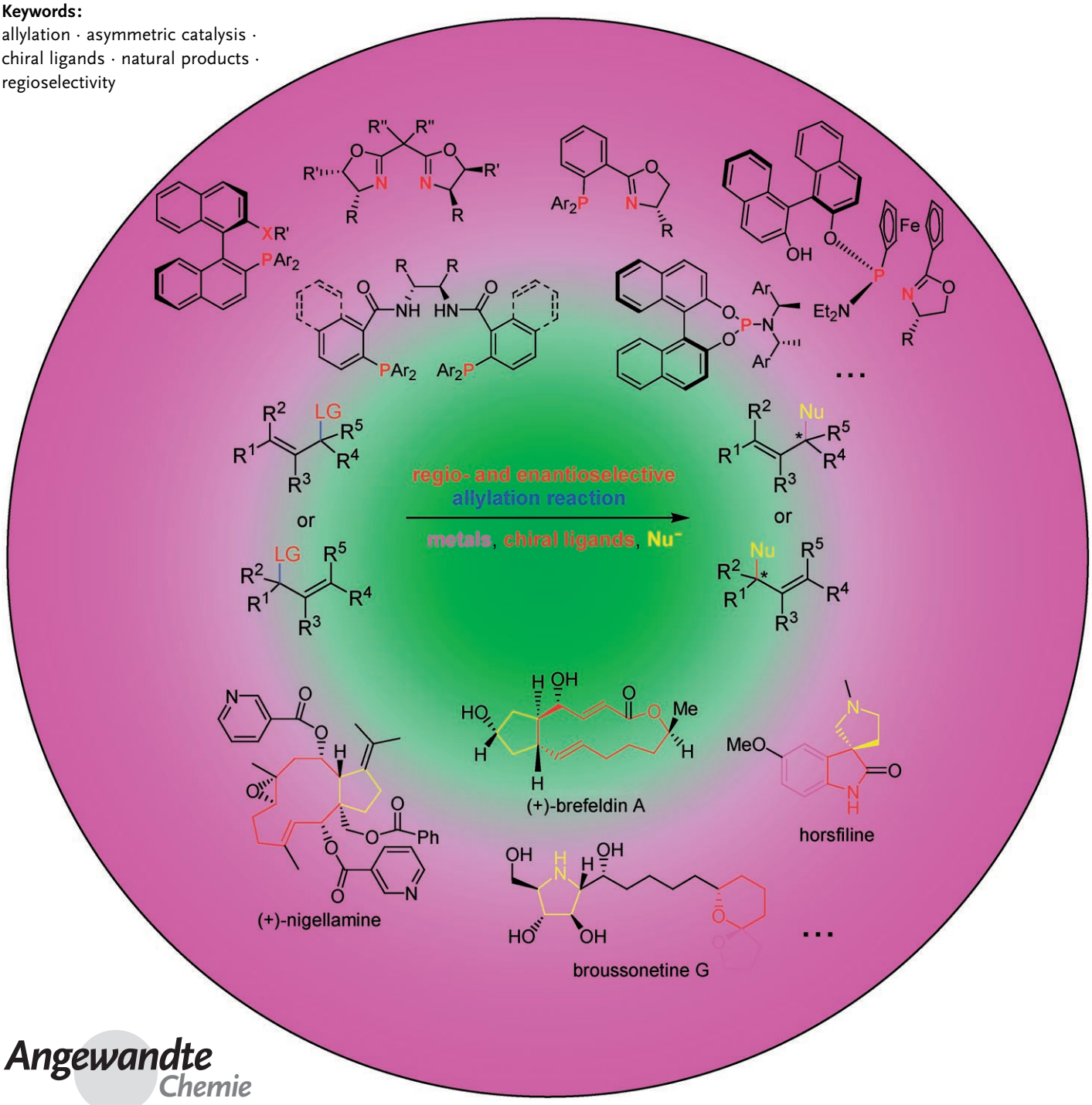


Metal-catalyzed enantioselective allylation, which involves the substitution of allylic metal intermediates with a diverse range of different nucleophiles or S_N2'-type allylic substitution, leads to the formation of C–H, –C, –O, –N, –S, and other bonds with very high levels of asymmetric induction. The reaction may tolerate a broad range of functional groups and has been applied successfully to the synthesis of many natural products and new chiral compounds.

From the Contents

1. Introduction

Metal-catalyzed asymmetric allylic substitution, which involves the attack of diverse nucleophiles at an allylic metal intermediate or S_N2'-type allylic substitution, has been investigated with great intensity. Besides a high level of asymmetric induction, the advantages of this method are its tolerance of a wide range of functional groups and a great flexibility in the type of bonds that can be formed. For example, H-, C-, N-, O-, and S-centered nucleophiles can be employed. Many ligands have been designed for the benchmark allylic alkylation with 1,3-diphenylallyl acetate. It should be noted that the asymmetric alkylation of unsymmetrical allylic substrates was seldom simultaneously regio- and enantioselective. However, useful results have recently been reported because of the availability of many new chiral ligands. In this Review, we will summarize some of the most typical more recent advances (between 1995 and January 2007) in this area, excluding those which have been summarized in previous reviews or highlights.[1]

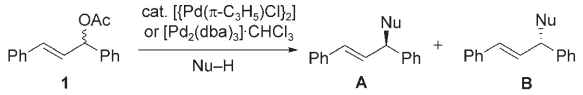
2. Palladium-Catalyzed Reactions

In this section, we will discuss the application of different types of chiral ligands in the reaction of 1,3-disubstituted symmetrical allylic substrates. Since many ligands are known,[**] only those that led to a synthetically attractive level of enantioselectivity (in most cases $\geq 95\%$ *ee*) will be discussed here.

2.1. Pd-Catalyzed Intermolecular Allylation with Symmetric 1,3-Disubstituted Allylic Substrates

2.1.1. Monodentate P Ligands

Although many C_2-symmetric bidentate chiral ligands have been used, malonate (**L1**–**L3**, **L5**, **L7**, and **L8**), amines (**L4**, **L6**, **L9**, **L11**, and **L12**), $B(OMe)_3$ (**L6**, the product is 1,3-diphenylallyl methyl ether), and $NaSO_2Tol$-*p* have been successfully allylated with 94% *ee* by using monodentate phosphorous ligands (Scheme 1, Figure 1). Certainly the configuration of the products depends on the structure of the ligand. It should be noted that the C=C bond in **L7** may also coordinate with the metal atom.



Scheme 1. dba = *trans,trans*-dibenzylidenacetone.

Racemic 1,3-diphenylallyl acetate may be kinetically resolved to afford the product **B1** ($Nu = CH(CO_2Me)_2$) in 84% *ee* with (*R*)-**1** being recovered with greater than 99% *ee* by using the chiral helical diphosphane ligand 2,15-bis(diphenylphosphanyl)hexahelicene (**L13**). Although it is potentially a bidentate ligand, **L13** behaves as a monodentate ligand in this reaction, according to the observations made by the authors (Scheme 2).[11]

Ligand **L6** can be used for a similar reaction of 1,3-diphenylallyl pivalate with $CH_2(CO_2Me)_2$, $CH_2(COMe)_2$, $CH_2(COMe)(CO_2tBu)$, or $AcNHCH(CO_2Et)_2$ to afford the products **B** in 96–100% yields and 94–97% *ee*.[7c] However, the results obtained with 3-penten-2-yl pivalate or acetate are unsatisfactory.[7a,c] The reaction of *N*-tosyl-*N*-allylamine with 4-methyl-4-hepten-3-yl acetate in the presence of **L6** afforded the product **D** with 91% *ee*, although in 38% yield (Scheme 3).[7a]

Ligands **L4** and **L6** have been successfully used for enantioselective allylation with 2-substituted-2-cyclohexenyl methyl carbonates to afford the product **E** in 90–99% *ee* (Table 1).

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

[**] The Supporting Information contains tables of chiral ligands for the transformation of symmetric allylic substrates as well as their experimental results.

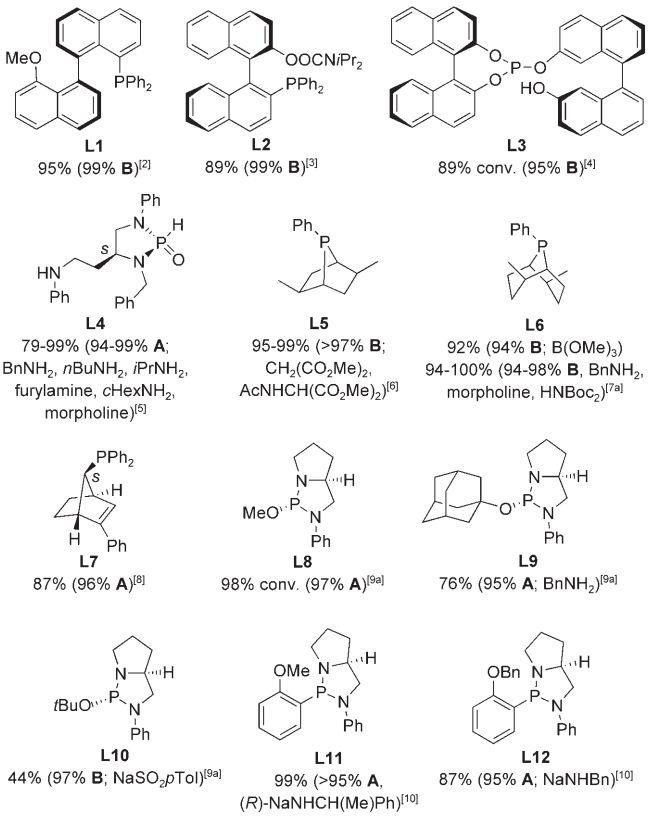
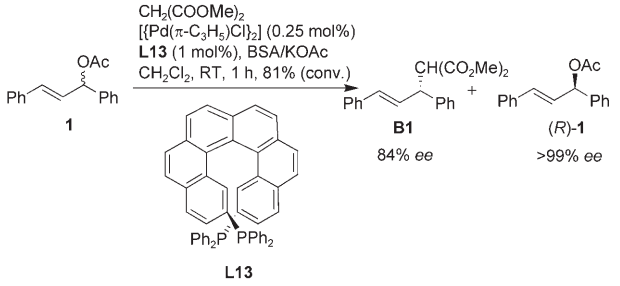
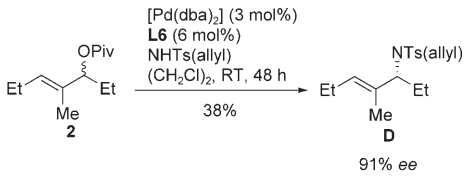


Figure 1. Selected examples of monodentate phosphorus ligands for Scheme 1. [a] Unless otherwise stated, $CH_2(CO_2Me)_2$ (**C**) was used as the pronucleophile.

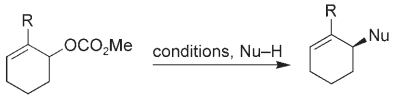


Scheme 2. BSA = *N*,*O*-bis(trimethylsilyl)acetamide.



Scheme 3.

Table 1: Asymmetric allylic amination or alkylation with 2-substituted cyclic allylic carbonates.



R	Conditions	Nu–H	Yield of **E** [%] (*ee* [%])	Ref.
Ph, 2-naphthyl, 4-$CF_3C_6H_4$, 4-FC_6H_4, 3-FC_6H_4, 2-FC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, $PhCH{=}CHCH_2$	[{Pd(π-C_3H_5)-Cl}$_2$]/**L4**, MeCN	morpholine, $BnNH_2$, *n*$BuNH_2$, $EtO_2CCH_2NH_2$	55–99 (91–99)	[5a]
Ph, TMSC≡C	[$Pd_2(dba)_3$]-·$CHCl_3$/**L6**/LiOAc, $ClCH_2CH_2Cl$	$CH_2(CO_2Me)_2$, TsNHR (R=Allyl, CH_2CO_2Et, benzyl)	71–97 (90–99)	[7b]

2.1.2. *Bidentate C,N Ligands*

Chiral imidazolium imine **L14** has been used as a bidentate ligand in the presence of a base in the reaction of malonate with 1,3-diphenylallyl acetate to afford the product **A1** in greater than 99% yield and 92% *ee* (Scheme 4).[12]

2.1.3. *Bidentate N,N Ligands*

Optically active C_2-symmetric bisoxazoline ligands have been used extensively for the highly enantioselective allylation of various nucleophiles with 1,3-diphenylallyl acetate. Two oxazoline rings may be tethered through a carbon (**L15**–

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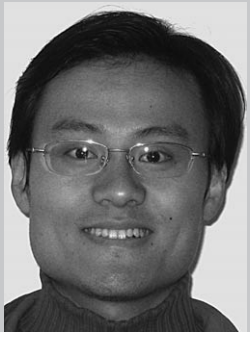
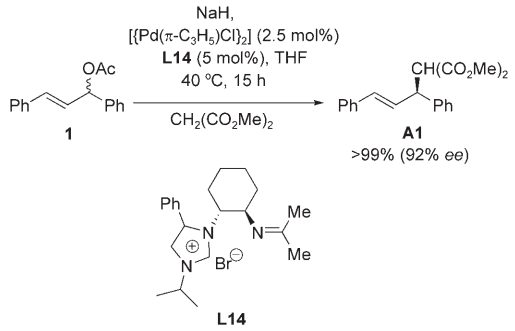


Zhan Lu was born in the Zhejiang Province. He received a BSc in Chemistry from Zhejiang University (2003). He is currently conducting PhD research in the research group of Prof. Shengming Ma at Zhejiang University.



Scheme 4.

18, **L20**, and **L21**) or nitrogen (**L19**) atom to afford a very practical level of enantioselectivity (>95% *ee*). Ligand **L22** with a monooxazoline and a pyridine ring afforded product **B** with greater than 99% *ee*. Phenanthroline derivative **L23**, diamine **L24**, and bis(sulfoximine) **L25** may also be used to afford product **B** (Figure 2).

Diaminooligothiophene **L26** should be used in the reaction of 1,3-diarylallyl carbonate to afford the corresponding products with high enantioselectivities. The PEG-supported chiral ligand **L27** afforded the corresponding products **G** in 78–99% *ee*, which makes the recycling of the chiral catalyst possible (Table 2).

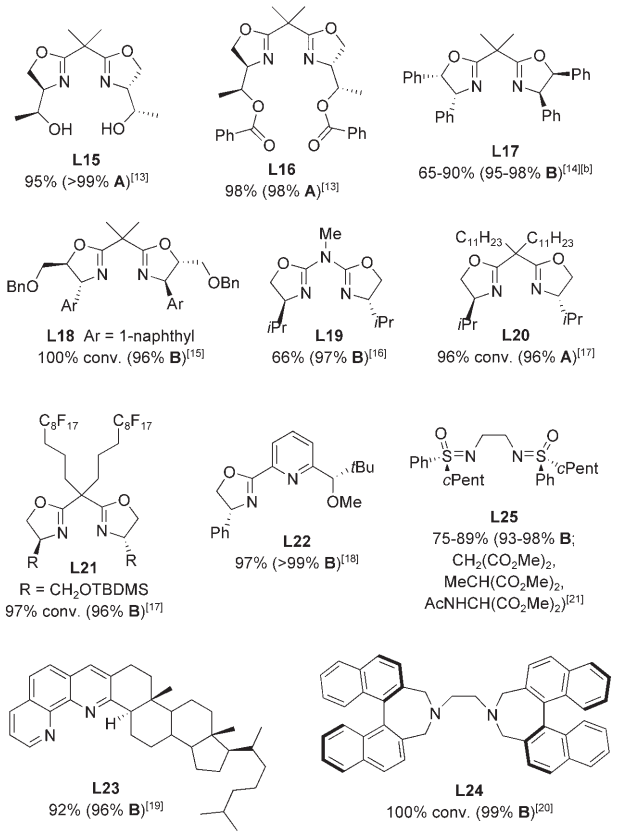
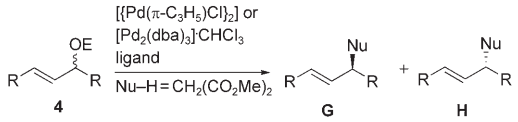


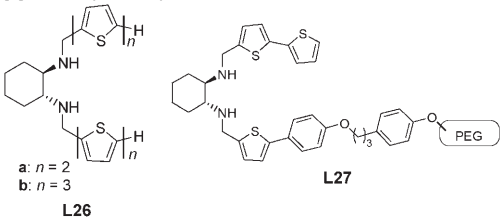
Figure 2. Selected bidendate N,N ligands for Scheme 1. Unless otherwise stated, $CH_2(CO_2Me)_2$ (**C**) was used as the pronucleophile. $MeCH(CO_2Me)_2$ was also used. $AcNHCH(CO_2Me)_2$ was also used. Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl.

Table 2: Asymmetric allylic alkylation with 1,3-disubstituted allyl carbonates or acetates.



Ligand	R	E	Yield [%] (*ee* [%])	Ref.
L26	Ph	CO_2Me	80–99 (>98–99 **G**)[a]	[22]
	p-ClC_6H_4	Ac	99 (95)	[22]
L27	Ph, Me, *p*-ClC_6H_4	CO_2Me	50–98 (78–99 **G**)	[23]

[a] $MeCH(CO_2Me)_2$ was also used.



2.1.4. *Bidentate N,P Ligands*

The combination of the oxazoline unit with a phosphane makes many bidendate N,P ligands which are not C_2 symmetric but highly effective for the benchmark reaction (**L28**–**L35**, Figure 3): In addition to $CH_2(CO_2Me)_2$, carbon pronucleophiles such as NaCp (Cp = cyclopentadienyl; with (*S*)-**L28a**), the indenyl anion (with (*S*)-**L28a**), $FCH(SO_2Ph)_2$/$CH_2(SO_2Ph)_2$ (with (*S*)-**L28b**), $CH_2(COMe)_2$ (with **L30**), $CH_2(COMe)CO_2Et$, $CH_2(COMe)SO_2Ph$, $CH_2(CN)CO_2Me$, $CH_2(CN)_2$ (with (*S*)-**L28b**), and nitrogen nucleophiles such as benzylamine or potassium phthalimide (with **L32**) may all be allylated enantioselectively (>95% *ee*). The combination of oxazine with a phosphane may also provide effective bidentate N,P ligands (**L36** and **L37**). Excellent results were obtained using ligands **L38**–**L43** which combine a phosphane with a nitrogen heterocycle.

The ferrocene unit has been widely introduced to build highly enantioselective chiral N,P ligands (**L44**–**L53**). Chiral complexes **L54** and **L55** were also used successfully in the asymmetric allylic alkylation of malonate with 1,3-diphenyl-2-propenyl acetate to afford products **B** or **A** (Scheme 1) in greater than 98% *ee*, respectively. Carbohydrates (**L56**–**L58**) and binaphthalenes (**L59**–**L63**) have been used as the chiral backbones for the oxazoline-phosphane ligands. A phosphite functionality may replace the phosphane moiety (**L64a**–**L66**). $CH_2(CO_2Me)_2$, $CH_2(CO_2Et)_2$, $CH_2(CO_2Bn)_2$, $CH_2(CO_2tBu)_2$, and $CHMe(CO_2Et)_2$ have all been allylated successfully in over 95% *ee* using chiral pyridine-phosphane ligands **L67** and **L68** and chiral prolinol-derived aminophosphane ligands **L69**–**L73**. Even the axially chiral ligand **L74** is very effective for the benchmark reaction to afford product **B** in 95% *ee*. Phosphanes with an imine (**L75**), amine (**L76**), or sulfoximine functionality (**L77**) are also synthetically very attractive. Finally, it should be noted that a surprisingly high yield (99%)

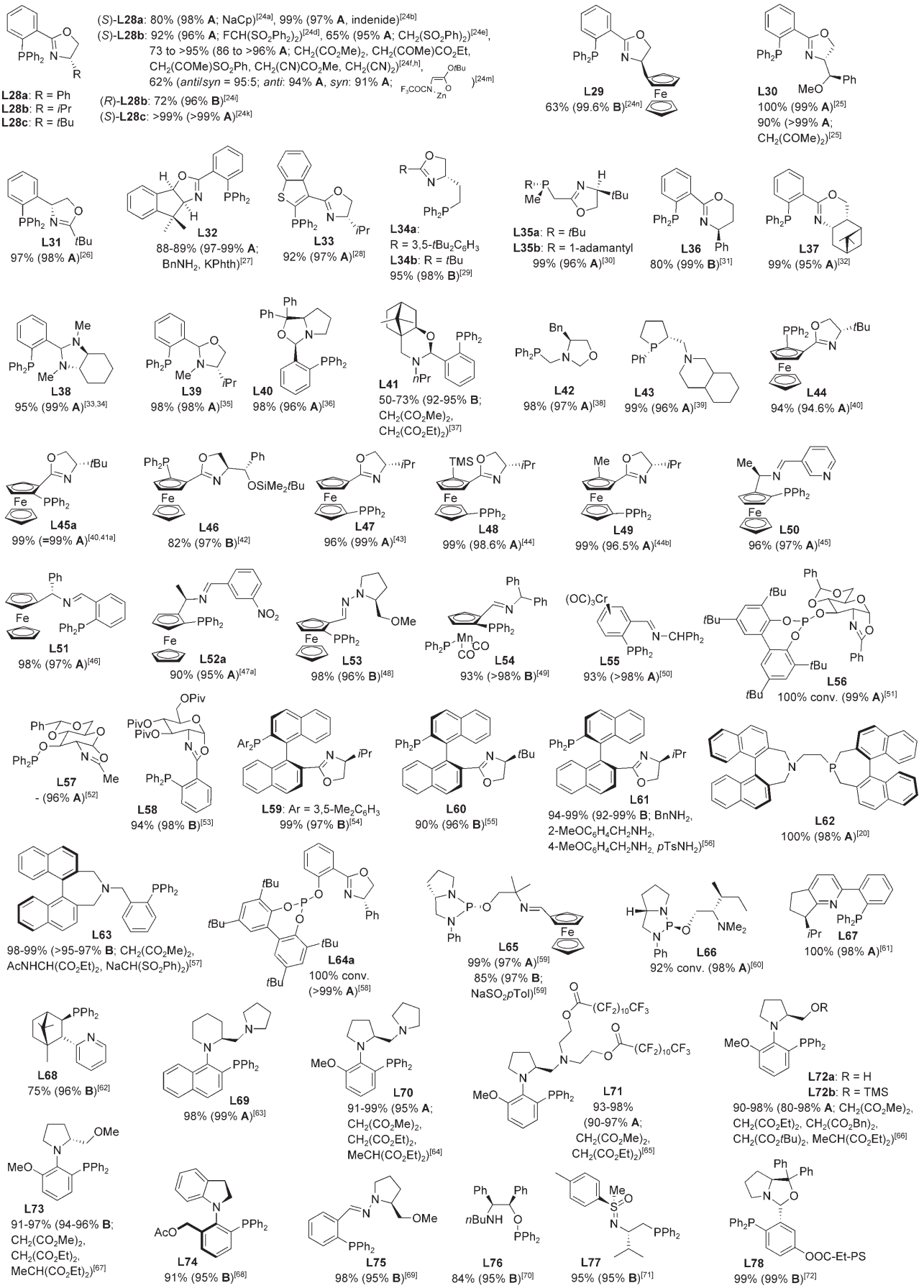


Figure 3. Selected chiral N,P ligands for Scheme 1. [a] Unless otherwise stated, $CH_2(CO_2Me)_2$ **C** was used as the nucleophile. Et-PS = ethylpolystyrene, Piv = pivalate, TMS = trimethylsilyl.

and enantioselectivity (99%) for the formation of product **B** was observed by using the potentially reusable polymer-supported chiral N,P ligand **L78**.

Ligand (*S*)-**L28b** may be used for the reaction of other 1,3-diaryl-substituted 2-propenyl acetates with potassium phtahlimide[24g] or $FCH(SO_2Ph)_2$[24d] to afford the related products **G** (Table 2) in 91–99% *ee*. Furthermore, the reaction of di(*p*-chlorophenyl)allyl acetate or di(*p*-bromophenyl)allyl acetate with malonate in the presence of **L32** produced the corresponding products **G** in 95–99% *ee*.[27] Chiral N,P ligands with ferrocene backbones are also useful in the reaction of 1,3-diphenylallyl carbonate or pivalate[74] with malonate (with **L50**, **L52b**, **L80**, and **L81**, Figure 4),[45,47a,74,75] $MeCH(CO_2Et)_2$ (with **L50**),[45] or benzylamine (with **L79**).[73] The reaction of malonate with di(*p*-chlorophenyl)allyl acetate[76] or 1,3-diphenylallyl pivalate[77] in the presence of chiral phosphane–Schiff base ligands **L82** and **L83** formed the product **H** (Table 2) in 94–95% *ee*.

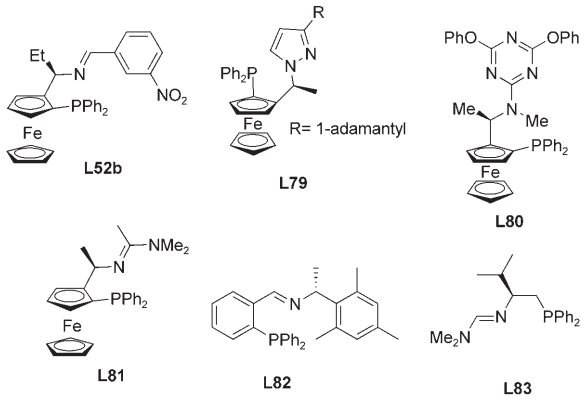


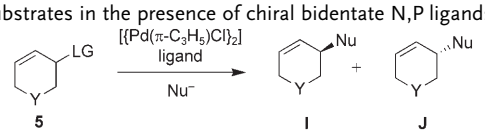
Figure 4. Selected N,P ligands for Table 2.

The reaction of cyclic allylic acetates with chiral oxazoline phosphite **L64b** (Table 3) or oxazoline phosphane **L84** (Table 3) afforded the related products in 96–99% *ee*. Ligand **L85** with a phosphanyl-substituted cyclopentadienyl manganese tricarbonyl moiety and an oxazoline ring showed excellent catalytic activity for the reaction of cyclic allyl acetate or chloride as well as heterocyclic allyl acetate with a range of nucleophiles (Table 3). Recyclable, PEG-supported chiral N,P ligand **L86** has been successfully developed for the reaction of malonate and benzylic amines (Table 3).

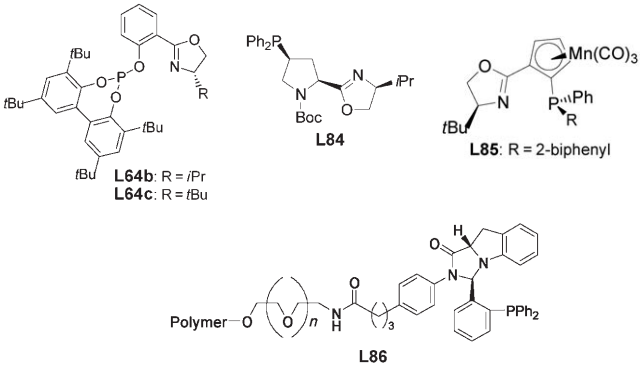
2.1.5. *Bidentate N,S or N,Se Ligands*

Optically active thioether-oxazoline ligands **L87**–**L90** can afford the products **A** or **B** (Scheme 1) with a very practical level of enantioselectivity (Figure 5); Thio- or selenoethers combined with a nitrogen heterocycle, such as **L91**–**L93** and **L96** or an imine **L94** and **L95**, as well as **L98** have also been demonstrated to afford the products **A** or **B**, respectively, with greater than 95% *ee*. Excellent results were even observed with simple acyclic chiral selenoether-amide ligands **L97** for the benchmark reaction to afford product **B**.

Table 3: Enantioselective allylation of various nucleophiles with cyclic allylic substrates in the presence of chiral bidentate N,P ligands.



Ligand	LG; Y	Nu–H/Na	Yield [%] (*ee* [%])	Ref.
L64b	OAc; $(CH_2)_{1,2}$	$CH_2(CO_2Me)_2$	– (98–99)	[58]
L84	OAc; –	$CH_2(CO_2Me)_2$	79 (96 **I**)	[78a]
L85	Cl; –	$NaC(OAc)(CO_2Me)_2$, $NaC(OAc)(CO_2Et)_2$	94–97 (98.5–99.5 **J**)	[79c]
	OAc; –, $(CH_2)_{1,2}$	$CH_2(CO_2Me)_2$	62–86 (93–98 **J**)	[79a]
	OAc; NBoc	$NaCH(CO_2Me)_2$, $NaC(OAc)(CO_2Me)_2$	77–97 (95–96 **J**)	[79d]
L86	OCO_2Me; –, $(CH_2)_{1,2}$ or $CHCO_2Me$	$CH_2(CO_2Me)_2$, $CH_2(CO_2Et)_2$	67–94 (89–98 **I**)	[80a]
L86	OCO_2Me; $(CH_2)_{1,2}$, $CHCO_2Me$ or NCO_2tBu	Bn_2NH, $(4\text{-MeO-}C_6H_4CH_2)_2NH$, $Bn(4\text{-MeO-}C_6H_4CH_2)NH$	59–99 (93–98 **I**)	[80b]



2.1.6. *Bidentate P,O Ligands*

In a similar manner, the combination of the amide carbonyl group with a phosphane led to the development of the highly enantioselective bidentate P,O ligands **L99**–**L101** for this reaction: carbon pronucleophiles such as $CH_2(CO_2Me)_2$ or $AcNHCH(CO_2Me)_2$ may be 1,3-diphenylallylated in greater than 95% *ee* (Figure 6).

In the bidentate P,O ligand **L102** a carboxylic acid is combined with a phosphane; this ligand is highly enantioselective for the reaction of 5-azacyclohex-2-enyl or cyclohex-2-enyl acetate **6** with lithium malonate (Scheme 5).

2.1.7. *Bidentate P,P Ligands*

The allylation of dimethyl malonate or benzylamine in the presence of bisphosphite **L103** afforded the products **B** in 99% *ee*. The same reaction with the ligands duphos (**L105**),

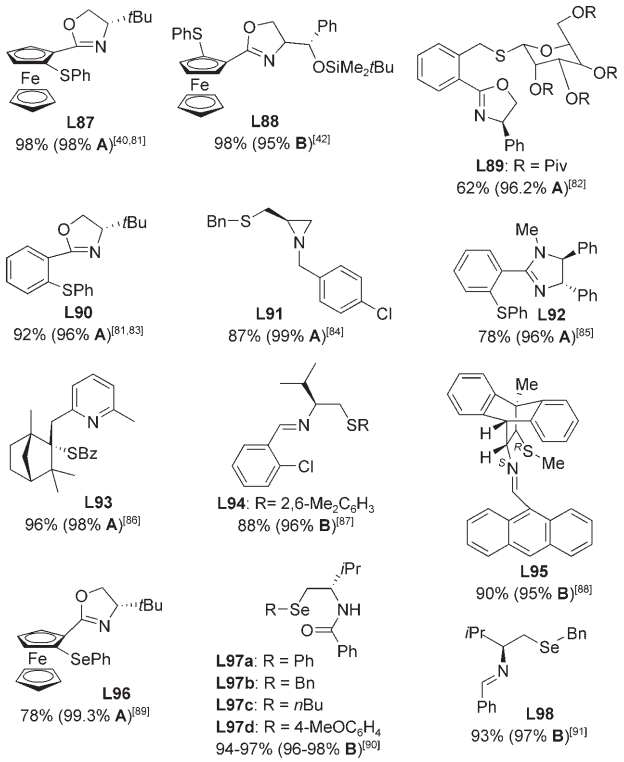
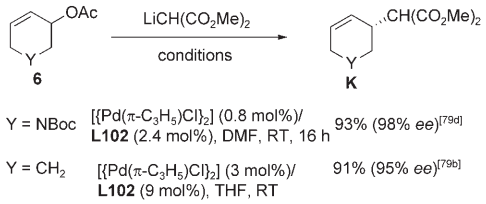


Figure 5. Selected N, P-, and Se ligand for Scheme 1. [a] $CH_2(CO_2Me)_2$ (**C**) was used as the pronucleophile. Bz = benzoyl.



Scheme 5. Boc = *tert*-butyloxylcarbonyl.

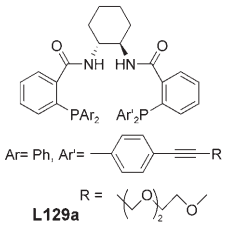
ducantphospholane (**L106**), duthixantphospholane (**L107**), and 1,2-bisphospholanylbenzene (**L108**) afforded the corresponding products **A** or **B** in 97–99% *ee*. Besides $CH_2(CO_2Me)_2$, carbon pronucleophiles such as $CH_2(CO_2Et)_2$, $CH_3CH(CO_2Me)_2$, and $CH_3CH(CO_2Et)_2$, as well as nitrogen nucleophiles such as benzylamine may be allylated in greater than 97% *ee* using rigid chiral spiro ligands **L110**, C_2-symmetric bisphosphane ligands **L111** and **L112** with a cyclobutane backbone, or chiral diphosphites **L113** and **L114** based on D-(+)-glucose. The axially chiral biphenyl ligands **L115** and **L116** can be used for the benchmark reaction of dimethyl malonate to afford product **A** in 95% *ee*. The axially chiral binaphthyl ligands **L117**–**L121a** displayed great tolerance for various nucleophiles such as the enolates of cyclohexanone, malonate and its analogues, 2-methylaziridine, 7-azabicyclo[4.1.0]heptane (with (*R*)-**L117**), potassium phthalimide, and sodium diformylamide (with (*S*)-**L117**) and afforded the corresponding allylation products with greater than 95% *ee*.

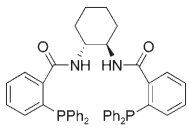
Ferrocene has also been widely applied as the backbone of the ligands (**L122**–**L126**). Carbon nucleophiles such as dimethyl malonate and nitrogen nucleophiles such as benzylamine, KNHTs, or KNHNHBz can be allylated in greater than 95% *ee* in the presence of these ligands. The chiral phosphanylphosphaferrocene **L127** has also been applied for the highly stereoselective preparation of **B**. The recycleable PEG-based pseudo-C_2-symmetric bisphosphane ligand **L128** with a cyclobutane backbone could also be prepared (Figure 6).

Various (pro)nucleophiles such as $CH_2(CO_2Me)_2$ (Table 4), $NaSO_2Ph$ (Table 4), LiO_2StBu (Table 4), 3-methyl-2-hydroxycyclopent-2-enone (Table 4), and

Table 4: Enantioselective allylation of various nucleophiles with 1,3-disubstituted allyl substrates in the presence of chiral bidentate P,P ligands (see also the equation in Table 2).

Ligand	R	E	Nu	Yield [%] (*ee* [%])	Ref.
(*R*)-**L117**	4-ClC_6H_4, 4-BrC_6H_4, 1-naphthyl	Ac	$CH_2(CO_2Me)_2$	60–95 (90–97 **G**)	[24i, 106d]
L129a	Me	CO_2Me	$NaSO_2Ph$	81 (>99 **H**)	[118]
	Et	CO_2Me	H_2O	94 (>99 **H**)	[119a]
	Me, Et	Ac	LiO_2StBu	43–51 (96–98 **H**)	[24c]
(*R*,*R*)-**L130**	Me	CO_2Me		83 (97 **H**)	[119c]
	Me	CO_2Me	$CH_3CH_2NO_2$	71 (97 **G**) (d.r. 11:1)	[119g]





$CH_3CH_2NO_2$ (Table 4) can be 1,3-diarylallylated with high enantioselectivity (≥97% *ee*). Hept-4-en-3-yl carbonate can be asymmetrically hydroxylated in the presence of a $[Pd_2(dba)_3]\cdot CHCl_3$ and (*R*,*R*)-**L130** catalyst using CH_2Cl_2/H_2O (9:1) as the solvent to afford the related optically active alcohol **H** (Nu = OH) in greater than 99% *ee* (Table 4).

Furthermore, the bidentate chiral *P*,*P* ligand (*R*,*R*)-**L130** is quite a general ligand for the reaction of various nucleophiles with cyclic allylic substrates: carbon (pro)nucleophiles such as dimethyl malonate, $NaCH(CO_2Bn)_2$, $FCH(CO_2Et)COMe$, $MeNO_2$, or $(Me)_2CHNO_2$, nitrogen nucleophiles such as phthalimide or $TsNH_2$, oxygen nucleophiles such as substituted phenols or enols, and sulfur nucleophiles such as

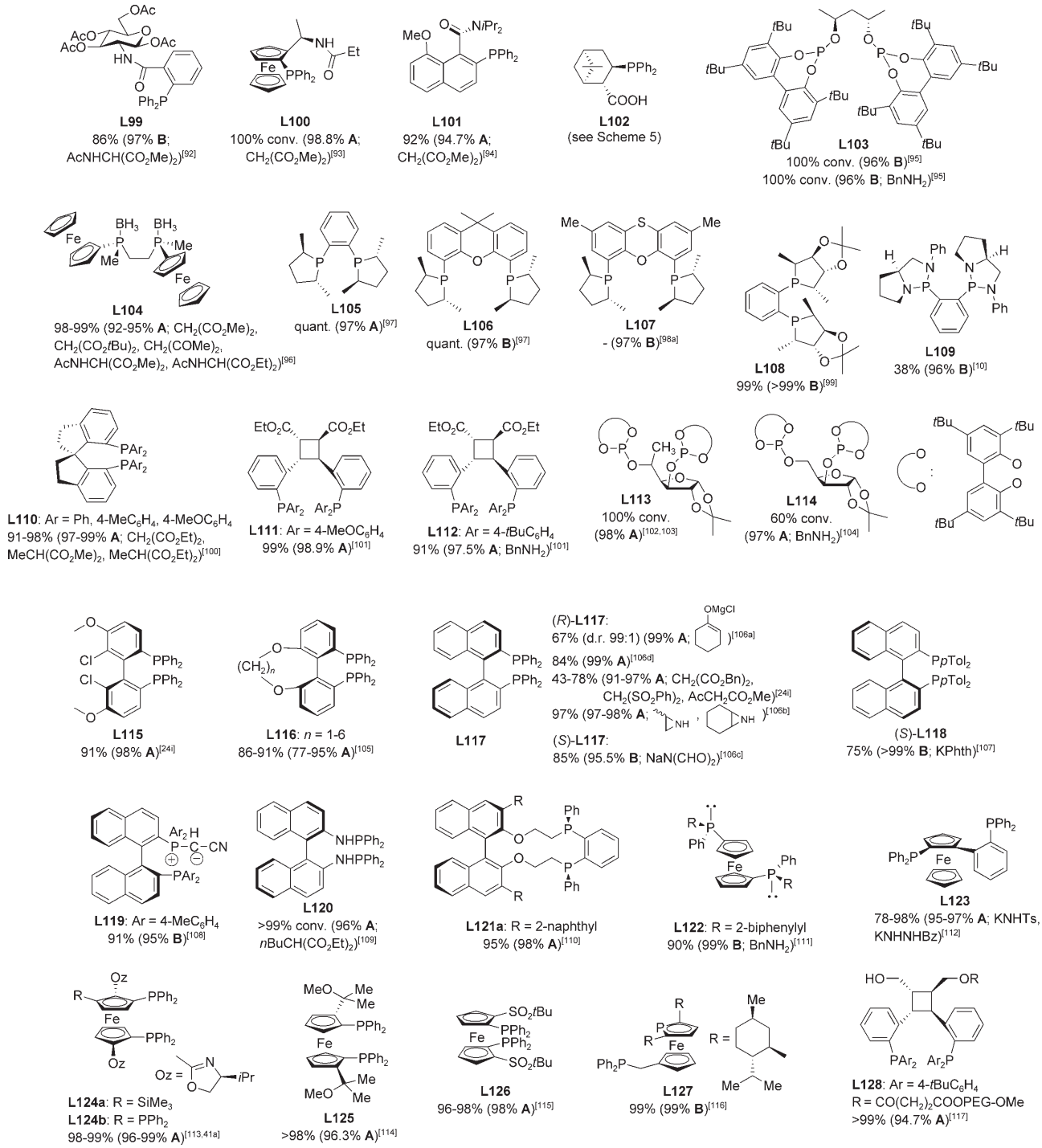
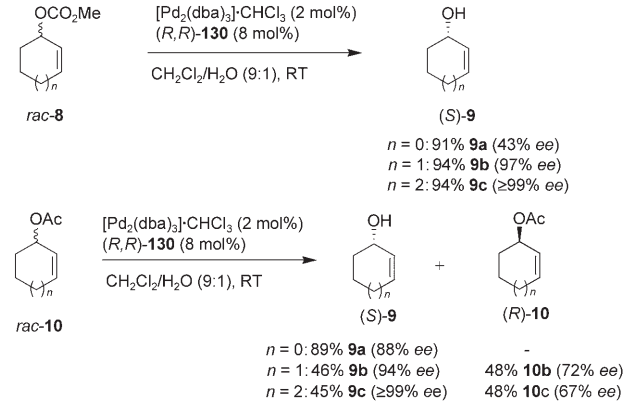


Figure 6. Selected P,O and P,P ligands for Scheme 1. PEG-OMe = polyethylene glycol monomethyl ether.

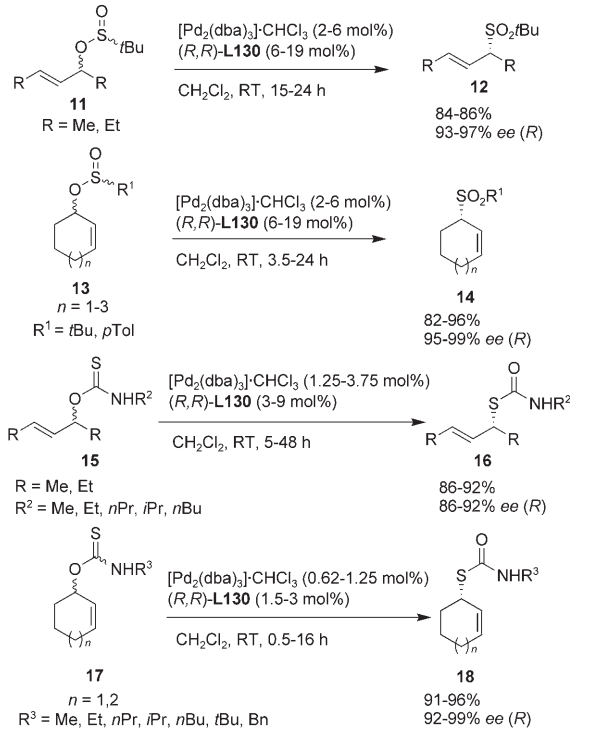
$NaSO_2Ph$ or (2-pyrimidyl)SH may all be cycloallylated to afford products **M** in greater than 95% *ee*. The opposite absolute configurations can be obtained by using (*S*,*S*)-**L130** and (*S*,*S*)-**L132** (Table 5).

Gais and co-workers reported the enantioselective deracemization of cyclic allylic carbonates **8** in the presence of water to give the related optically active cyclic allylic alcohols (*S*)-**9** ($n = 1$ or 2, with 97 and $\geq 99\%$, respectively).[119a] Acetates *rac*-**10** can be kinetically resolved to afford the optically active cyclic allylic alcohols **9** with the *S* configuration in high enantiopurity and the remaining acetates **10** with the *R* configuration and a moderate *ee* value (Scheme 6).[119a]

The enantioselective rearrangement of racemic allyl sulfines and allyl sulfinamides in the presence of a $[Pd_2(dba)_3]\cdot CHCl_3$ and (*R*,*R*)-**L130** catalyst led to the efficient preparation of the optically active allylsulfones **12** and **14** as well as thiocarbamates **16** and **18** with 86–99% *ee* (Scheme 7).[122]

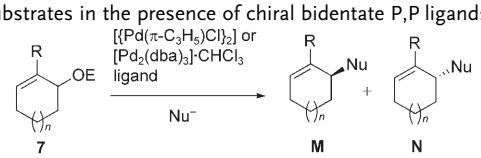


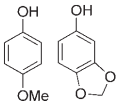
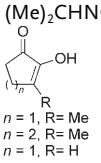
Scheme 6.



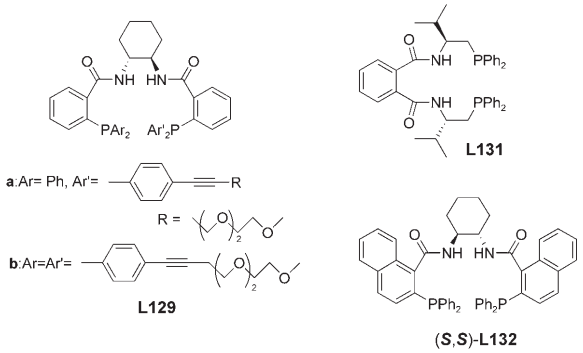
Scheme 7.

Table 5: Enantioselective allylation of various nucleophiles with cyclic allylic substrates in the presence of chiral bidentate P,P ligands.[a]



Ligand	E	*n*	Nu—H/Na	Yield [%] (*ee* [%])	Ref.
L131	Piv	2	$CH_2(CO_2Me)_2$	64 (>99 **M**)	[77b, 120]
L129	CO_2Me	0,1	$NaCH(CO_2Bn)_2$, NaPhth, $NaSO_2Ph$	88–99 (96–99 **M**)	[118]
(*R*,*R*)-**L130**	Ac	1	$CH_2(CO_2Me)_2$	65–83 (94–>95 **M**)	[121]
(*R*,*R*)-**L130**	Ac	1	4-$MeOC_6H_4OH$, phthalimide	40–96 (92–98 **M**)	[121]
(*R*,*R*)-**L130**	Ac	0	$FCH(CO_2Et)COCH_3$	89 (94–96 **M**)	[119b]
(*R*,*R*)-**L130**	CO_2Me	1		88–90 (95–97 **M**)	[119f]
(*R*,*R*)-**L130**	CO_2Me[b]	1	(2-pyrimidyl)SH	63 (96 **M**)	[119e]
(*R*,*R*)-**L130**	CO_2Me	1	$TsNH_2$, phthalimide	93 (97 **M**)	[119i]
(*S*,*S*)-**L130**	CO_2Me	0–2	$MeNO_2$, $(Me)_2CHNO_2$	50–99 (94–99 **N**)	[119h]
(*S*,*S*)-**L132**	CO_2Me	0,1	 *n* = 1, R= Me; *n* = 2, R= Me; *n* = 1, R= H	72–99 (91–96 **N**)	[119c]

[a] R = H unless stated otherwise. [b] R = CO_2Me.



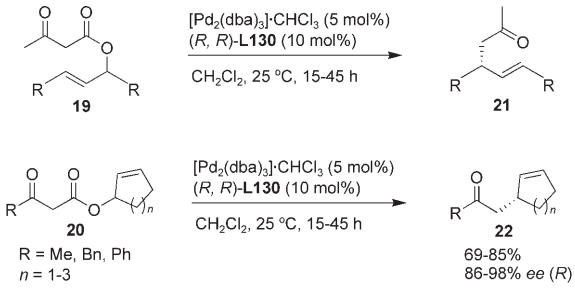
Optically active γ,δ-unsaturated enones **21** or **22** may be conveniently prepared in yields of 69–85% and with 86–98% *ee* by the aysmmetic decarboxylative allylation of **19** or **20** (Scheme 8).[123]

The highly regioselective reaction of bis(indole) derivatives **23** with 2-cyclopentenyl acetate provided monocyclopent-2-enylated bisindoles **24** with 99% *ee* (Scheme 9).[124]

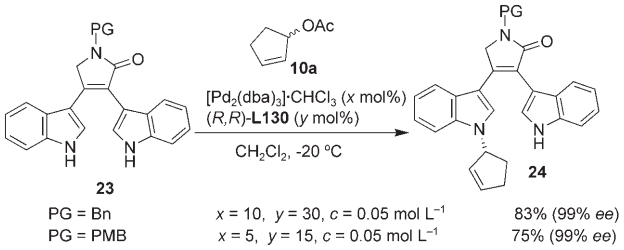
The reaction of β-keto ester **25** with cyclic allyl acetate **10a** or allyl carbonate **8b** constructed two chiral centers efficiently in the products **26** (87–91% yields) in high enantioselectivity (96–99% *ee*) and diastereoselectivity (Scheme 10).[125]

2.1.8. *Bidentate P,S Ligands*

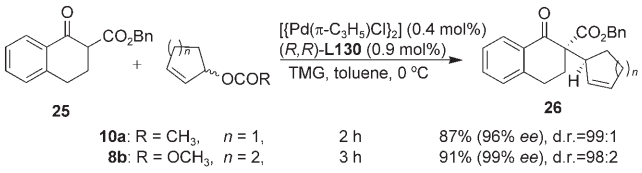
Dimethyl malonate, benzylamine, and potassium phthalimide can be allylated in the presence of bidentate *P*,*S* ligands **L133** or **L134** with ferrocenyl backbones to afford the related products **B** in 96–99.5% *ee*. The bidentate chiral P,S ligand **L135** based on a (η^5-cyclopentadienyl)(η^4-cyclobutadiene)cobalt backbone showed a very similar level of enantioselectivity. The binaphthalene framework has also been used in the successful synthesis of ligand **L136**. Furthermore, Evans et al.[130] designed a series of mixed P,S ligands: Compound



Scheme 8.



Scheme 9. PMB = *p*-methoxybenzyl, PG = protecting group.



Scheme 10. TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine.

L137 was found to be very efficient for the 1,3-diphenylallylation of dimethyl or di-*tert*-butyl malonate and dimethyl 2-methylmalonate; while ligand **L138** is the best for the benzylamination. The chiral ligands **L139** and **L140a** are slightly less effective. Performing the benchmark reaction in the presence of ligand **L141** with a chiral sulfoxide functionality afforded product **B** in 97% *ee*. The use of the polymer-supported chiral phosphanyloxanthiane ligand **L142** in the reaction with benzylamine provided product **B** with 99% *ee* (Figure 7).

Kinetic resolution of 1,3-diphenylallyl acetate with phosphane-phosphane sulfide **L143** occurred with 62% conversion to afford product **B1** with 80% *ee* and the remaining substrate (*R*)-**1** with greater than 98% *ee* (Scheme 11).[135]

This ligand is also very effective for the amination of ethyl 1,3-diphenylallyl carbonate with benzylamine, allylamine, morpholine, piperidine, and potassium phthalimide to afford the related allylamines **28** with 89–97% *ee* (Scheme 12).[136]

Moreover, the cycloalk-2-enyl acetates **10** reacted with dimethyl malonate in the presence of **L144** to afford the product **29** with 94–96% *ee*. The benzylamination reaction showed a similar level of enentioselectivity (Scheme 13).[132]

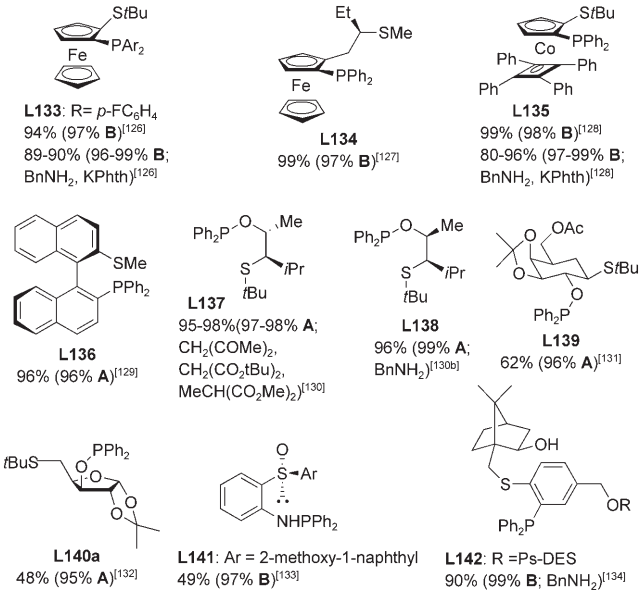
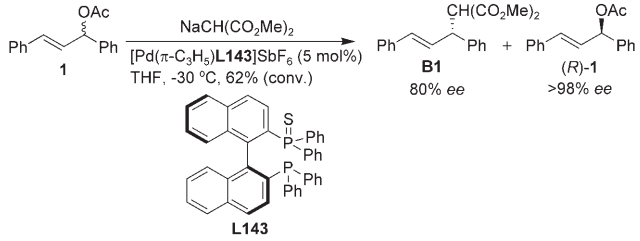
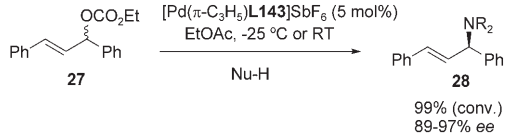


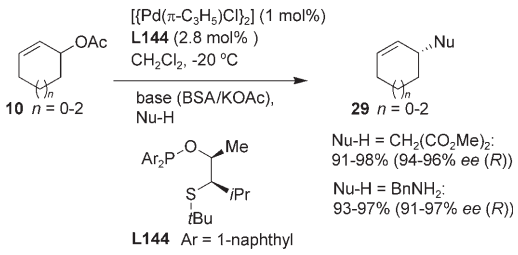
Figure 7. Selected P,S ligands for Scheme 1. $CH_2(CO_2Me)_2$ (**C**) was used as the pronucleophile. Ps-DES = polystyrene-diethylsilyl.



Scheme 11.



Scheme 12. Nu–H = $BuNH_2$, allylamine, morpholine, piperidine, potassium phthalimide.

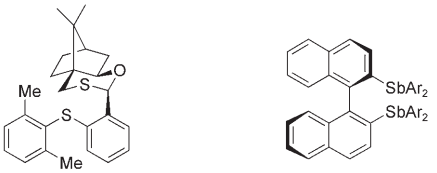


Scheme 13.

2.1.9. *Bidentate S,S and Sb,Sb Ligands*

Catalysis of the benchmark reaction of $CH_2(CO_2Me)_2$, $MeCH(CO_2Me)_2$, and $MeCH(CO_2Et)_2$ using [{Pd(π-C_3H_5)Cl}$_2$] and the chiral sulfideoxathiane ligand **L145**

afforded the corresponding products **B** in 96–99% *ee* while 2,2′-bis[di(*p*-tolyl)stibanyl]-1,1′-binaphthyl (binasb, **L146**) provided product **A** in 96% *ee* (Figure 8).



L145
92-100% (96-99% **B**; $(CH_2(CO_2Me)_2$, $MeCH(CO_2Me)_2$, $MeCH(CO_2Et)_2$)[137]

L146: Ar = *p*Tol
84% (96% **A**)[138]

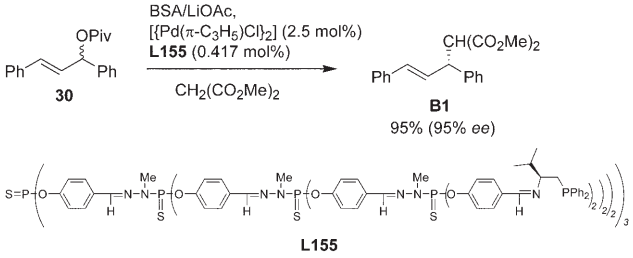
Figure 8. Selected S,S and Sb,Sb ligands **L145** and **L146** for Scheme 1.

2.1.10. *Multidentate Ligands*

The reaction of dimethyl malonate with 1,3-diphenylallyl acetate in the presence of the chiral N,N′,P,P′ ligands **L147**–**L149** afforded products **A** or **B** with ≥96% *ee*,[139] while the use of chiral ligand **L150** containing two oxazoline-pyridine units in the same reaction afforded enantiomer **A** with greater than 98% *ee*. The chiral ligand **L151**, in which the nitrogen atom in the pyridine moiety can chelate together with one of the two amines to the palladium center, is also quite effective. The bis(oxazoline-phosphane) ligand **L152** and the bis-(oxazine)-phosphane ligand **L153** afforded products **A** (97% *ee*) an **B** (95% *ee*), respectively (Figure 9).

Besides $CH_2(CO_2Me)_2$, $BnCH(CO_2Me)_2$ and $PhCH(CO_2Me)_2$ can also be allylated with 1,3-diphenylallyl carbonate by using the $[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$/**L151** catalyst system to afford the products **H** in 88–89% yields and 97–99% *ee* (Table 2).[141] The reaction of $CH_2(CO_2Me)_2$, $AcNHCH(CO_2Me)_2$, $CF_3CONHCH(CO_2Me)_2$, or $PhCONHNH_2$ with 3-penten-2-yl acetate in the presence of the chiral phosphane-bisoxazoline **L154** afforded the corresponding products in 98% yield and 85–95% *ee* (Table 2).[144]

The reaction of dimethyl malonate with 1,3-diphenylallyl pivalate in the presence of chiral imino-phosphanyl dendrimer **L155**, afforded product **B1** in 95% yield and 95% *ee* (Scheme 14).[145]



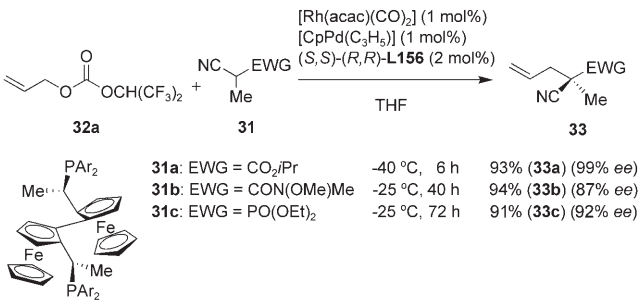
Scheme 14.

2.2. *Enantioselective Intermolecular Allylation with Unsubstituted Allyl Acetates, allyl Carbonates, and Allyl Alcohols*

2.2.1. *Allylation with Carbon Nucleophiles*

2.2.1.1. *Stabilized Nucleophiles*

The reaction of allyl 1,1,1,3,3,3-hexafluoroisopropyl carbonate (**32a**) with α-cyanopropanoate (**31a**) using $[Rh(acac)(CO)_2]$ and $[Pd(Cp)(C_3H_5)]$ as a two-component catalyst system with (*S*,*S*)-(*R*,*R*)-trap (**L156**) afforded α-allylation product **33a** in 93% yield and 99% *ee*.[146] This catalyst system was also applicable to the enantioselective allylation of *N*-methoxy-*N*-methyl-2-cyanopropionamide (**31b**) and diethyl 1-cyanoethylphosphonate (**31c**; Scheme 15). However, the



Scheme 15. acac = acetylacetonate, EWG = electron-withdrawing group.

reaction of allyl acetate **32b** with isopropyl-α-(3,4-dichlorophenyl)-α-cyano acetate and (*S*,*S*)-**L130** afforded the α-allylation product in 100% conversion, but with low enantioselectivity (60% *ee*).[147]

The allylation of α-nitropropionate **34** catalyzed with $[Pd_2(dba)_3]\cdot CHCl_3$ and the ferrocence-based P,P ligand **L157** containing an azacrown ether unit afforded the corresponding α-allylation product 4-enoate (*R*)-**35** in 92% yield and 80% *ee* (Scheme 16).[148]

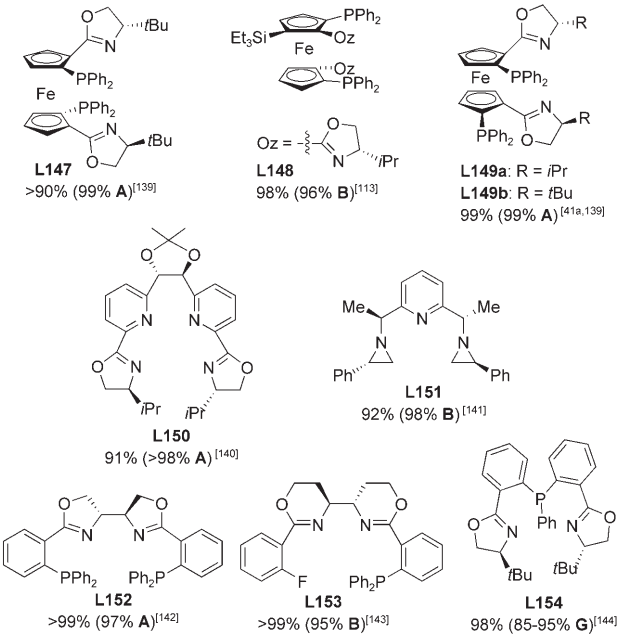
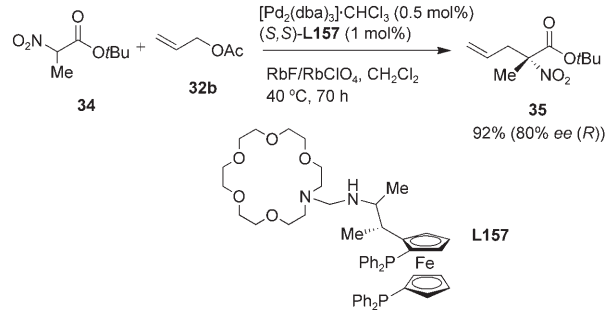
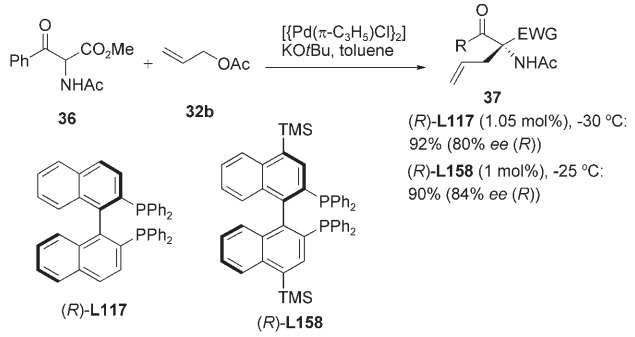


Figure 9. Selected multidentate ligands for Scheme 1. $CH_2(CO_2Me)_2$ (**C**) was used as the pronucleophile.



Scheme 16.

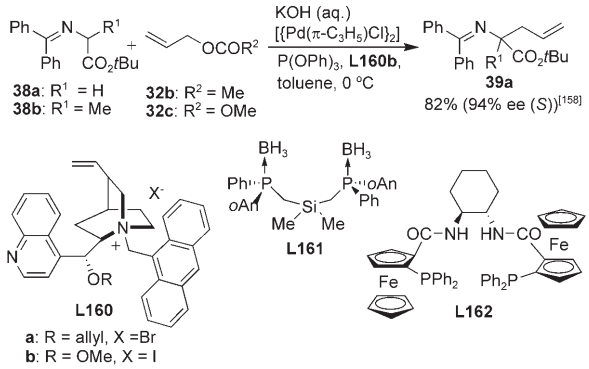
Even α-acetamido-substituted β-keto ester **36** can be allylated with **32b**, with the asymmetric induction being better with (*R*)-**L158**[149] than with (*R*)-**L117** (Scheme 17).[150] However, the enantioselectivities of the reactions of β-keto phosphonates and α-methoxycarbonyl phosphonates are rather low.[151]



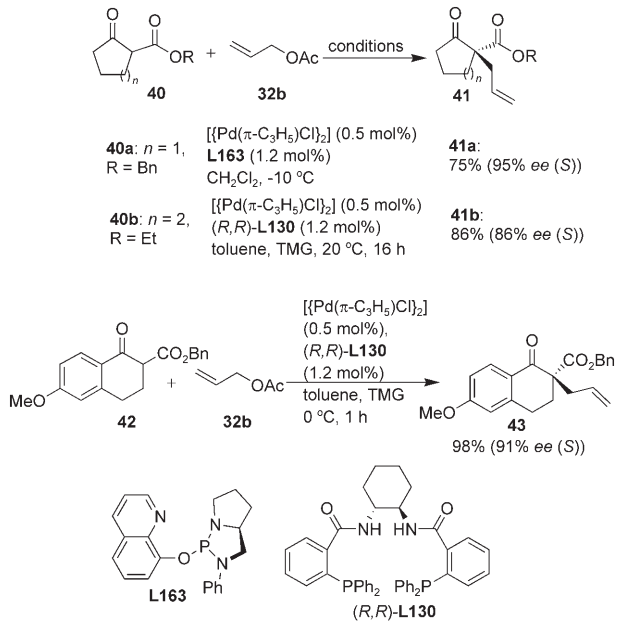
Scheme 17.

Prochiral cyclic nucleophiles such as 1,5-disubstituted barbituric acid derivatives and alanine-derived azalactone gave low enantioselectivities in the reaction with allyl acetate.[152–154] The reaction of *N*-(diphenylmethylene)glycinate **38a** in the presence of the chiral phase-transfer catalyst **L160a** and PPh_3[155] or the bidentate chiral P,P ligands **L161**[156] and **L162**[157] afforded the product **39a** with low enantioselectivity (43–61% *ee*). However, the corresponding reaction of **38a** with allyl carbonate in the presence of [{Pd(π-C_3H_5)Cl}$_2$], $P(OPh)_3$, and the chiral phase-transfer catalyst **L160b** afforded the α-allylation product **39a** with up to 94% *ee* (Scheme 18).[158] The reaction of *tert*-butyl α-methyl-*N*-(diphenylmethylene)glycinate (**38b**) with allyl carbonate **32c** afforded the product **39b** in only 75% *ee*.[157]

Cyclic α-alkoxycarbonyl ketones can also be allylated in the α position: in the presence of the chiral ligand quiphos (**L163**), the reaction of allyl acetate (**32b**) with β-keto ester **40a** afforded α-allyl-β-keto ester **41a** in 75% yield and 95% *ee* (Scheme 19).[159] The use of (*R*,*R*)-**L130** in the reaction of **32b** with α-ethoxycarbonylcyclohexanone (**40b**) or benzocyclohexanone **42** afforded **41b** or **43** with relatively low enantioselectivities (86 and 91% *ee*, respectively).[125] However, the reaction using (*R*)-binap ((*R*)-**L117**) afforded the product with only 64% *ee* (Scheme 19).[160]



Scheme 18. An = $MeOC_6H_4$.

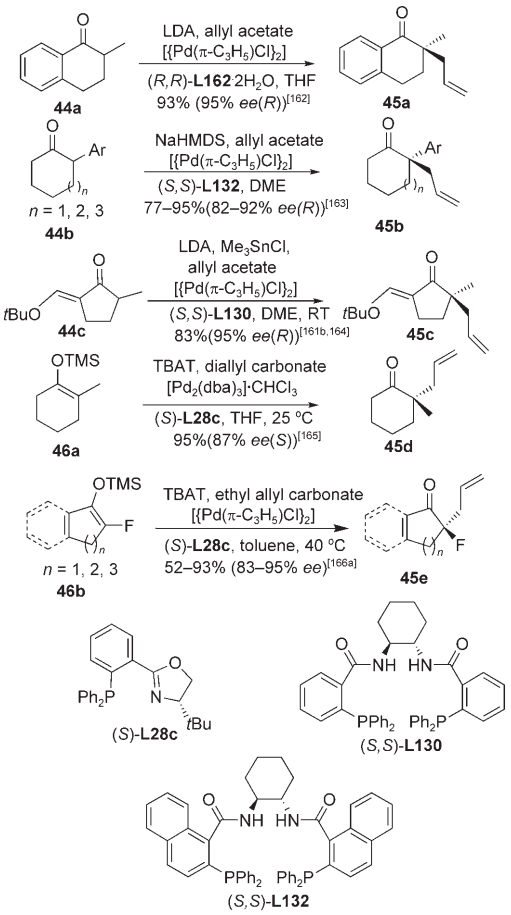


Scheme 19.

2.2.1.2. *Enolates of Ketones*

Although the carbanions of malonate derivatives and β-keto esters have been used sucessfully as nucleophiles for the asymmetric allylic alkylation reactions, enolates of ketones usually give unsatisfactory results. The successful development of the palladium-catalyzed asymmetric allylation using ketone enolates as the nucleophiles was reported by Trost et al. in 1999: under the optimized reaction conditions, the α-allylated product (*R*)-**45a** could be isolated in 99% yield and 88% *ee* by using the catalyst system [{Pd(π-C_3H_5)Cl}$_2$]/(*S*,*S*)-**L130**.[161a] In 2001, Hou, Dai, and co-workers reported that ferrocene-based bidentate ligand **L162** (Scheme 18) with two molecules of crystal water is a more efficient ligand, and affords **45a** in 93% yield and 95% *ee* (Scheme 20).[162]

Trost et al. also reported the palladium-catalyzed asymmetrc allylic alkylation of α-aryl ketones **44b** in the presence of (*S*,*S*)-**L132** to afford α-allylated ketones **45b** in good yields and enantioselectivities.[163] Furthermore, the reaction of cyclopentanone derivative **44c** has been used as a key step for the total synthesis of hamigeran.[161b,164] The research



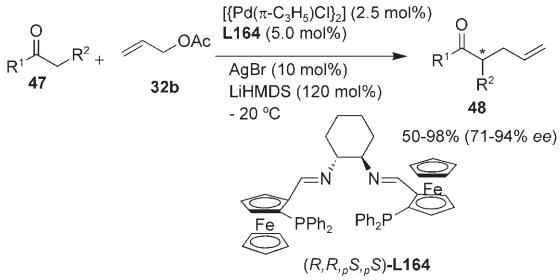
Scheme 20. LDA = Lithium diisopropylamide, DME = 1,2-dimethyloxyethane, HDMS = hexamethyldisilazide, TBAT = tetrabutylammonium triphenyldifluorosilicate.

groups of Stoltz and Paquin used (*S*)-**L28c** to achieve the enantioselective allylation of enol silyl ethers **46a** and **46b** to prepare cyclic ketones **45d** and **45e** in high yields and good enantioselectivity (Scheme 20).[165,166a] The similar reaction of enol trimethylsilyl ether **46a** in the presence of **L130** afforded **45a** or **45e** with only 82% *ee* (*R*).[161b]

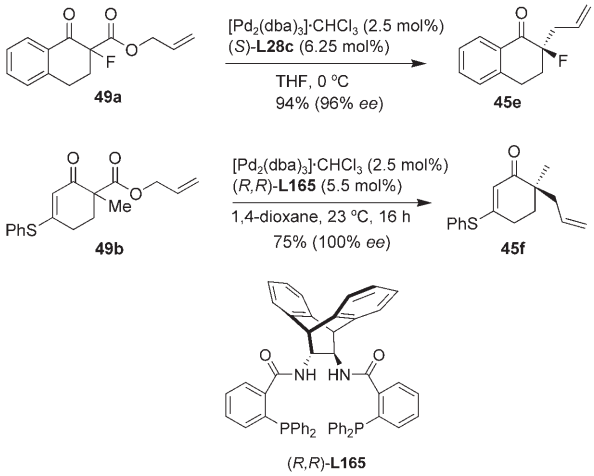
Furthermore, the reaction of acyclic ketones **47** with allyl acetate (**32b**) in the presence of $[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2.5 mol%) and chiral bisiminoferrocene ligand **L164** (5 mol%) afforded γ,δ-unsaturated enones **48** with good to excellent enantioselectivities, especially for α-alkoxy, acetoxy, or phenyl-substituted ketones (Scheme 21).[167]

Nakamura et al. reported that racemic allyl α-fluoro-β-keto ester **49a** may be converted into the corresponding optically active α-fluoro-α-allyl bicyclic ketone **45e** by the palladium-catalyzed enantioselective extrusion of carbon dioxide in the presence of ligand (*S*)-**L28c** (Scheme 22).[166b] A similar decarboxylative allylation of **49b** with (*R,R*)-**L165** was reported to afford cyclohexenone derivative (*R*)-**45f** with 100% *ee*.[168]

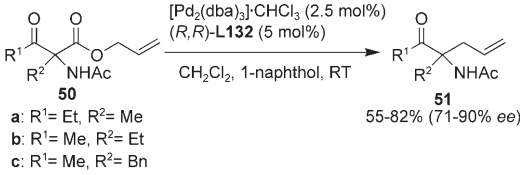
A similar reaction was also observed for acyclic α-acetamido-substituted allyl β-keto esters **50** and afforded optically active γ,δ-unsaturated α-acetamidoenones **51** with up to 90% *ee* (Scheme 23).[169]



Scheme 21. R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, *c*Hex, 2-furyl; R^2 = Me, OMe, OEt, O*i*Pr, Ph, OAC, OPh.



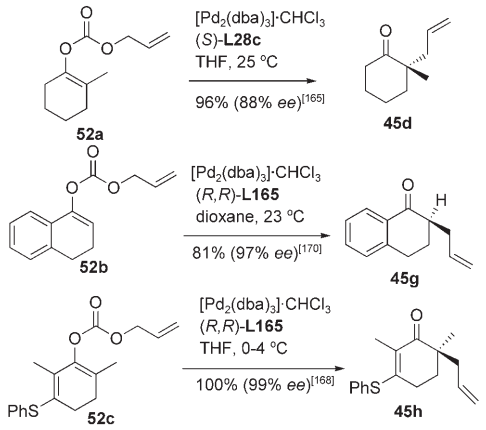
Scheme 22.



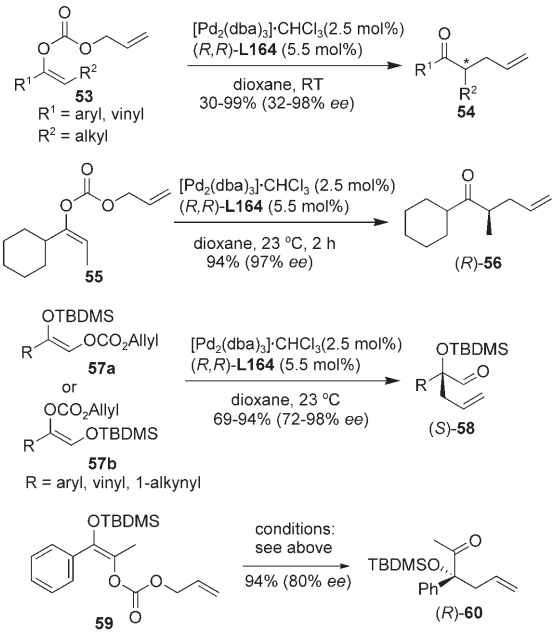
Scheme 23.

1-Cyclohexenyl allyl carbonate **52a** may also undergo an enantioselective Caroll rearrangement: after optimization, the reaction could be performed reliably in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ and (*S*)-*t*Bu-phox ((*S*)-**L28c**) to provide (*S*)-α-methyl-α-allyl cyclohexanone (**45d**) in 96% yield and 88% *ee*,[165] which has been successfully applied to the total synthesis of (−)-dichroanone.[165c] Even the stereogenic tertiary carbon center in **45g**, which has the possibility to undergo racemization, was created in high yield and enantioselectivity by using (*R,R*)-**L165**.[170] A similar extrusion of CO_2 from the 1,3-dien-2-yl allyl carbonate **52c** provided **45h** in excellent yield and enantioselectivity (Scheme 24).[168]

Recently, Trost et al. also achieved a palladium-catalyzed asymmetric CO_2-extrusion reaction of acyclic 1-alkenyl allyl carbonates **53** to afford a range of γ,δ-unsaturated enones **54** in excellent yields (up to 99%) and enantioselectivities (up to 98% *ee*, Scheme 25).[171a] These reactions proceeded via the



Scheme 24.



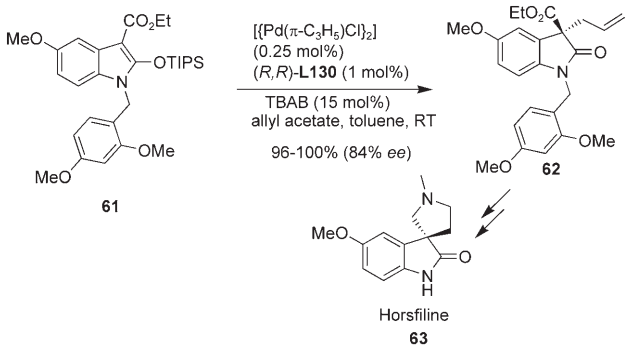
Scheme 25.

formation of a π-allylpalladium intermediate, extrusion of CO_2, and a subsequent intramolecular nucleophilic attack of the enolate on the π-allylpalladium moiety to form enone **54**. For example, the reaction of allyl carbonate (*E*)-**55** afforded the α-methyl-γ,δ-enone (*R*)-**56**.[171a] 2-Silyloxypent-4-enals **58** and ketone (*R*)-**60** can be prepared in a similar manner.[171b]

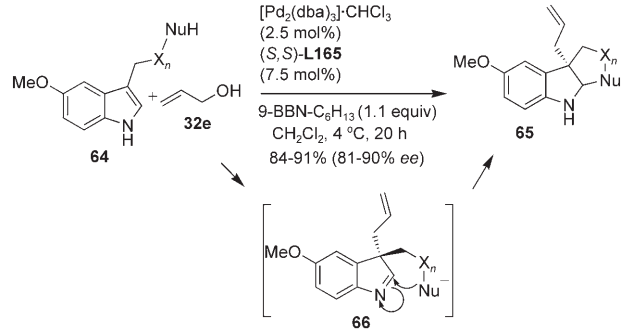
2.2.1.3. Indoles

The intermolecular allylation of indole derivative **61** has been used to synthesize the oxindole alkaloid **62** for the total synthesis of horsfiline (**63**, Scheme 26).[172]

Furthermore, Trost and Quancard developed an enantioselective C3-allylation of 3-substituted indoles **64** with allyl alcohol in the presence of 9-BBN-C_6H_{13} to give the corresponding indolenines **65** with 81–90% *ee* via the intermediacy of **66** (Scheme 27).[173]



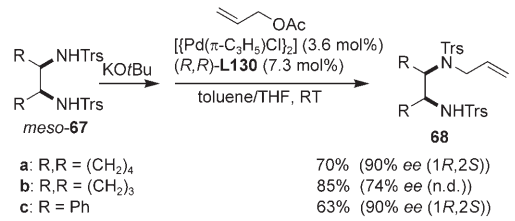
Scheme 26. TIPS = triisopropylsilyl.



Scheme 27. $X_n = CH_2$, CH_2CH_2, *o*-C_6H_4; Nu = O, NBoc, $C(CO_2Me)_2$. 9-BBN = 9-borabicyclo[3.3.1]nonyl.

2.2.2. Amides or Amines

The enantioselective allylation of *N*-[*o*-(*tert*-butyl)phenyl]amides with allyl acetate and the catalyst system [{Pd(π-C_3H_5)Cl}$_2$]/(*S*)-**L117** afforded axially chiral anilides with low enantioselectivities (up to only 56% *ee*)[174] The enantioselectivity observed in the palladium-catalyzed desymmetrization of *meso*-bis(trisylamide)s **67** with allyl acetate depends on the nature of the R group (Scheme 28).[175]

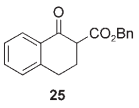
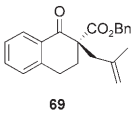
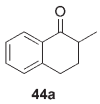
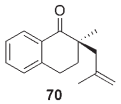
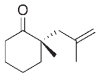
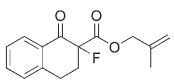
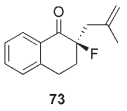
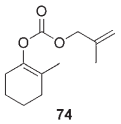
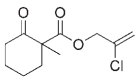


Scheme 28. Trs = 2,4,6–(*i*Pr)$_3$$C_6H_2SO_2$. n.d.: Configuration not determined.

2.3. Enantioselective Allylation with 2-Substituted Allyl Acetates and Carbonates

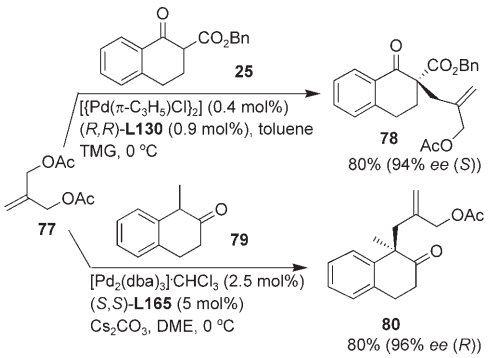
The reaction of 2-methylallyl acetate with bicyclic β-keto ester **25** in the presence of the catalyst system [{Pd(π-C_3H_5)Cl}$_2$] and (*R*,*R*)-**L130** afforded the α-allylated product (*S*)-**69** in 81% yield and 95% *ee* (Table 6).[125] Decarboxylative allylic alkylation of **72** led to fluoride **73** in 96% yield and

Table 6: Enantioselective allylation with 2-substituted allyl carbonates and acetates.

Substrate	Product	Yield [%] (*ee* [%])	Ref.
 25	 69	81 (95 (*S*))	[125]
 44a	 70	77 (87 (*R*))	[162]
 46a	 71	79 (91 (*S*))	[165]
 72	 73	96 (99 (*R*))	[166b]
 74	**71**	89 (91 (*S*))	[165]
 75	 76	87 (91 (*S*))	[165b]

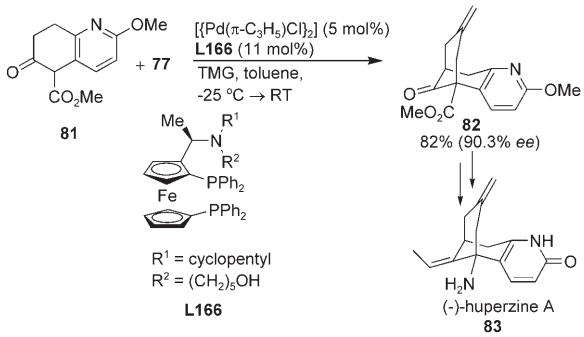
99% *ee*.[166b] Using **38a** or azalactone as prochiral nucleophiles, the reaction afforded the products with low enantioselectivities (10–47% *ee*).[154,155] The reaction of the lithium enolate of α-methylbenzocyclohexanone (**44a**) with 2-methylallyl carbonate in the presence of (*S*,*S*)-**L130** yielded (*R*)-α-methyl-α-(2-methylallyl)benzocyclohexanone (**70**) with 47% *ee*; however, the same reaction with **L162** afforded the same product (*R*)-**70** with 87% *ee*.[161,162] The reaction of trimethylsilyl enol ether of α-methylcyclohexane **46a** with bis(2-methylallyl) carbonate and the decarboxylative reaction of 2-methylallyl-2-methylcyclohex-1-enyl carbonate (**74**) in the presence of (*S*)-**L28c** afforded the same product (*S*)-**71** with 91% *ee*.[165] The decarboxylation of chloride **75** led to the formation of product (*S*)-**76** in 87% yield and 91% *ee*.[165b]

In the presence of the catalyst derived from [{Pd(π-C_3H_5)Cl}$_2$] and (*R*,*R*)-**L130** or (*S*,*S*)-**L165**, only one carbon–oxygen bond in 2-(acetoxymethyl)allyl acetate **77** is cleaved, which allows reaction with bicyclic β-keto ester **25**[125] and benzocyclohexanone derivative **79**[163] to afford the allylated products **78** and **80** with 94–96% *ee* (Scheme 29).



Scheme 29.

The doubly allylated product **82**, which is the key intermediate in the total synthesis of (−)-huperzine A (**83**), was efficiently prepared from the reaction of bicyclic β-keto ester **81** and **77** in the presence of the chiral ferrocene-based ligand **L166** in 82% yield and 90% *ee* (Scheme 30).[176] In this reaction, both carbon–oxygen bonds in **77** were cleaved to form a six-membered ring.



Scheme 30.

2.4. Allylation with 1- or 3-Substituted 2-Propenyl Acetates or Carbonates

The lack of regiocontrol is often a problem with these substrates; in general, the linear product is usually formed rather than or together with the branched isomers.

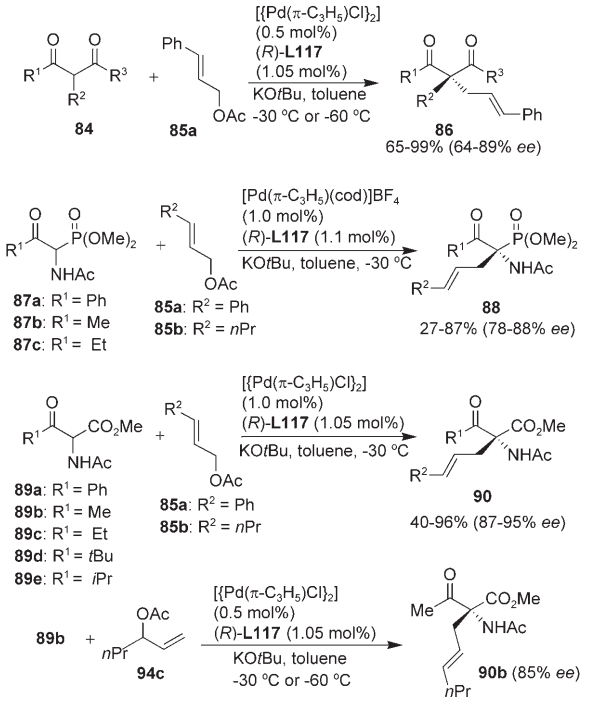
2.4.1. Formation of Linear Products

In the reactions discussed in this section, the chiral centers are usually formed within the structure of the nucleophiles. In the presence of the palladium complex of (*R*)-binap ((*R*)-**L117**), the regio- and enantioselective allylations of 2-alkyl-1,3-diketones **84**,[160] α-acetamido-β-keto phosphonates **87**,[151] and α-acetamido-β-keto esters **89**[150] provided the corresponding α-allylated linear products **86**, **88**, and **90** in moderate to good yields and high *ee* values (Scheme 31).

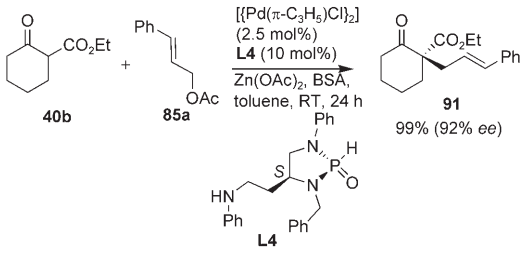
Similarly, 4,4′-bis(trimethylsilyl)-binap (**L158**) also proved to be an effective chiral ligand for the reaction of cinnamyl acetate (**85a**) with α-acetamido-β-keto ester **89a** to afford the α-allylated-α-acetamido-β-keto ester **90a** in 68% yield and 93% *ee*.[149] By contrast, it should be noted that the reaction of α-acetamido-β-keto ester **89b** with nonlinear hexen-3-yl acetate **94c** afforded the related linear product **90b** with somewhat lower enantioselectivity (Scheme 31).[150]

Asymmetric allylic substitution of α-(ethoxycarbonyl)cyclohexanone (**40b**) with cinnamyl acetate (**85a**) under the catalysis of 2.5 mol% [{Pd(π-C_3H_5)Cl}$_2$] and diaminophosphane oxide **L4** afforded chiral cyclohexanone derivative **91** in a highly enantioselective manner (Scheme 32).[177]

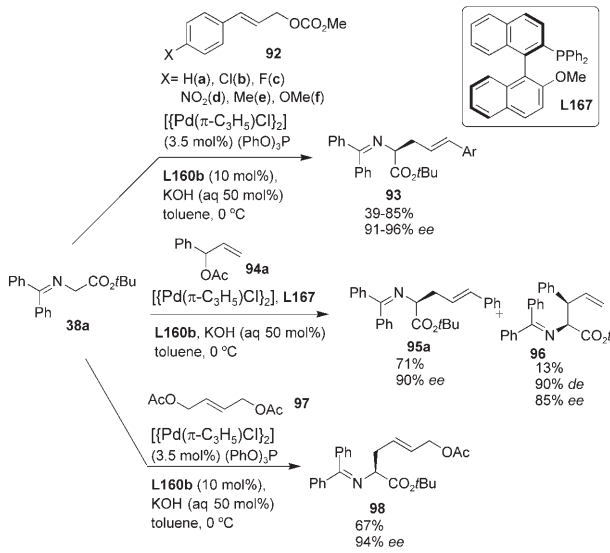
The palladium-catalyzed asymmetric allylic alkylation of substituted cinnamyl carbonates **92** with *N*-(diphenylmethy-



Scheme 31. cod = 1,5-cyclooctadiene.



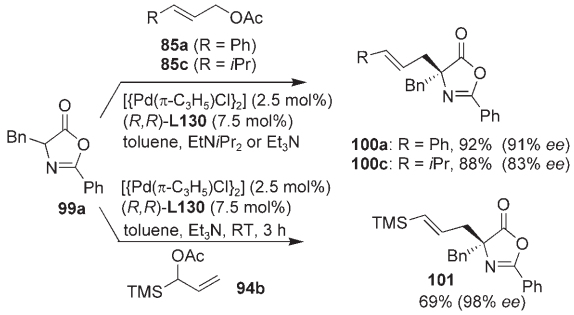
Scheme 32.



Scheme 33.

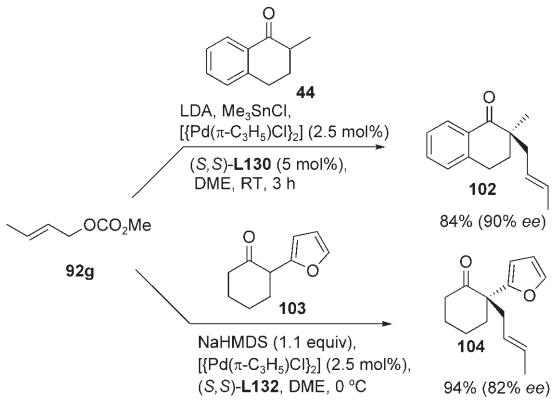
lene)glycinate **38a** was achieved using the chiral quaternary ammonium salt **L160b** as the phase-transfer catalyst. In this way linear α-amino acid derivatives **93** could be obtained with 91–96% *ee* and in moderate to good yields in the absence of any chiral phosphane ligands (Scheme 33).[158] However, the reaction of **38a** with branched 1-phenyl-2-propenyl acetate (**94a**) in the presence of $[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$, **L167**, and chiral phase-transfer catalyst **L160b** afforded the two regioisomeric α-allylation products **95a** and **96** with a relatively low regioselectivity, but good enantioselectivity (90%) for the linear product **95a** (Scheme 33)[158b] The reaction of 1,4-diacetoxybut-2(*E*)-ene ((*E*)-**97**) with **38a** in the presence of the catalyst system $[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]/(PhO)_3P$ and the chiral phase-transfer catalyst **L160b** afforded the linear monosubstitution product **98** in 67% yield and 94% *ee* (Scheme 33).[158b]

Trost and Ariza reported that the reaction of linear allylic acetates **85a** or **85c** with azalactone **99a** in the presence of (*R*,*R*)-**L130** also afforded the related linear products **100a** and **100c** with 91 and 83% *ee*, respectively.[154] In contrast, the reaction of branched trimethylsilyl-substituted allylic acetate **94b** afforded the linear product **101** with a much higher enantioselctivity (Scheme 34).[154]



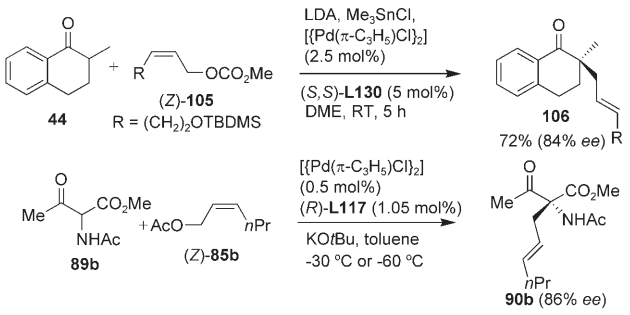
Scheme 34.

Similar reactions of α-substituted cyclic ketones **44**[161] and **103**[163] with (*E*)-2-butenyl carbonate (**92g**) also afforded linear products: the α,α-disubstituted cyclic ketones **102** and **104** were formed with 90 and 82% *ee*, respectively (Scheme 35).



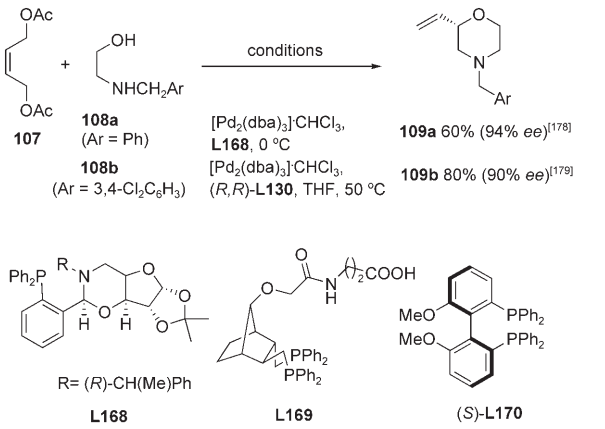
Scheme 35.

Isomerization of the double bond from *Z* to *E* was observed in the reaction of alk-2(*Z*)-enyl carbonate (*Z*)-**105** with ketone **44**[161b] or (*Z*)-2-hexenyl acetate ((*Z*)-**85b**) with α-acetamido-β-keto ester **89b**[150] to afford (*E*)-**106** and (*E*)-**90b**, respectively (84 and 86% *ee*, respectively; Scheme 36).



Scheme 36.

Morpholine derivatives **109a,b** can be constructed with 90–94% *ee* by the asymmetric intermolecular and subsequent intramolecular allylic substitution of 1,4-diacetoxy-(*Z*)-2-butene (**107**) with aminoalcohols **108a**[178] and **108b**[179] as well as **L168** and **L130**, respectively (Scheme 37).[178] This



Scheme 37.

protocol has been applied to the total synthesis of NAS-181.[178] However, the reaction of 2-butene-1,4-biscarbonate in the presence of pyridine-phosphane ligand **L67**,[180] chiral BHMP-β-Ala **L169**,[181] (*S*)-MeO-biphep **L170**,[182] or (*R*)-binap ((*R*)-**L117**)[183] afforded the related products with low to modest enantioselectivity (44–71.4% *ee*).

2.4.2. Formation of Branched Products

Concepts such as the *trans* effect of the ligand must be utilized to form the branched products. In addition, in the π-allylpalladium intermediate with chiral ligands, a large group can be incorporated in the chiral ligand to hide the less substituted terminal of the allylic intermediate so that the nucleophile attacks the more substituted position of the allylic intermediate to afford the branched product.

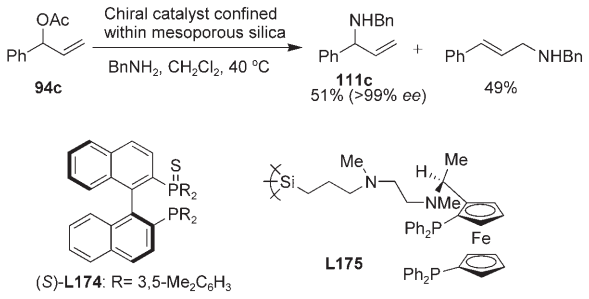
2.4.2.1. Nucleophiles

Although palladium catalysts usually favor the formation of the linear product,[103b,136,184] several specially designed ligands have been tested for their ability to achieve the enantioselective formation of the chiral branched products. Hayashi et al. developed a palladium-catalyzed enantioselective allylation of sodium malonate with 3-aryl-1-propen-3-yl acetates **94** in the presence of the sterically bulky monodentate phosphane ligand MeO-MOP ligand (**L167**) by selective substitution to afford the branched product **110a** (87% *ee*) as the major product.[1j,185] In addition, Pfaltz and co-workers demonstrated that the regio- and enantioselectivity of allylic alkylations can be tuned by systematic modification of the electronic and steric properties of the ligands in the palladium catalysts. By using the new type of chiral oxazoline ligands **L171** and **L172**, good regio- and enantioselectivitities were observed in the reaction with 3-(1′-naphthyl)-1-propen-3-yl acetate (**94e**) or **85d**.[186,187] However, low regioselectivitities were observed for other substrates with R = 2-naphthyl, phenyl, methyl, or $(CH_3)_2C{=}CH$. Pàmies et al. also noticed that high enantioselectivity (92% (*S*)) could be realized by using the similar chiral biphenol phosphite-oxazoline ligand **L64c**.[58] In 2001, ferrocene-binol ligand **L173a** was designed by Dai, Hou, and co-workers to achieve high regio- and enantioselectivity in the palladium-catalyzed allylic alkylation of monosubstituted allylic acetates **85d,e** to afford the branched products **110b,c** (Table 7).[188]

2.4.2.2. Amines

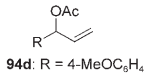
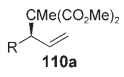
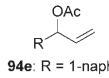
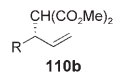
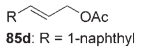
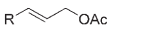
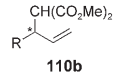
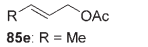
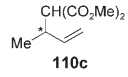
The enantioselective allylic amination of (*E*)-crotyl acetate in the presence of the chiral bidentate P,S ligand **L174** afforded the branched buten-3-ylamine with high regioselectivity, but with only 65% *ee*.[136,189] The complex formed between palladium dichloride and chiral ligand **L175** confined within mesoporous silica catalyzed the reaction of **94c** with benzylamine to provide branched allylic amine **111a** with greater than 99% *ee*, although with very poor regioselectivity (Scheme 38).[190]

The X-ray analysis of chiral ligand **L176** shows there is a hydrogen bond between the free OH group of the ligand and benzylamine as shown in **112**. The formation of this bond results in delievery of the amine to the more sterically hindered terminal, thus resulting in enantioselective allylic amination of benzylamine with branched allylic acetates **94** to

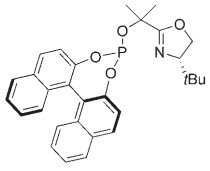


Scheme 38.

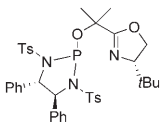
Table 7: Enantioselective allylation with 1- or 3-substituted 2-allylic acetates.

Ligand	Substrate	Product	Yield [%] b/l[a] (*ee* [%])	Ref.
L167	 **94d**: R = 4-MeOC$_6$H$_4$	 **110a**	96 90:10 (87)	[1j, 185]
L171	 **94e**: R = 1-naphthyl	 **110b**	91 96:4 (96)	[186]
L172	 **85d**: R = 1-naphthyl	**110b**	85–95 98:2 (98)	[187]
L173	 **85d**: R = 1-naphthyl	 **110b**	97 >99:1 (97)	[188]
	 **85e**: R = Me	 **110c**	83 >97:3 (94)	[188]

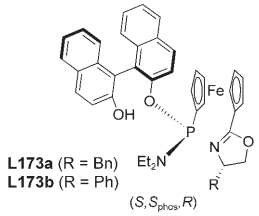
[a] Ratio of the products with branched and linear carbon chains.



L171



L172



L173a (R = Bn)
L173b (R = Ph)

(S, S_{phos}, R)

give the branched allylbenzylamine **111** in yields of 76–94% and 84–98% *ee* (Scheme 39).[1i,188]

2.4.2.3. *Phenols*

Branched allyl aryl ether **113a** may also be prepared with 90% *ee* and high regioselectivity (>96:4) by the allylation of *p*-methoxyphenol with (*E*)-crotyl carbonate (**92g**, Scheme 40).[1p] The reaction with hexen-3-yl carbonate **94f** produced a similar branched product, but with relatively lower regio- and enantioselectivities.[191]

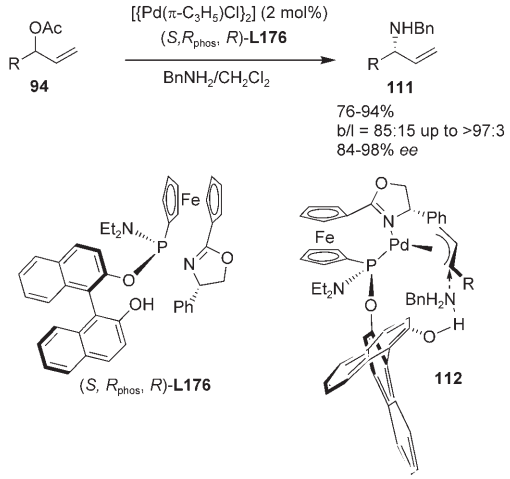
2.4.2.4. *Sodium Sulfinate*

Branched allyl sulfone **114** was prepared from the reaction of the linear (*E*)-crotyl methyl carbonate (**92g**) with sodium benzenesulfinate and the ligand (*R*,*R*)-**L130** (Scheme 41).[192]

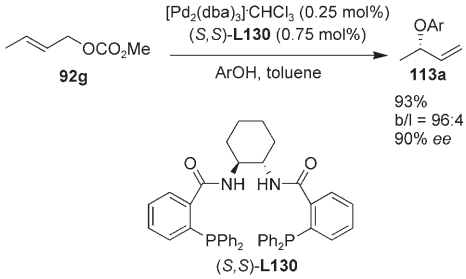
2.5. Allylation with 1,1 or 3,3-Disubstituted 2-Propenyl Acetates

2.5.1. *Reduction*

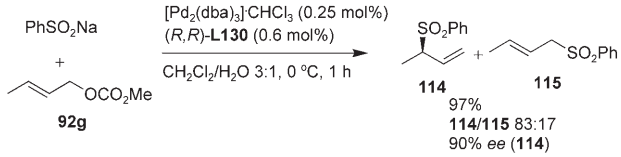
Hayashi et al.[1j,193] reported that optically active terminal alkene (*R*)-**117** could be prepared in 86% yield and 90% *ee* through the H^- ion provided by formic acid attacking at the more sterically hindered terminal of **116** (Scheme 42). In



Scheme 39. R = Ph, 1-naphthyl, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-thienyl, Me.



Scheme 40. Ar = *p*-MeOC$_6$H$_4$.



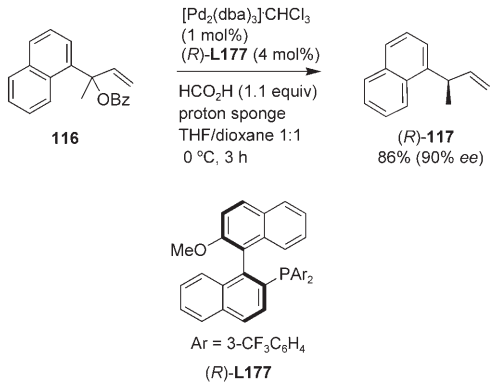
Scheme 41.

1998, Fuji et al. observed that the asymmetric reduction of (*Z*)-3-phenyl-3-(α-naphthyl)-2(*E*)-propenyl carbonate with [Pd$_2$(dba)$_3$]·CHCl$_3$ and **L177** as the catalyst system afforded (*S*)-3-(2′-naphthyl)butene (*S*)-**117** as the major product in 79% yield with 82% *ee*.[194]

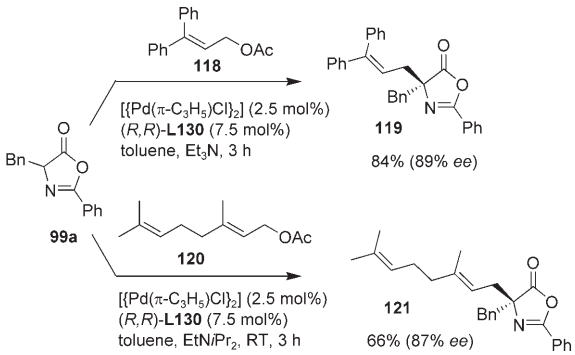
2.5.2. *Carbon Nucleophiles*

Trost and Ariza showed that the reaction of 3,3-disubstituted allylic acetates **118** or **120** with azalactone **99a** as the nucleophile provided linear products **119** and **121** with 89 and 87% *ee*, respectively (Scheme 43).[154]

Linear products **123** and **127** with higher enantioselectivity were also formed in the reaction of 3-methyl-2-butenyl acetate (**122**), 3-methylbuten-3-yl acetate (**125**), and 3-phenylbuten-3-yl acetate (**126**) with **99a** in the presence of **L130**.



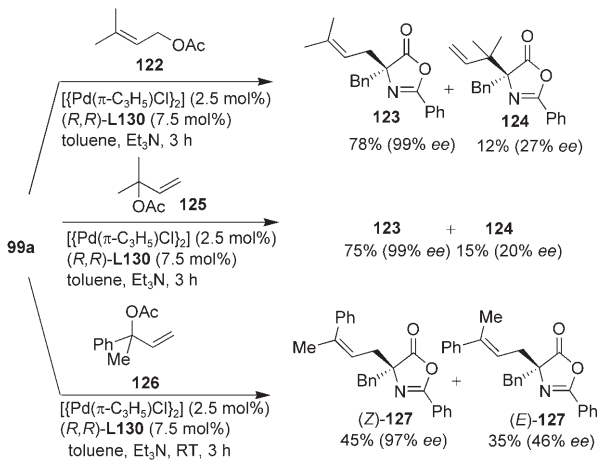
Scheme 42.



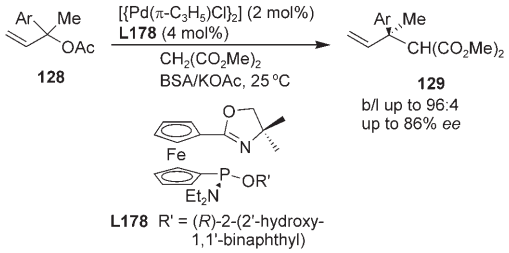
Scheme 43.

However, it is quite interesting to note that the reaction of the less hindered acetates **122** and **125** also formed the branched product **124**, albeit with low yields and enantioselectivity (Scheme 44).[154]

Furthermore, Hou and Sun noticed that the branched product **129** may also be produced as the major product (with 86% *ee*) in the related reaction of 2-aryl-3-buten-2-yl acetates **128** with dimethyl malonate in the presence of the chiral



Scheme 44.

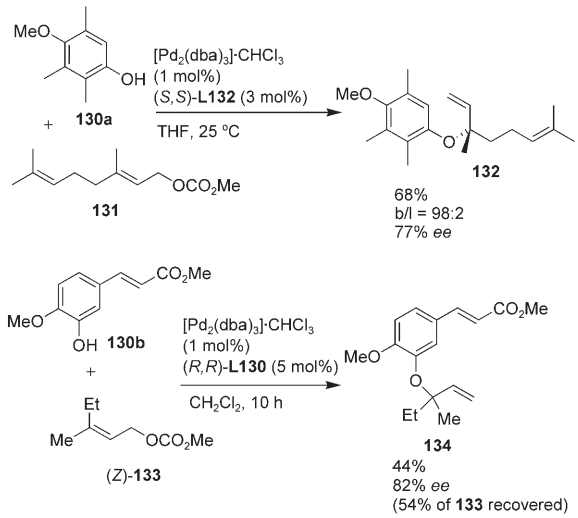


Scheme 45. Ar = Ph, 1-naphthyl, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4.

ferrocene-based ligand **L178** (Scheme 45).[195] The experimental results showed that the regio- and enantioselectivities of the reaction were controlled by the steric hindrance of the substituent on the oxazoline ring, and the configuration of the product was determined by the chirality of the phosphane.

2.5.3. Allylation of Phenols

Trost and Toste demonstrated that the reaction of substituted phenol **130a** with 2,6-dienyl carbonate **131** in the presence of (*S*,*S*)-**L132** led to the formation of the branched allyl aryl ether **132** in high regioselectivity (98:2) and 77% *ee*.[196] Tertiary allylic aryl ether **134** was prepared in a similar manner in 44% yield and 82% *ee* from the enantioselective reaction of carbonate (*Z*)-**133** with phenol **130b** in the presence of (*R*,*R*)-**L130**. However, the conversion was quite low (Scheme 46).[197]



Scheme 46.

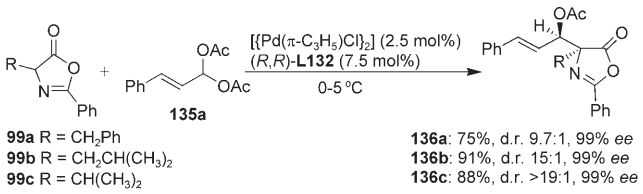
2.6. Allylation of 1,3-Disubstituted Unsymmetrical Substrates

2.6.1. Allylation with 3-Substituted Allylic gem-Diacetates

Trost et al. developed the enantioselective alkylation of the alanine-derived azalactone **99** with allylic *gem*-diacetate **135a** and ligand (*R*,*R*)-**L132** to produce α-cinnamylazalac-

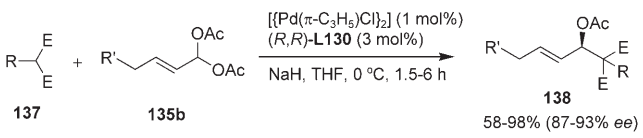
tones **136** with high regio- and diastereoselectivity, as well as excellent enantioselectivity (Scheme 47).[198]

The regioselective reaction of allylic *gem*-diacetate **135b** with various soft carbonucleophiles **137** afforded allylic



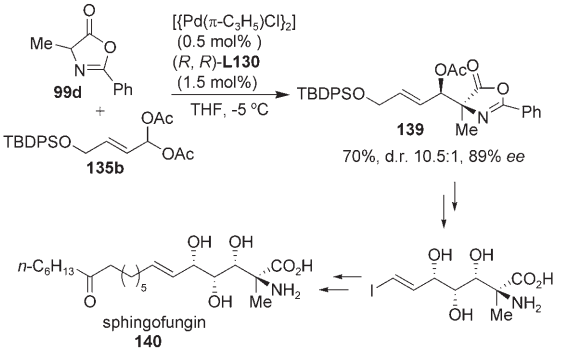
Scheme 47.

acetates **138** with 87–93% *ee* (Scheme 48).[199] This protocol has been applied as the key step in the total synthesis of sphingofungin (**140**) by using **135b** and **99d** as the substrates



Scheme 48. R = Me, Bn, OMOM, NHTroc; E = CO_2Me, CO_2Bn,CN, SO_2Ph; R′ = TBDPSO. MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, Troc = 2,2,2-trichlorethoxycarbonyl.

to prepare the fully substituted azalactone **139** (Scheme 49).[200] It should be noted that the regioselectivity in all these reactions is very high, with the nucleophile attacking the carbon atom connected to the acetoxy group.

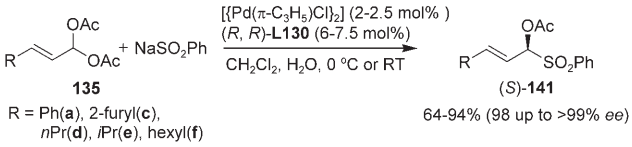


Scheme 49.

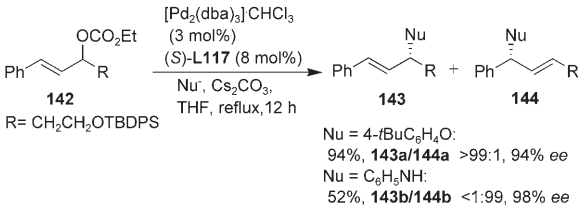
Besides the above reaction, Trost et al. also found that $NaSO_2Ph$ can also be used as the nucleophile, and its reaction with *gem*-diacetates **135** afforded the related products **141** (98 to > 99% *ee*) with the same regioselectivity (Scheme 50).[201]

2.6.2. *Allylation with 1,3-Disubstituted Unsymmetrical Allyl Carbonates and Furanonyl Carbonates*

Asymmetric allylations of a racemic 1,3-disubstituted unsymmetric substrate usually affords a mixture of regioisomeric products with low regio- or enantioselectivity.[54,56,63,141,189,202] However, excellent regio- and stereoselectivities were observed for the reaction of 4-*tert*-butylphenol with unsymmetrical 1-alkyl-3-phenylallyl carbonates **142** to afford **143a** in very high yield and stereoselectvity. A complete reversal of regioselectivity was observed when aniline was used as the nucleophile, and afforded **144b** in 52% yield and 98% *ee* (Scheme 51).[203]



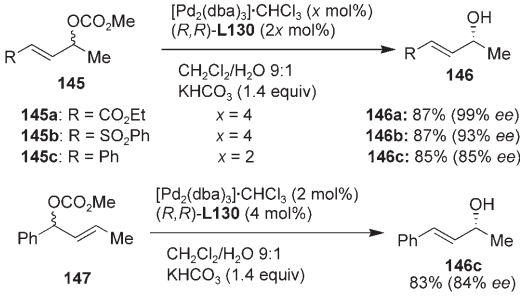
Scheme 50.



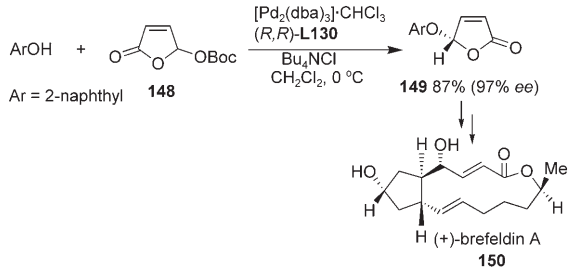
Scheme 51.

Gais et al. reported that the dynamic kinetic resolution of unsymmetrical 1,3-disubstituted allyl carbonates **145a**,**b** with H_2O formed the optically active allyl alcohols **146a**,**b** with high enantioselectivity, but that the corresponding reaction of substrates with R = CN or $P(O)(OEt)_2$ afforded the related products with low enantioselectivity. In this case the electronic effect of the R and Me groups determines the regioselectivity. The reaction of 4-phenyl-3-buten-2-yl carbonate (**145c**) or 1-phenyl-2-butenyl carbonate (**147**) afforded the same product **146c** with very similar *ee* values (Scheme 52).[204] It is clear that the substitution took place at the less sterically hindered methyl-substituted position.

Asymmetric transformation of 2(5*H*)-furanone **148** with 2-naphthol was applied by Trost et al. to prepare the optically active 5-aryloxyfuranone **149** (87% yield and 97% *ee*), which has been used in the total synthesis of (+)-brefeldin A (**150**, Scheme 53).[205]



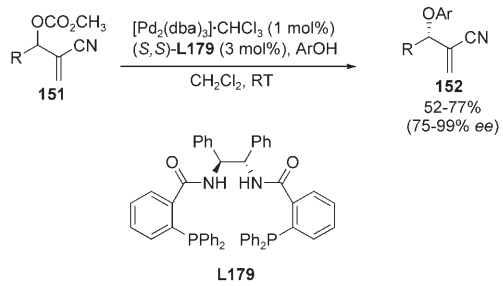
Scheme 52.



Scheme 53.

2.7. Allylation with 1,2- or 2,3-Disubstituted Allyl Carbonates

The carbonates **151** of the Baylis–Hillman adducts were also used by Trost et al. as the substrates in the palladium-catalyzed enantioselective allylation of phenols to afford the branched allyl aryl ethers **152** in yields of 52–77% and 75–99% *ee* (Scheme 54).[206]

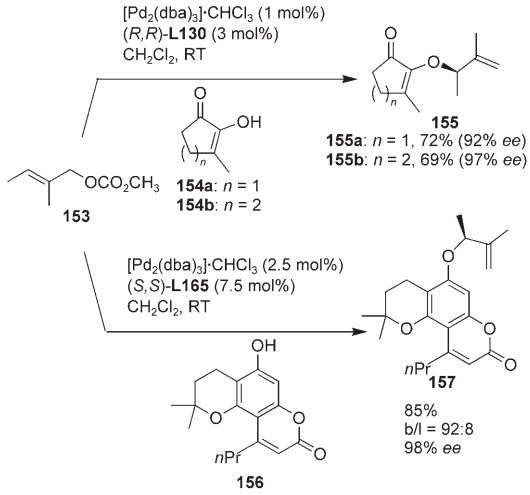


Scheme 54. R = *n*Pr, $PhCH_2CH_2$, $TBDMSO(CH_2)_3$, $tBuO_2CCH_2CH_2$, $C(OCH_2CH_2O)CH_2CH_3$; Ar = 4-$MeOC_6H_4$, 3-MeC_6H_4, 2-IC_6H_4, 2-naphthyl, 3,4-$(OCH_2O)C_6H_3$, 2-$(CHCHCO_2Et)C_6H_4$.

The same research group also reported that the enantioselective allylation of cyclic α-hydroxy-α,β-unsaturated α-hydroxy ketone **154** or phenol derivative **156** with 2-methylbut-2(*E*)-enyl carbonate **153** in the presence of ligand **L130** or **L165** afforded the branched ethers **155** or **157**, respectively, with 92–98% *ee* (Scheme 55).[119c,196]

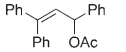
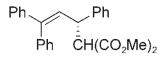
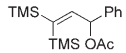
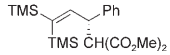
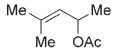
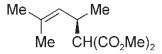
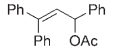
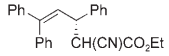
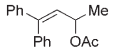
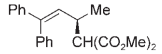
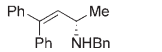
2.8. Allylation with 1,3,3- or 1,2,3-Trisubstituted 2-Alkenyl Acetates

By using the catalysis system $[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$/**L123**, asymmetric allylic alkylation of 1,1,3-triphenyl-1-alken-3-yl acetate (**158a**) with sodium malonate afforded the corresponding product (*S*)-**159a** with 85% *ee*, with the nucleophile attacking the less-substituted end.[112] Better results were obtained with **L138**[130a] and with (phosphanylaryl)oxazoline ligand **L28c**,[207] **L58**,[53] and **L28b** (90–95 *ee* (*S*) with R = aryl).[24h] Sudo and Saigo reported that **L32** is an effective ligand for the asymmetric allylic amination of **158b** (98% *ee*, Table 8).[27]



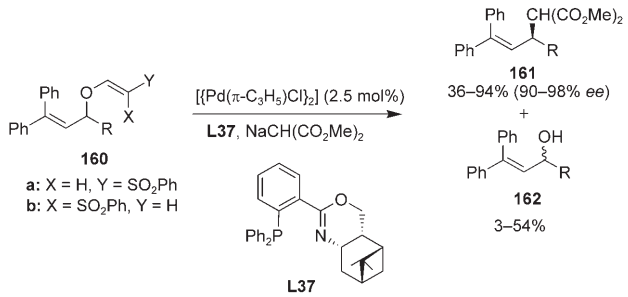
Scheme 55.

Table 8: Reaction of 1,1,3-trisubstituted allyl acetates with nucleophiles.

Ligand	Substrate	Product	Yield [%] (*ee* [%])	Ref.
L138	 **158a**	 **159a**	94 (94)	[130a]
(*S*)-**L28c**	 **158b**	 **159b**	69 (86)	[207]
L58	 **158c**	 **159c**	45 (92)[a]	[53]
(*S*)-**L28b**	 **158a**	 **159d**	74 (96)	[24h]
L58	 **158d**	 **159e**	83 (88)	[53]
L32	**158b**	 **159f**	82 (98)	[27]

[a] 36% of the other regioisomer was formed.

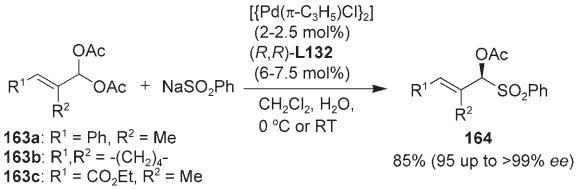
Evans and Brandt reported a similar reaction of 3,3-diphenylallyl 2-phenylsulfonylvinyl ethers **160** in the presence of chiral ligand **L37** (Scheme 56).[208] The reaction of either *E* isomer **160a** or *Z* isomer **160b** afforded malonate deriva-



Scheme 56. R = Me, Et, *n*Pr, *n*Bu, $BnOCH_2$, $BnO(CH_2)_2$, $TBSO(CH_2)_3$, $TBSO(CH_2)_4$.

tive **161** with 90–98% *ee*. However, the yields of the hydrolysis products **162** from the *E* isomer **160a** are higher.

The reaction of 2,3-substituted *gem*-diacetates **163** with $NaSO_2Ph$ afforded the related sulfone **164** with 95 to >99% *ee* and with the same regioselectivity shown in Schemes 47–50 (Scheme 57).[201]

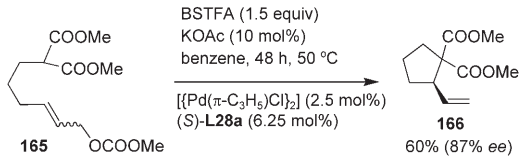


Scheme 57.

2.9. Intramolecular Allylation

2.9.1. Allylic Cycloalkylation with Carbon Nucleophiles

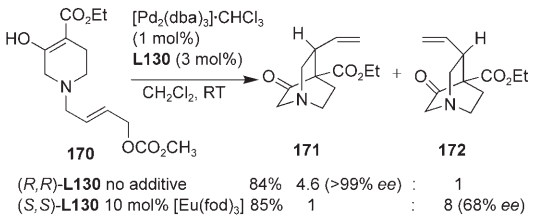
The vinylcyclopentane skeleton **166** was constructed in 60% yield with 87% *ee* by the enantioselective intramolecular allylic alkylation of 7,7′-bis(methoxycarbonyl)hept-2-enyl carbonate **165** in the presence of **L28a** (Scheme 58).[209]



Scheme 58. BSTFA = *N*,*O*-bis(trimethylsilyl)trifluoroacetamide.

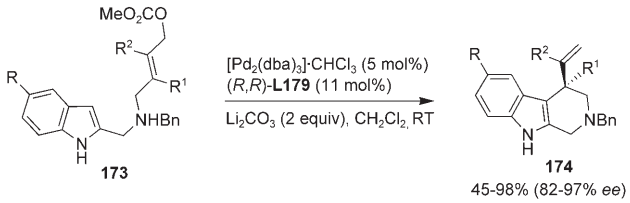
An intramolecular reaction of alka-2,4-dienyl ester **167** bearing a malonate moiety in the presence of (*S*)-**L28c** was successfully applied as the key step in the total synthesis (+)-nigellamine (**169**, Scheme 59).[210]

A similar intramolecular reaction of β-keto ester allyl carbonate **170** in the presence of chiral ligand **L130** yielded a 4.6:1 mixture of ethyl 3-oxo-8-vinylquinuclidine-4-carboxylates **171** (>99% *ee*) and **172** in 84% yield; the addition of $[Eu(fod)_3]$ afforded a 1:8 mixture of **171** **172** (68% *ee*) in 85% yield (Scheme 60).[211]



Scheme 60. fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl 3,5-octanedionate.

The 4-vinyl-1,2,3,4-tetrahydro-β-carbolines **174** were efficiently prepared in high regio- and stereoselectivities by the palladium-catalyzed asymmetric cyclization of indolyl-substituted allyl carbonate **173** in the presence of chiral ligand (*R*,*R*)-**L179**, (Scheme 61).[212]

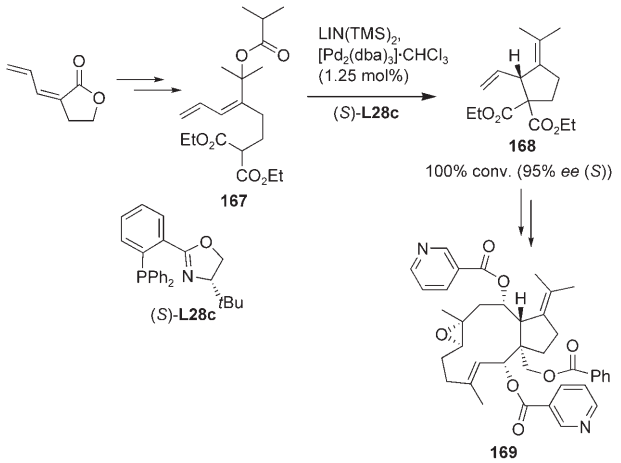


Scheme 61. R = H, OMe, Cl, Me; R^1,R^2 = H, Me.

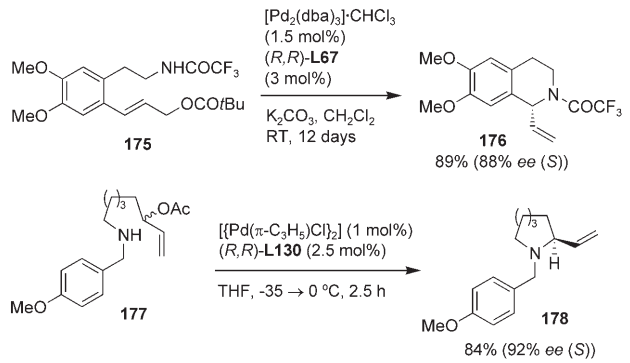
2.9.2. Cycloallylation with Amides or Amines

The palladium-catalyzed asymmetric intramolecular allylic amination of esters **175** and **177** with chiral pyridine-phosphane ligand **L67** or Trost ligand **L130** afforded the bicyclic amide **176** (89% yield, 88% *ee*)[213] and monocyclic amine **178**, respectively (84% yield, 92% *ee*; Scheme 62).[192]

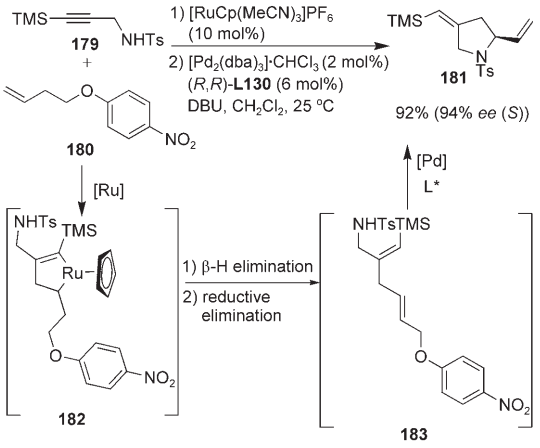
Trost et al. observed that the amine group could react intramolecularly even with an allylic ether moiety in **183**—which was prepared from the ruthenium-catalyzed cyclometalation of **179** and **180**—to afford cyclic N-tosylamide **181** (92% yield, 94% *ee*; Scheme 63).[214]



Scheme 59.

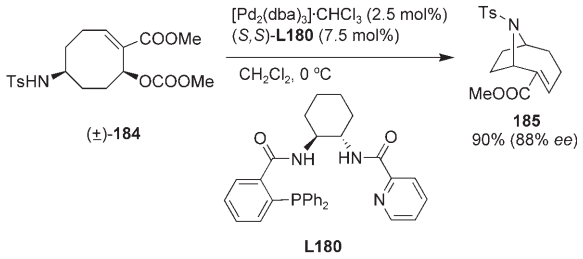


Scheme 62.



Scheme 63. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

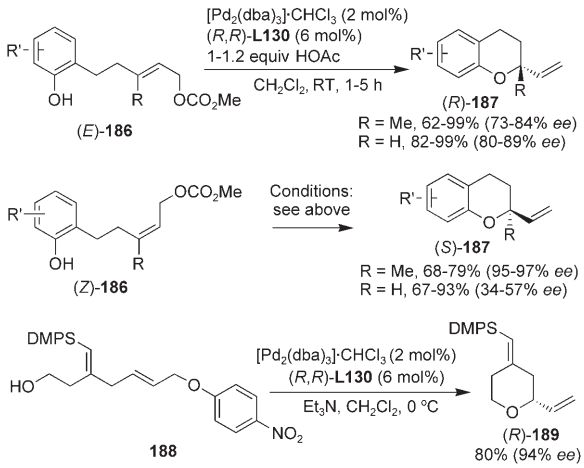
The bicyclic tosylamide **185** (88% *ee*) was formed in 90% yield from the intramolecular amination of the racemic aminocyclooctene carbonate **184** in the presence of ligand **L180** (Scheme 64).[119i]



Scheme 64.

2.9.3. Cycloallylation with Phenols and Alcohols

The intramolecular asymmetric allylation of phenols was reported by Sinou and co-workers, but the enantioselectivity of the product was low (53%).[215] However, the highly enantioselective intramolecular asymmetric allylic substitution of 5-(2′-hydroxyaryl)-2(*E*)-pentenylmethyl carbonates **186** for the synthesis of chiral chromans *R*-**187** was successfully demonstrated by Trost et al. When the ligand (*R*,*R*)-**L130** was used, the configuration of the double bond in the substrates was found to have a profound impact on the enantioselectivity and the absolute configuration of the chiral chroman products. In all the cases shown in the first two equations of Scheme 65, trisubstituted *Z* alkenes gave the highest *ee* values (95–97%) among all the substrates with R = Me, and significantly higher than their *E* isomers. In contrast, disubstituted *E* alkenes (R = H) gave substantially higher *ee* values than their *Z* isomers.[216] This method has been applied successfully in the total synthesis of chiral chromans, furaquinocin, and siccanin.[217] The intramolecular asymmetric allylic alkylation of the allylphenyl ether **188** also afforded pyran derivative **189** in 80% yield and 94% *ee* (Scheme 65).[214]



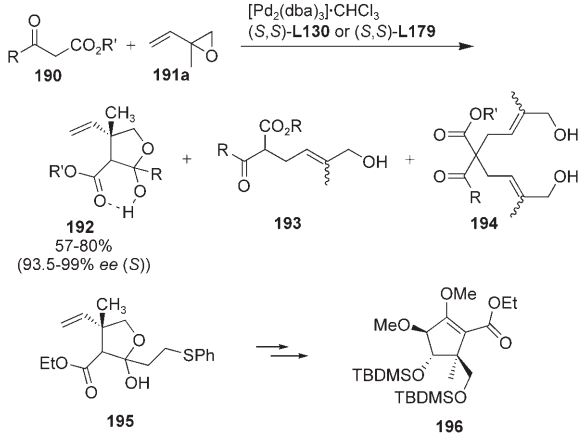
Scheme 65. R′ = H, 4-Me, H, 4-MeO, 2-MeO-4-Me, 4-F, 2,5-$(MeO)_2$-3,4-Me_2, 3-MeO-5-Me, 3,5,6-Me_3BnO. DMPS = dimethylphenylsilyl.

2.10. Allylation with Vinylic Epoxides

Cleavage of the allylic carbon–oxygen bond in vinylic epoxides a basic alkoxide moiety forms π-allylpalladium intermediates, which may allow base-free conditions to be employed.

2.10.1. Carbon Nucleophiles

Regio- and enantioselective allylic alkylation of β-keto esters **190** with vinylic epoxide **191a** and (*S*,*S*)-**L130** or (*S*,*S*)-**L179** led to the efficient preparation of optically active semiacetal **192** as the major product (Scheme 66).[218] The tetrahydrofuran derivative **195** prepared by this type of reaction was used as the key intermediate for the total synthesis of viridenomycin via **196.**[219]

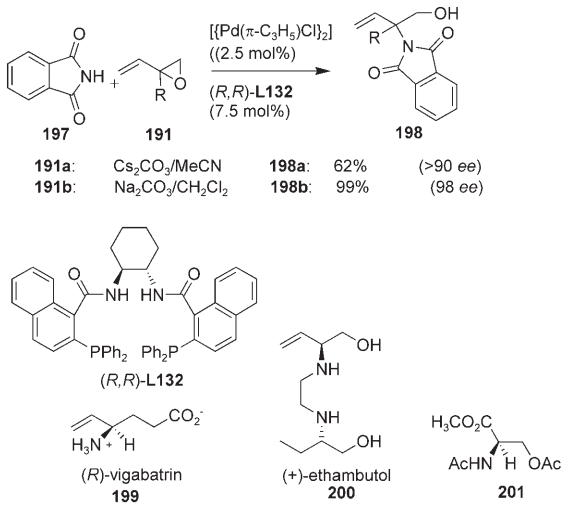


Scheme 66.

2.10.2. Nitrogen Nucleophiles

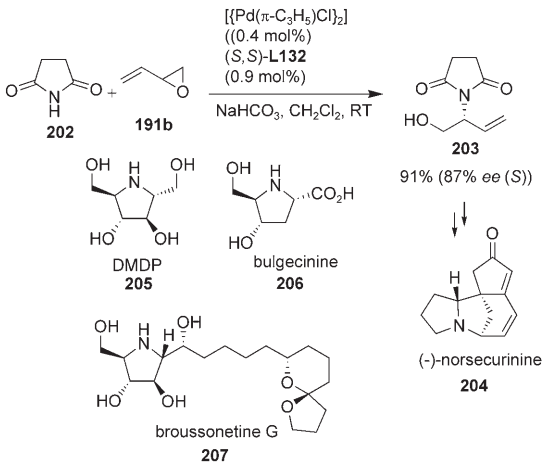
Allylation can also be performed using phthalimide as the pronucleophile. The palladium-catalyzed dynamic kinetic amination of vinylic epoxides **191a**,**b** by phthalimide in the

presence of (*R*,*R*)-**L132** afforded the corresponding α-amino homoallyl alcohols **198a**,**b** in high regio- and enantioselectivity. The power of this transformation has been demonstrated by the effecient total syntheses of (*R*)-vigabatrin **199**, (+)-ethambutol **200**, and (*R*)-serine **201** (Scheme 67).[220]



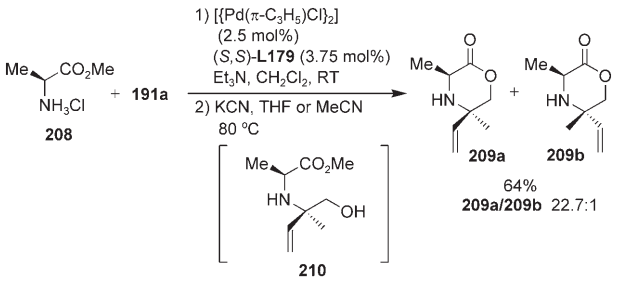
Scheme 67.

This strategy has also been used in the synthesis of (−)-norsecurinine (**204**), which was accomplished in nine steps and 11% overall yield (Scheme 68).[221] (+)-DMDP (**205**), (−)-bulgecinine (**206**), and (+)-broussonetine G (**207**) can also be prepared by this method.[222]



Scheme 68.

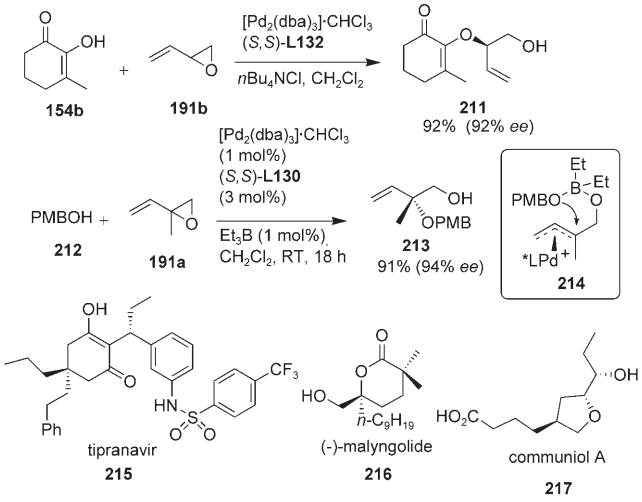
The diastereoselective aminaton of vinylic epoxide **191a** with α-aminopropanoate hydrochloride (**208**) and ligand **L179** gave α-amino ester derivative **210**, which smoothly cyclized in the presence of potassium cyanide to afford morpholin-2-one **209a** with high diastereoselctivity (**209a**/**209b** 22.7:1; Scheme 69).[223]



Scheme 69.

2.10.3. Oxygen Nucleophiles

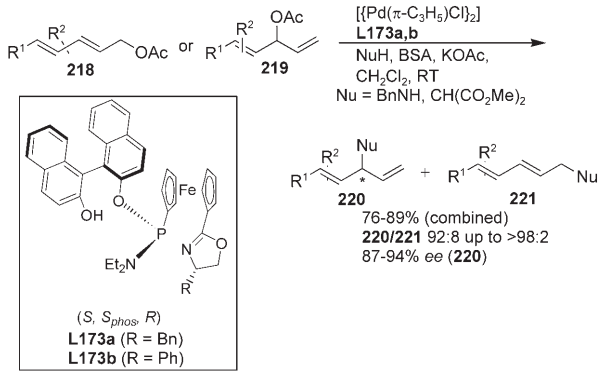
Trost and Radinov developed the enantioselective O-alkylation of 3-methyl-2-hydroxycyclohex-2-enone (**154b**) with butadiene monoepoxide **191b** and (*S*,*S*)-**L132** to provide allyl vinyl ether **211** in high regio- and enantioselectivity.[119c] The reaction of 2-methyl-1,3-butadiene-1-epoxide (**191a**) with *p*-methoxybenzyl alcohol (**212**) and the chiral ligand **L130** afforded optically active homoallylic alcohol **213** (91% yield, 94% *ee*) via the intermediacy of π-allylpalladium intermediate **214** (Scheme 70).[224] The beauty of this method has been demonstrated in the total synthesis of tipranavir (**215**),[225a] (−)-malyngolide (**216**),[225b] and the revised structure of communiol A (**217**).[225c]



Scheme 70. PMB = *p*-methoxybenzyl.

2.11. 2,4-Dienylation with 2,4-Dienyl acetates or 1,4-Dien-3-yl Acetates

Ligands **L173a**,**b** have been applied in the enantioselective reaction of the linear 2,4-dienyl acetates **218** and branched 1,4-dien-3-yl acetates **219** with benzylamine or malonate (Scheme 71).[226] The regioselectivity is between 92:8 and >98:2 in favor of the branched products **220** (87–94% *ee*).

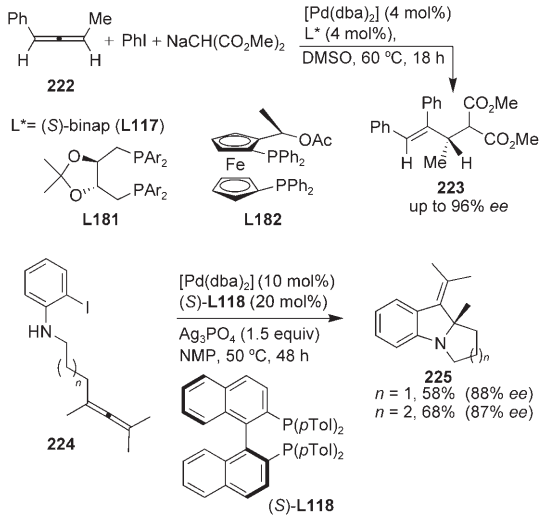


Scheme 71. R^1 = Ar, Me; R^2 = Me, H.

2.12. Alkylation with Allenes

2.12.1. Carbo- or Hydrometalation of Allenes

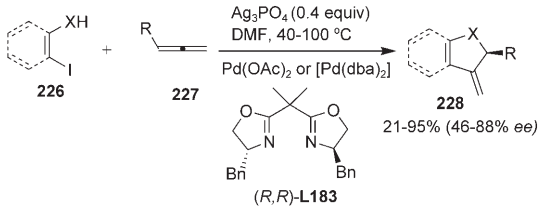
The π-allylpalladium intermediate formed by the carbopalladation of racemic 1-phenyl-1,2-butadiene (**222**) reacted with sodium malonate in the presence of the chiral phosphane ligands (*S*)-binap (**L117**), (+)-MOD-diop (**L181**; Ar = 4-methoxy-3,5-dimethylphenyl), or (*R*)-(*S*)-bppfOAc (**L182**) to give 2-allylic malonate **223** (up to 96% *ee*).[227] The intramolecular carbopalladation of allene and the subsequent asymmetric allylic amination of 2-(*N*-allenyl)aminophenyl iodides **224** constructed tricyclic products **225** efficiently (Scheme 72).[228]



Scheme 72. NMP = *N*-methylpyridinone.

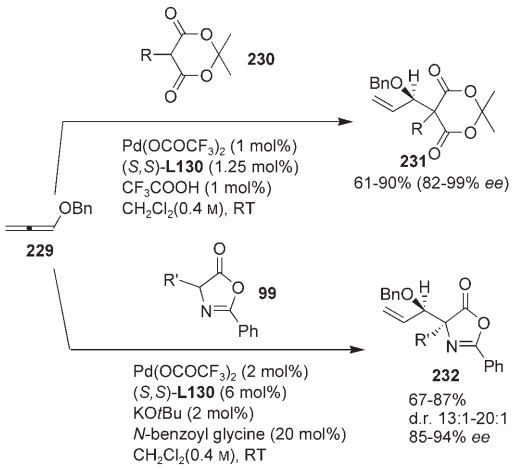
Zenner and Larock developed the reaction of aryl or vinyl iodides with a nucleophilic substituent in the *ortho* or allyl position of **226** with allenes **227** in the presence of a palladium catalyst and the chiral bisoxazoline ligand (*R*,*R*)-**L183** to afford five- and six-membered heterocycles and carbocycles **228** in 21–95% yields and 46–88% *ee* (Scheme 73).[229]

Initiated by the hydropalladation of 1,2-propadienyl benzyl ether **229**, the formed π-allyl intermedidate would react with substituted Meldrum's acid ester **230** as the pronucleophile to afford disubstituted Meldrum's acid **231**



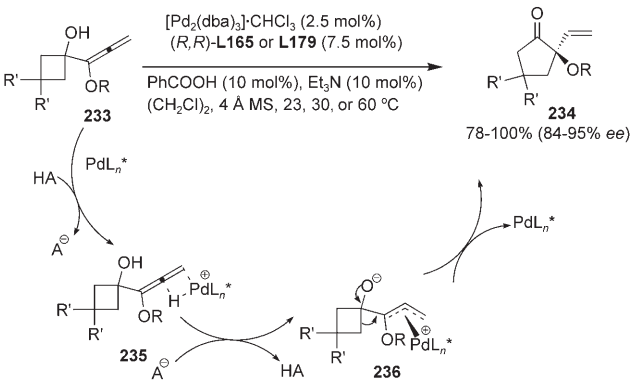
Scheme 73. XH = OH, NHTs, CH_2OH, COOH, $C(CH_3)_2OH$, $CH(COOEt)_2$; R = *n*Pr, *n*Oct.

in 61–90% yields with 82–99% *ee*.[230] The related reaction of α-alkylated azalactone **99** afforded the corresponding branched product **232** with fairly high diastereoselectivity (d.r. 13:1 to 20:1) and 85–94% *ee* (Scheme 74).[231]



Scheme 74. R = Me, $(CH_3)_2CHCH_2$, allyl, Bn, 2-$C_4H_3OCH_2$, OH; R′ = Me, $(CH_3)_2CHCH_2$, allyl, Bn, $CH_3S(CH_2)_3$.

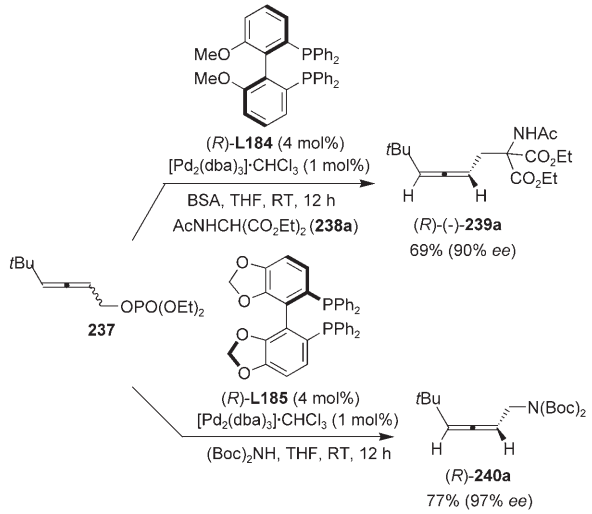
The asymmetric ring expansion of allenylcyclobutanols **233** was realized by Trost and Xie by using a similar hydropalladation to generate the π-allylpalladium intermediate **236**, which was followed by the ring expansion and asymmetric substitution with the in situ generated carbon nucleophile to afford 2-vinyl-2-alkoxycyclopentanone **234** (Scheme 75).[232]



Scheme 75. R = H, Ph, Et, $(CH_2)_4$, $(CH_2)_2CO_2Et$; R′ = Bn, PMB, $(CH_2)_{10}CH_3$, $(CH_2)_2$–CH=CH_2, $(CH_2)_3$–CH=CH_2, $(CH_2)_2$–C≡C–CH_3

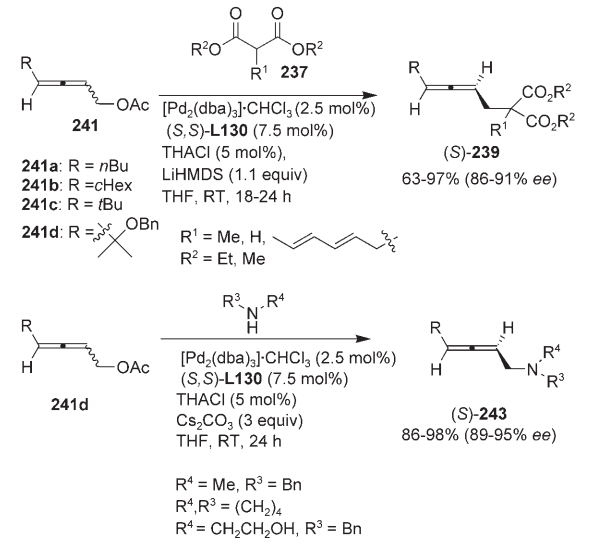
2.12.2. 2,3-Allenyl Acetates

The asymmetric alkylation of 2,3-allenyl phosphonate **237** with soft carbon nucleophile 2-acetoamidomalonate **238a** proceeded efficiently in the presence of the palladium complex of (*R*)-**L184** to afford the axially chiral allene (*R*)-**239a** in 69% yield and 90% *ee* via a vinyl-π-allylpalladium intermediate.[233] Murahashi and co-workers also reported the formation of chiral 2,3-allenylamine **240a** in 77% yield and 97% *ee* by allenylic amination (Scheme 76).[234]



Scheme 76.

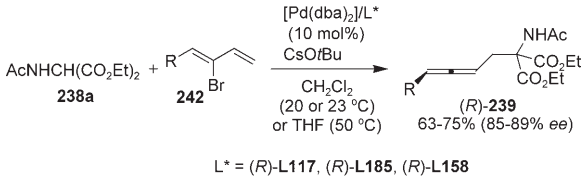
Trost et al. also reported that a similar dynamic kinetic asymmetric transformation of racemic 2,3-allenyl acetates **241** with malonates or amines in the presence of (*S*,*S*)-**L130** afforded allenes (*S*)-**239** or (*S*)-**243** in 63–98% yields and up to 95% *ee* (Scheme 77).[235] These reactions provide an excellent entry to the synthesis of these optically active functionalized allenes.



Scheme 77. THACl = tetrahexylammonium chloride.

2.13. 2,3-Dienylation of 2-Bromo-1,3-dienes

Hayashi and co-workers reported that axially chiral allenes **239** can also be prepared with 85–89% *ee*, via a similar vinyl-π-allylic palladium intermediate, by using 2-bromo-1,3-dienes **242** as the strating material (Scheme 78).[236,149]



L* = (*R*)-**L117**, (*R*)-**L185**, (*R*)-**L158**

Scheme 78. R = Ph, *t*Bu, CH_2SiMe_3.

2.14. Enantioselective Desymmetrization of Symmetric Allyl Substrates with Two Leaving Groups

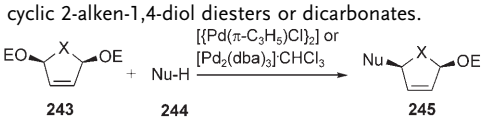
2.14.1. Enantioselective Allylation of Cyclic 2-Alken-1,4-diol Diesters or Dicarbonates

Desymmetrization of 2,5-dibenzoyloxy-2,5-dihydrofuran (**243a**) with 1-nitroethylphenyl sulfone **244a** afforded 2,5-dihydrofuran derivative **245aa** in 91% yield and 93% *ee*.[237] The reaction is quite general: a similar reaction of **243a** with **244b** afforded **245ab** with 92% *ee*.[238] The reaction of 1,4-dibenzoyloxy-2-cyclopentene (**243b**), 1,4-diacetoxy-2-cyclopentene (**243c**), 1,4-dibenzoyloxy-2-cyclohexene (**243e**) with various carbon nucleophiles produced the related products **245b**, **245c**, and **245e** with high enantioselectivity (≥95% *ee*, Table 9).[119h,239,130a,240,24d,242] However, ligands **L152** and **L130** are not very effective, and the reaction of **243b** or **243f** with dimethyl malonate in the presence of these two ligands afforded monoalkylated products *anti*-**245bd** and **245fd**, respectively, with modest enantioselectivity.[142,241] The reaction of *cis*-1,4-dibenzoyloxy-2-cyclohexene (**243e**) with α-(methoxycarbonyl)acetamide (**244g**) in the presence of the chiral monodentate phosphoramidite ligand **L188** afforded the α-allylated amide **245eg** in 83% yield and 99.4% *ee*, although in low diastereoselectivity.[243] Various nitrogen nucleophiles, such as homoallyl nosylamine **244h**, diphenylcarbamate **244i**, 6-chloropurine (**244j**), 4-methoxypyrimidin-2-one (**244k**), and trimethylsilylazide (**244l**) reacted similarly to provide the related products **245dh**, **bi**, **aj**, **bj**, **ak**, **el** with synthetically useful enantioselectivities (93–99%, Table 9).[244–248]

The regio- and enantioselective formation of a C–N bond has been realized by Trost and Dong in the reaction of 5-bromo-1*H*-pyrrole-*N*-methoxy-2-carboxamide (**246**) with *tert*-butyl-2-cyclopenten-1,4-diyl dicarbonate (**243g**) under the catalysis of $[Pd_2(dba)_3]\cdot CHCl_3$ and (*R*,*R*)-**L130** to afford the N-allylated pyrrole **247** as an intermediate. The piperazinone **248** could be prepared in 82% yield and 97.5% *ee* by a subsequent intramolecular allylic amination (Scheme 79).[249]

meso-Biscarbonate **243d** can be desymmetrized with H_2O in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ and (*R*,*R*)-**L130** to

Table 9: Enantioselective allylic alkylation with cyclic 2-alken-1,4-diol diesters or dicarbonates.



243 **244** **245**

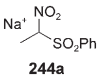
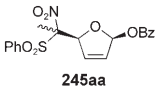
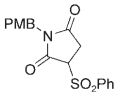
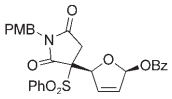
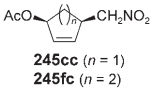
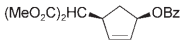
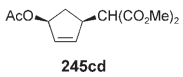
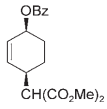
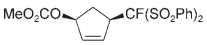
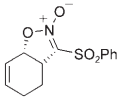
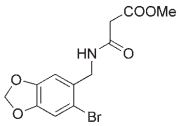
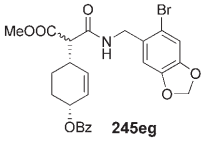
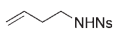
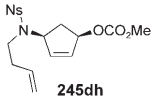
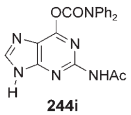
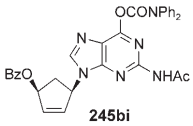
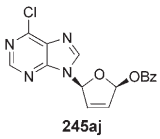
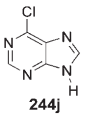
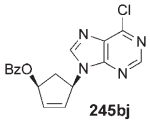
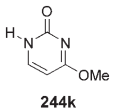
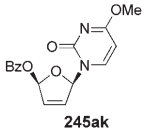
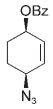
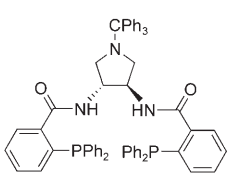
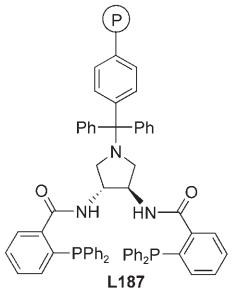
Pronucleophile	243	Ligand	Product	Yield [%] (*ee* [%])	Ref.
 **244a**	**243a** X = O, E = Bz	(*R*,*R*)-**L130**	 **245aa**	91 (93)	[237]
 **244b**	**243a** X = O, E = Bz	(*R*,*R*)-**L130**	 **245ab**	67 (92) d.r. 7:3	[238]
CH_3NO_2	**243c** X = CH_2, E = Ac **243f** X = $(CH_2)_2$, E = Ac	(*S*,*S*)-**L130**	 **245cc** (*n* = 1) **245fc** (*n* = 2)	75–84 (99)	[119h]
$CH_2(CO_2Me)_2$	**243b** X = CH_2, E = Bz	**L186** **L187**	 **245bd**	98 (98) 98 (96)	[239] [239]
$CH_2(CO_2Me)_2$	**243c** X = CH_2, E = Ac	**L144**	 **245cd**	85 (96)	[130a]
$CH_2(CO_2Me)_2$	**243e** X = $(CH_2)_2$, E = Bz	(*S*,*S*)-**L130**	 **245ed**	68 (95)	[240]
$CHF(SO_2Ph)_2$	**243d** X = CH_2, E = CO_2Me	(*R*,*R*)-**L130**	 **245de**	87 (95)	[24d]
$CH_2(NO_2)SO_2Ph$	**243e** X = $(CH_2)_2$, E = Bz	(*S*,*S*)-**L130**	 **245ef**	87 (99)	[242]
 **244g**	**243e** X = $(CH_2)_2$, E = Bz	**L188**	 **245eg**	83 (99.4) d.r. 54:46	[243]
 **244h**	**243d** X = CH_2, E = CO_2Me	(*S*,*S*)-**L130**	 **245dh**	89 (99)	[244]
 **244i**	**243b** X = CH_2, E = Bz	(*S*,*S*)-**L165**	 **245bi**	50 (96)	[245]
 **244j**	**243a** X = O, E = Bz	(*R*,*R*)-**L179**	 **245aj**	85 (93)	[246]
 **244j**	**243b** X = CH_2, E = Bz	(*S*,*S*)-**L179**	 **245bj**	76 (94)	[247]
 **244k**	**243a** X = O, E = Bz	(*S*,*S*)-**L179**	 **245ak**	65 (98)	[246]

Table 9: (Continued)

Pronucleophile	**243**	Ligand	Product	Yield [%] (*ee* [%])	Ref.
$TMSN_3$	**243e** X = $(CH_2)_2$, E = Bz	(*S*,*S*)-**L130**	 **245el**	88 (95)	[248]

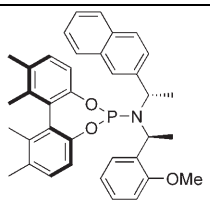


L186

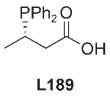


L187

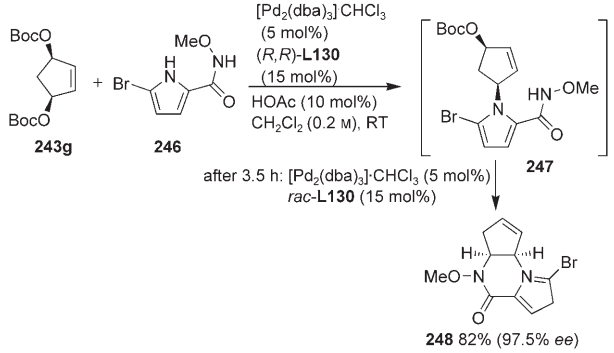
P = JandJEL (0.174 mmol% g^{-1})



L188



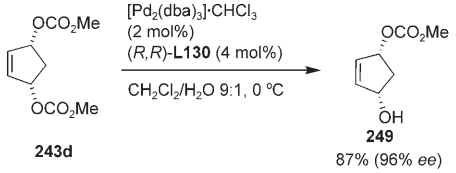
L189



243g **246** **247** **248** 82% (97.5% *ee*)

Scheme 79.

afford the optically active 4-hydroxy-2-cyclopentenyl carbonate **249** in 87% yield and 96% *ee* (Scheme 80).[204]

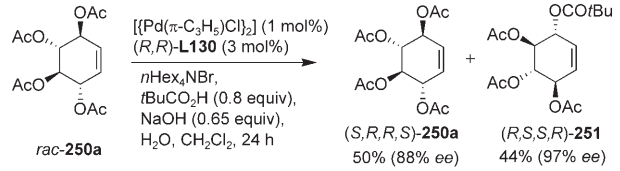


243d **249** 87% (96% *ee*)

Scheme 80.

Tetraacetoxycyclohexene *rac*-**250a** can be kinetically resolved with the catalyst system of [{Pd(π-C_3H_5)Cl}$_2$]/(*R*,*R*)-**L130**, to afford the remaining starting material (*S*,*R*,*R*,*S*)-**250a** with 88% *ee* and the product (*R*,*S*,*S*,*R*)-**251** with 97% *ee* (Scheme 81).[250]

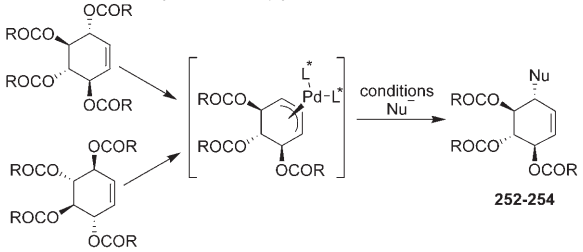
Trost et al. showed that the dynamic kinetic asymmetric reaction of the more reactive alkyl carbonate **250b** (R = OCH_2CCl_3) with various nucleophiles afforded the mono-adducts **252**–**254** very efficiently.[250,251] The reaction of **250a** with benzoic acid in the presence of [{Pd(π-C_3H_5)Cl}$_2$], (*R*,*R*)-**L130**, and NaOH as a base afforded bisbenzoate **255** in 85% yield and greater than 99% *ee* (Table 10).[251]



rac-**250a** (*S*,*R*,*R*,*S*)-**250a** 50% (88% *ee*) (*R*,*S*,*S*,*R*)-**251** 44% (97% *ee*)

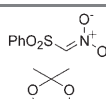
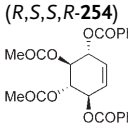
Scheme 81.

Table 10: Dynamic kinetic asymmetric transformation of tetramethyl carbonate or tetrakis(trichloroethyl) carbonates.



250a : R = CH_3
250b : R = OCH_2CCl_3

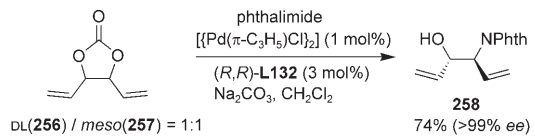
252-254

Substrate	Nu–H/Na	Method[a]	Product	Yield [%] (*ee* [%])	Ref.
250b		A	(*R*,*S*,*S*,*R*-**252**)	81 (88)	[250]
250b		A	(*R*,*S*,*S*,*R*-**253**)	95 (96)	[251]
250b	Bn_2NH	A	(*R*,*S*,*S*,*R*-**254**)	89 (95)	[251]
250a	$PhCO_2H$	B	 (*R*,*S*,*S*,*R*)-**255**	85 (>99)	[251]

[a] Method A: $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol%), (*R*,*R*)-**L130** (7.5 mol%), Cs_2CO_3, THF. Method B: [{Pd(π-C_3H_5)Cl}$_2$] (4 mol%), (*R*,*R*)-**L130** (12 mol%), THAB, NaOH, CH_2Cl_2.

Recently, Trost and Aponick developed the palladium-catalyzed asymmetric allylic amination of DL- and *meso*-1,2-

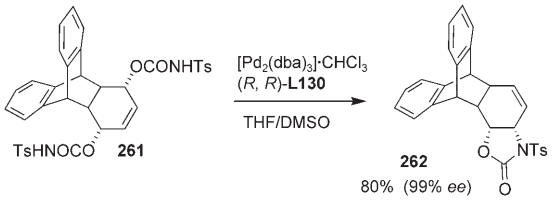
divinylethylene carbonates (**256** and **257**) in the presence of (*R*,*R*)-**L132** to afford protected chiral 4-amino-1,5-hexadien-3-ol **258** with greater than 99% *ee* (Scheme 82).[252]



Scheme 82.

The desymmetrization of *cis*-1,4-dicarbamate-2-cyclopentene **259a** by an intramolecular allylic amination with **L130**,[253] **L186**, **L187**,[239] or **L190**[255] affords the optically active bicyclic product **260a** with greater than 96% *ee*. Only low enantioselectivity (50% *ee*) was realized for the reaction of **259b** in the presence of **L152**,[142] while the reaction in the presence of **L191** afforded **260b** with greater than 99% *ee*.[254] The analogous reaction of **259a**,**b** with **L130** gave the corresponding products in 70–85% yields and 99% *ee*.[253] The use of the polymer-supported C_2-symmetric ligand **L192** led to lower enantioselectivity, but no significant decrease in either the yield or *ee* value was observed for the formation of **260b** after recycling four times (Table 11).[254]

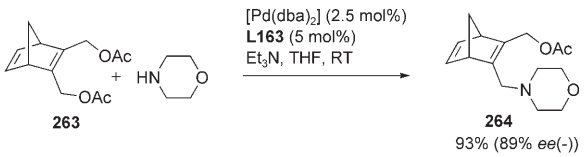
A similar reaction was observed by Trost and Patterson for biscarbamate **261** as substrate, which afforded the related cyclic carbamate **262** with high stereoselectivity (Scheme 83).[256]



Scheme 83.

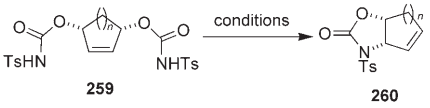
2.14.2. Desymmetrization of Acyclic 2-Alken-1,4-diol Diesters by Allylation

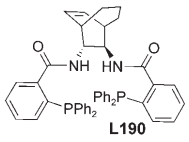
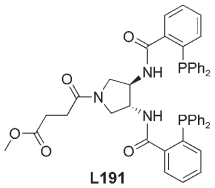
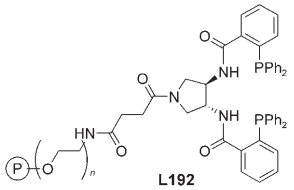
Morpholine was alkylated with 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene (**263**) in the presence of **L163** to give the monoaminated product (−)-**264** in 93% yield and 89% *ee* (Scheme 84).[257]



Scheme 84.

Table 11: Desymmetric allylic alkylation of *cis*-1,4-dicarbamate-2-cyclopentene.



Ligand	Substrate	Product	Yield [%] (*ee* [%])	Ref.
L186/**L187**	**259a** *n* = 1	**260a** *n* = 1	99 (99)	[239]
 **L190**	**259a** *n* = 1	**260a** *n* = 1	69 (96)	[255]
 **L191**	**259b** *n* = 2	**260b** *n* = 2	97 (>99)	[254]
 **L192**	**259b** *n* = 2	**260b** *n* = 2	77–81 (91–92)	[254]
(*R*,*R*)-**L30**	**259a**,**b** *n* = 1,2	**260a**,**b** *n* = 1,2	70–85 (99)	[253]

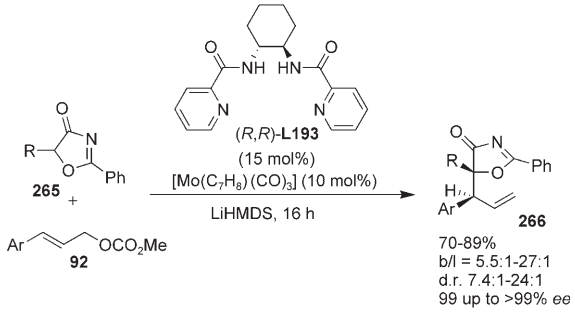
In general, palladium-catalyzed enantioselective allylations proceed via π-allylpalladium intermediates, which may be attacked by various nucleophiles to afford the enantiomerically enriched products. 1,3-Diphenylallyl acetate is usually used to test the efficiency of new chiral ligands. With unsymmetric allylic substrates, the regioselectivity may be controlled by the steric and electronic effects of the substituent(s), and the catalyst(s) determining the relative stability of the η^1- or η^3-allylmetallic intermediates formed by oxidative addition and the alkene–metal complexes after the substitution. [{Pd(π-C_3H_5)Cl}$_2$], [$Pd_2(dba)_3$]·$CHCl_3$, and [Pd(dba)$_2$] are usually used as the palladium scoure, and with the ligands developed by the Trost group, the chemistry is already very useful in asymmetric synthesis.

3. Molybdenum-Catalyzed Enantioselective Allylation[1e]

In 2004, Belda and Moberg published an account of a highly regio- and enantioselective molybdenum-catalyzed allylation.[1e] The carbonyl complexes, such as [$Mo(CO)_6$], [$Mo(CO)_3(EtCN)_3$], and [(C_7H_8)$Mo(CO)_3$], are usually used as the Mo source and the chiral pyridylamides are the best and most useful ligands. Dimethyl malonate and other malonate derivatives are often used as the nucleophiles. Unsymmetric 1- or 3-substituted allyl carbonates, acetates, and phosphates afforded products with execellent regio- and enantioselectivity. Mechanistic studies have provided conclusive evidence that the Mo-catalyzed allylic alkylation pro-

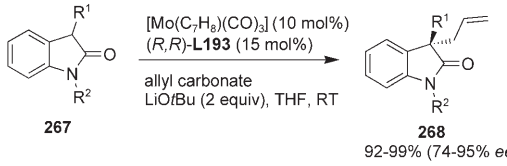
ceeds with overall retention of the configuration through a mechanism involving both an oxidative addition and nucleophilic attack.[1e]

Recently, Trost et al. reported that the reaction of cinnamyl carbonates **92** with 5*H*-alkyl-2-phenyloxazol-4-ones **265** in the presence of $[Mo(CO)_3C_7H_8]$ and the bispyridine **L193** afforded the branched α-allyl α-hydroxycarboxylic acid derivatives **266** in yields of 70–89% and with good regioselectivity and excellent enantioselectivity (Scheme 85).[258]



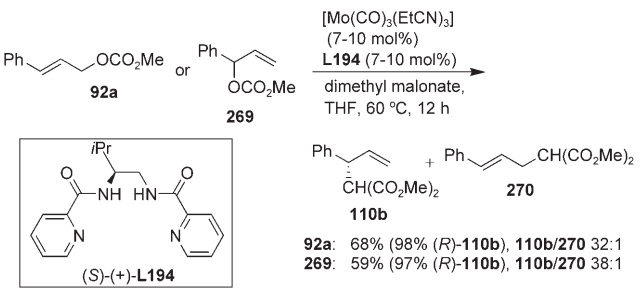
Scheme 85. R = Me, *n*Bu, Allyl, *s*Bu, *i*Pr, *c*Hex, Ph; Ar = Ph, 2-thienyl, 2-BrC_6H_4, 2,4-$(MeO)_2C_6H_3$.

3-Alkyl-2-oxindoles **267** have also been allylated with allyl carbonate in the presence of (*R*,*R*)-**L193** to afford 3-allyl-2-oxindoles **268** in 92–99% yields and 74–95% *ee* (Scheme 86).[259]



Scheme 86. R^1 = Alkyl; R^2 = Me, Bn, MOM, allyl.

Very recently, C_1-symmetric pyridine-substituted diamine (*S*)-(+)-**L194** was shown to be an efficient chiral ligand for the molybdenum-catalyzed asymmetric allylic alkylation of dimethyl malonate with isomeric carbonate **92a** and **269**: the branched product **110b** was afforded with excellent regio- and enantioselectivities (> 30:1, 97–98% *ee*, Scheme 87).[260]



Scheme 87.

4. Iridium-Catalyzed Enantioselective Allylation

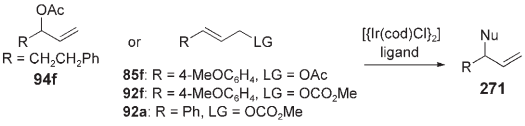
4.1. Intermolecular Reactions

4.1.1. Allylation with 1- or 3-Substituted 2-Propenyl Acetates, Carbonates, or Phosphates

4.1.1.1. Carbon Nucleophiles

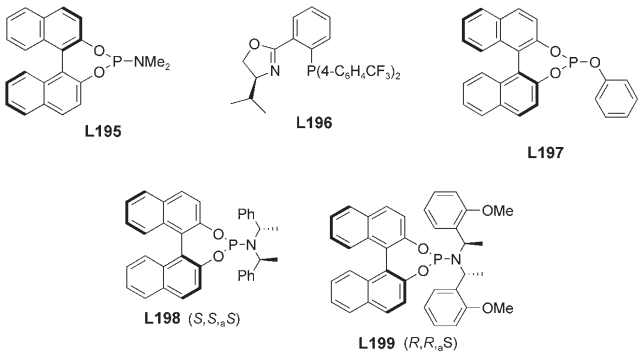
The reaction of 5-phenyl-1-penten-3-yl acetate (**94f**) with sodium malonate in the presence of chiral ligand **L195** afforded the branched product (*R*)-**271a** with 93% *ee* and high regioselectivity.[261] Sodium malonate was allylated with cinnamyl acetate **85f**, cinnamyl carbonate **92f**, or carbonate **92a** in the presence of iridium complexes with chiral ligands such as phosphane-oxazoline **L196**,[262] (*S*)-1,1′-binaphthyl-2,2′-diylphenyl phosphite **L197**,[263] chiral phosphorous amidite **L198**,[264] and **L199**,[265a–c] to afford the branched products **271** in excellent yields and with high regioselectivity (99:1) and enantioselectivity (95–98% *ee*). Nitroethane and ethyl α-nitroacetate can also be allylated with **92a** to afford the branched products **271d** and **271e**, respectively, with high regio- and enantioselectivities (Table 12).[265d]

Table 12: Iridium-catalyzed enantioselective allylic alkylation of various nucleophiles with unsymmetrical allylic substrates.

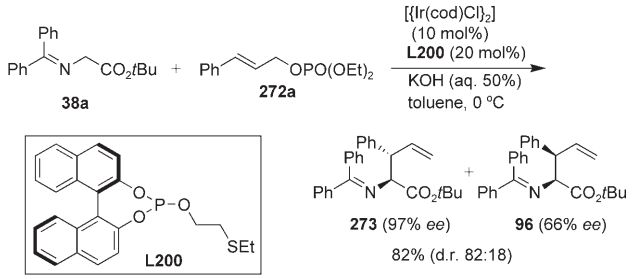


Ligand	Substrate	Pronucleophile	Product	Yield [%] (*ee* [%])	Ref.
L195	**94f**	$NaCH(CO_2Me)_2$	**271a**	99 (93 (*R*))	[261]
L196	**85f**	$NaCH(CO_2Me)_2$	**271b**	98 (95 (*R*))	[262]
L197	**92f**	$CH_2(CO_2Me)_2$	**271b**	99 (96 (*S*))	[263]
L198	**92a**	$NaCH(CO_2Me)_2$	**271c**	88 (96 (*S*))	[264]
		$NaCH(CO_2Me)_2$	**271c**	82 (98 (*R*))	[265a–c]
		$CH_3CH_2NO_2$[a]	**271d**	85[b] (98 (*S*), 96 (*S*))	[265d]
L199	**92a**	$CH_2(CO_2Et)NO_2$[a]	**271e**	90 (98 (*S*))	[265d]

[a] With diastereomer (*S*,S_a,*S*)-**L199** as the ligand. [b] d.r. = 1.

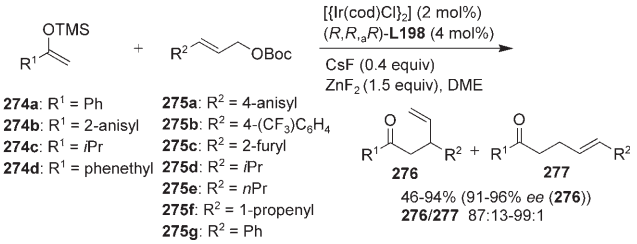


The reaction of cinnamyl phosphate **272a** with **38a** using the catalyst system [{IrCl(cod)}$_2$]/**L200** afforded an 82:18 mixture of branched diastereoisomers **273** (97% *ee*) and **96** (66% *ee*) in 82% combined yield; this reaction is complementary with that shown in Scheme 33 (Scheme 88).[266]



Scheme 88.

The branched enones **276** were produced in a highly selective manner by the reaction of trimethylsilyl enol ethers of acyclic methyl ketones **274** with allyl carbonates **275** in the presence of chiral phosphoramidite ligand **L198** (Scheme 89).[267]



Scheme 89.

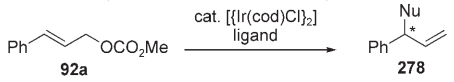
4.1.1.2. Allylation with Amines or Amides

The iridium-catalyzed enantioselective allylic amination of cinnamyl carbonate **92a** with morpholine, *p*-iodoaniline, diethyl amine, and *N*-benzyl-*N*-tosylamine afforded the products **278a–d** in yields of 72–92% and 96–98% *ee* as well as very high regioselectivity (≥98:2, Table 13).[268–271] The absolute configurations of the products can be nicely controlled through the appropriate choice of the ligands.

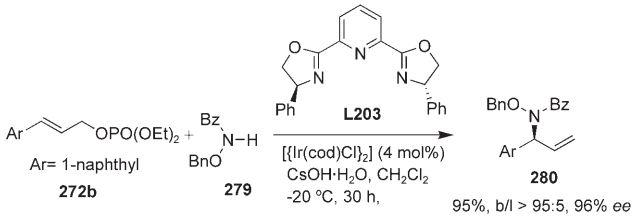
The iridium complex of ligand **L203** (pybox) was a good catalyst for the enantioselective allylic amination of 3-aryl-substituted allyl phosphate **272b**; the branched amine products **280** were formed with good regio- and enantioselectivity when *N*-(benzyloxy)benzamide (**279**) was employed as a nucleophile (Scheme 90).[272]

Singh and Han very recently demonstrated that allylamine **282** can be prepared (70–92% yield, 92 to >99% *ee*) by the regio- and enantioselective decarboxylative allylic amidation reaction of allylbenzyl imidodicarbonates **281** (Scheme 91).[273]

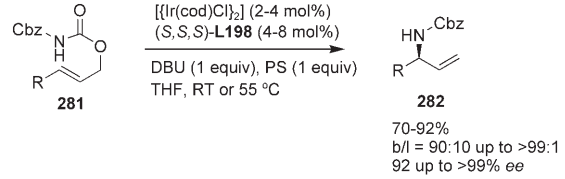
Table 13: Iridium-catalyzed enantioselective allylic amination with **92a**.



Ligand	Nu–H	Product	Yield [%] (*ee* [%])	Ref.
L198	morpholine	**278a**	92 (97 (–))	[268]
L201 (*S*,*S*$_a$*S*) Ar= 1-naphthyl	4-IC$_6$H$_4$NH$_2$	**278b**	92 (96)	[269]
L202	HNEt$_2$	**278c**	72 (97)	[270]
L199 (*S*,*S*$_a$*S*)	*p*-TsNHBn	**278d**	92 (98 (*S*))	[271]



Scheme 90.

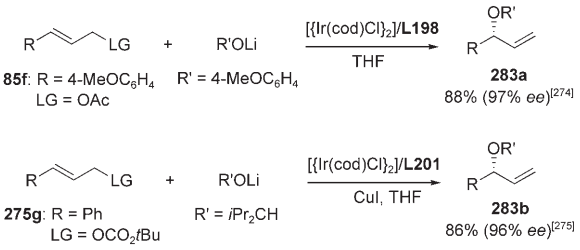


Scheme 91. R = alkyl, alkenyl, (hetero)aryl. Cbz = benzyloxycarbonyl. PS = proton sponge

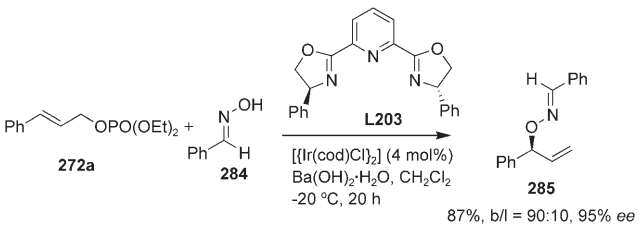
4.1.1.3. Allylation of Phenols, Alcohols, and Oximes

Hartwig and co-workers found that lithium *p*-methoxyphenolate or lithium 2,4-dimethyl-3-pentanolate may be allylated with *p*-methoxycinnamyl acetate (**85f**) or cinnamyl carbonate **275g** in the presence of [{IrCl(cod)}$_2$] and the chiral ligand **L198** or **L201** to afford the branched allylic ethers **283** in yields of 86–88% and 96–97% *ee*. The regioselectivity is 98:2 or greater (Scheme 92).[274–275]

The allylation of oxime **284** with **272a** proceeded smoothly to give the branched (*E*)-benzaldehyde-*O*-1-phenyl-2-propenyloxime **285** with high enantioselectivity (Scheme 93).[272]

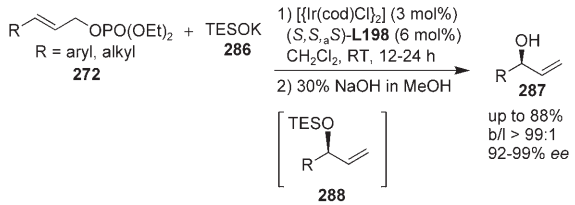


Scheme 92.



Scheme 93.

Carreira and co-workers developed an efficient synthesis of chiral allyl alcohols **287**. Regioselective iridium-catalyzed allylic etherification of a wide range of aryl- and alkyl-substituted allyl phosphates **272** with potassium silanolate **286** in the presence of (*S*,*S*$_a$*S*)-**L198** afforded allyl silyl ethers, which upon hydrolysis provided optically active allylic alcohols **287** (92–99% *ee*, Scheme 94).[276]



Scheme 94. TES = triethylsilyl.

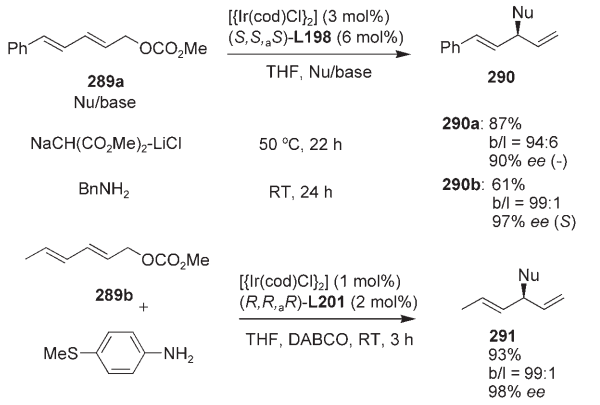
4.1.2. 2,4-Dienylations

Iridium-catalyzed alkylation of sodium malonate, benzylamine, or substituted aniline with 5-substituted 2,4-dienylmethyl carbonate **289a** or **289b** provides the branched products **290a**,**b** or **291**, respectively (Scheme 95).[277,278]

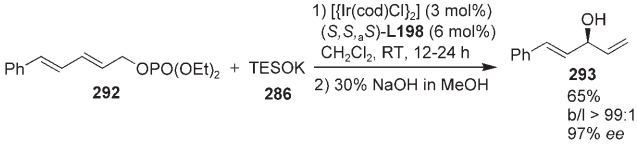
Carreira and co-workers reported a similar etherification and hydrolysis reaction of 5-phenyl-2,4-pentadienyl phosphate **292** with potassium silanolate **296** that afforded 1-phenyl-1,4-pentadien-3-ol **293** in 65% yield and 97% *ee* (Scheme 96).[276]

4.2. Intramolecular Reactions

In 2004, the Helmchen research group reported the enantioselective iridium-catalyzed intramolecular allylic alkylation of **294** for the formation of the optically active carbocycles **295** (96–97% *ee*).[279] Cyclic amines **298** can be

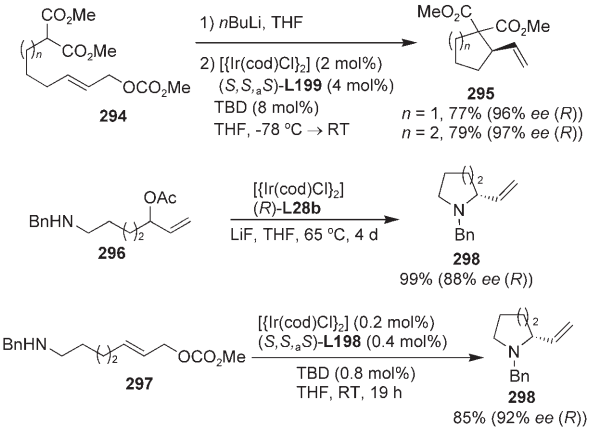


Scheme 95. DABCO = 1,4-diazabicyclo[2.2.2]octane.



Scheme 96.

prepared in an analogous manner by the reaction of aminoallyl acetate **296** or aminoallyl carbonate **297** (Scheme 97).[280]



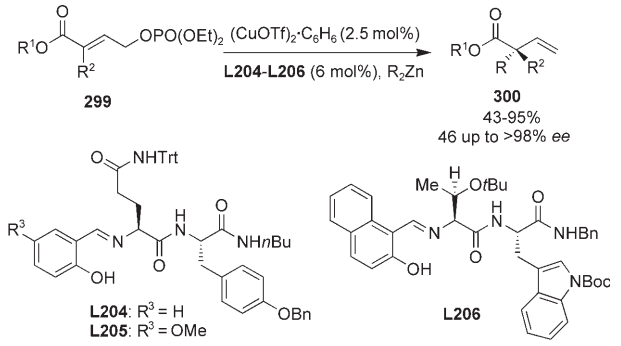
Scheme 97.

Compared to the palladium-catalyzed allylation reaction, the iridium- or molybdenum-catalyzed allylation occurred at the more substituted end to afford the sterically and electronically preferred alkene–metal complexes, which may explain the preferred formation of the branched products.[281]

5. Copper-Catalyzed Enantioselective Allylation[1f]

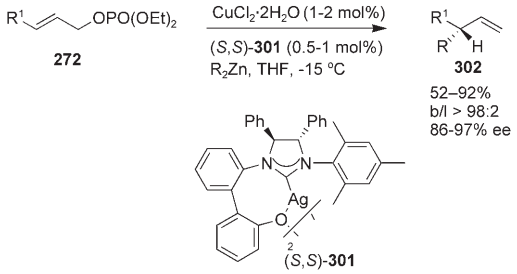
In general, copper-catalyzed enantioselective allylations proceed with an S_N2' mechanism, which makes the reaction regiospecific.[1f] Among the 3-substituted and 2,3-, or 3,3-disubstituted allylic acetates, carbonates, phosphates, halides, ethers, and other allyl compounds, the phosphates and halides have shown the best selectivity. Both Grignard and organo-

zinc reagents can be applied to this reaction, however, the reaction of aryl metal reagents has not been well established. Copper(I) and copper(II) salts are both useful catalysts for this reaction, and chiral amines, phosphoramidites, Schiff bases, and bidentate carbene derivatives are all suitable ligands. In 2005, Hoveyda and co-workers demonstrated a copper-catalyzed coupling reaction of α,β-unsaturated esters **299** bearing a γ-phosphate group with dialkylzinc reagents using 6 mol% of the chiral amino acid derivatives **L204–L206** to afford the 3-enoates **300** in high regioselectivity (46 to >98% *ee*, Scheme 98).[282a] It should be noted that the enantioselective allylations of α,β-unsaturated γ-chloro enoates with Grignard reagents can be achieved with a chiral Lewis base, without the need for a copper catalyst.[282b]



Scheme 98. R = Me, Et, *i*Pr, $Me_2CH(CH_2)_3$, $AcO(CH_2)_4$; R^1 = Me, *t*Bu; R^2 = Me, Ph. Tf = trifluormethansulfonyl, Trt = triphenylmethyl.

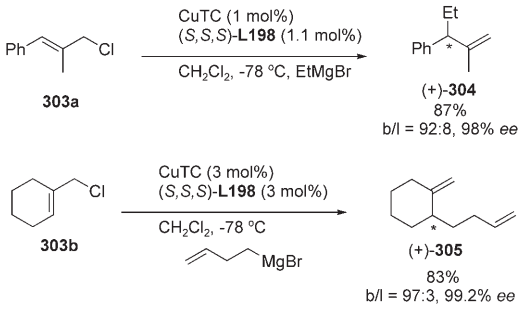
The reaction of 3-substituted allyl phosphate **272** with dialkylzinc in the presence of the optically active silver complex **301** efficiently produced the terminal olefins **302** with high regioselectivity (>98:2) in yields of 52–92% and 86–97% *ee* (Scheme 99).[283]



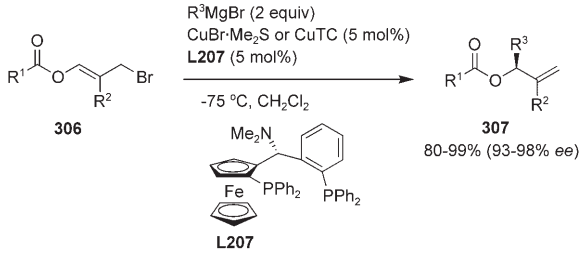
Scheme 99. R = Me, Et, *i*Pr, *n*Bu; R^1 = Ph, *o*-$NO_2C_6H_4$, C_7H_{15}, Cy.

This S_N2' reaction of 2,3-disubstituted allyl chlorides **303a** and **303b** with Grignard reagents has also been used for the synthesis of the related terminal alkenes (+)-**304** and (+)-**305**, respectively, with 98 and 99.2% *ee*, respectively (Scheme 100).[284]

Recently, Feringa and co-workers used this copper-catalyzed S_N2' allylation of Grignard reagents with 3-acetoxyallyl bromides **306** in the presence of the ligand (*R*,*S*)-(−)-taniaphos (**L207**) to prepare chiral allyl esters **307** in yields of 80–99% and very high enantioselectivity (Scheme 101).[285]



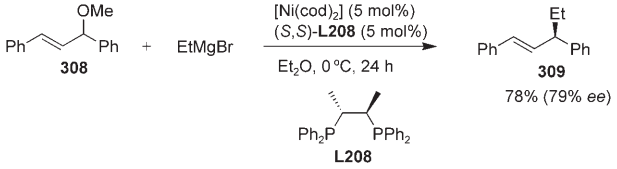
Scheme 100. TC = thiophene carboxylate.



Scheme 101. R^1 = Styryl, Mes, Ph; R^2 = H, Me; R^3 = alkyl.

6. Nickel-Catalyzed Enantioselective Allylation

The nickel-catalyzed coupling reaction of 3-allyl phosphate with phenylboronic acids afforded the correspong products with only 12–13% *ee*.[286,287] The asymmetric cross-coupling reaction of 2-cyclohexenyl acetate with phenyl boronic acid using [Ni(acac)$_2$] and **L45b** as the catalyst system afforded 3-phenylcyclohexene in 81% yield and 50% *ee*. A lower *ee* value was observed in the corresponding reaction of 3-penten-2-yl acetate.[286] With [Ni(cod)$_2$] and (*S*,*S*)-**L208** as the catalyst system, 1,3-diphenylallyl methyl ether **308** was able to couple with EtMgBr to afford the chiral alkene (*R*)-**309** with 79% *ee* (Scheme 102).[288]



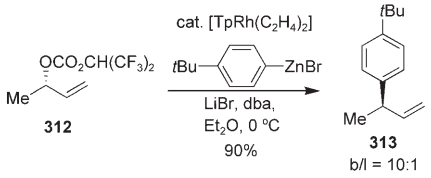
Scheme 102.

Many chiral ligands were screened in the asymmetric intramolecular allylic amination of **310** in the presence of [Ni(cod)$_2$], with (*R*)-MeOBiphep (**L184**) being the best, affording the chiral vinylglycinol derivative **311** with 75% *ee* in 88% yield (Scheme 103)[289]

7. Rhodium-Catalyzed Enantioselective Allylation

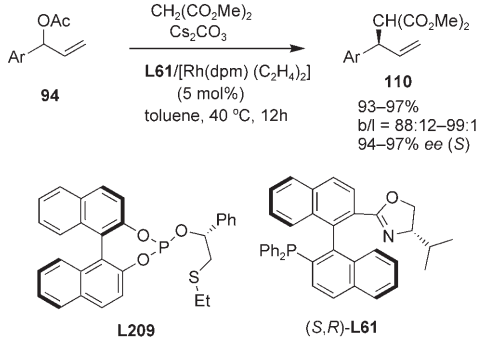
The rhodium-catalyzed inversion of the absolute configuration of the optically active unsymmetric allylic carbonate **312** with aryl zinc halides was observed by Evans and Uraguchi (Scheme 104).[290]

Scheme 103.



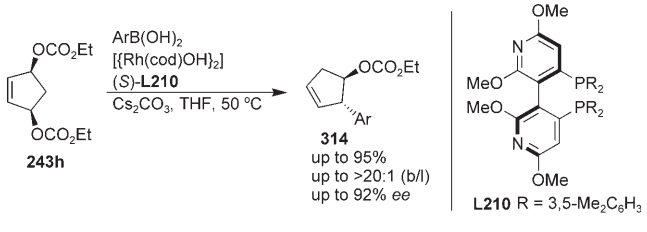
Scheme 104. Tp = hydrotris(pyrazolyl)borate.

In 1999 Pregosin and co-workers reported the rhodium-catalyzed enantioselective intermolecular reaction of cinnamyl or 1-phenyl-3-pentenyl acetate in the presence of the thioether-substituted phosphite ligand **L209** or P,N ligand **L61** to afford the allylation products in modest regio- and enantioselectivity.[202a] Hayashi et al. reported a similar allylic alkylation of racemic 1-aryl-2-propenyl acetates **94** with dimethyl malonate in the presence of a rhodium catalyst generated from $[Rh(dpm)(C_2H_4)_2]$ (dpm = dipivaloylmethanato) and the chiral phosphane-oxazoline (*S*,*R*)-**L61** to afford **110** with 94–97% *ee* and high regioselectivity (88:12 to 99:1, Scheme 105).[291]



Scheme 105. Ar = Ph, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4.

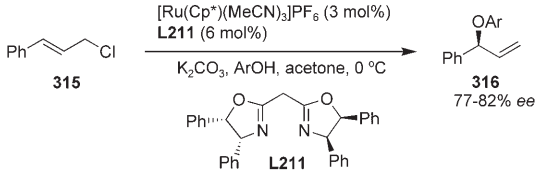
Desymmetrization of 2-cyclopentene-1,4-dicarbonate **243h** may also be realized with $ArB(OH)_2$ to afford cyclopentenyl carbonate **314** with up to 92% *ee* (Scheme 106).[292]



Scheme 106.

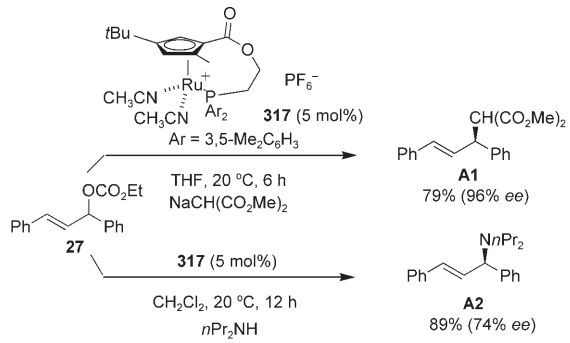
8. Ruthenium-Catalyzed Enantioselective Allylation[1g]

The reaction of cinnamyl chloride (**315**) with phenols in the presence of $[Ru(Cp^*)(MeCN)_3]PF_6$ and chiral bisoxazoline ligand **L211** as the catalyst can also give the branched products **316** with moderate *ee* values and very poor regioselectivities (1.6:1–2.2:1, Scheme 107).[293]



Scheme 107. Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4.

The ruthenium complex **317** catalyzed the enantioselective allylation of malonate with 1,3-diphenylallyl carbonate **27** to afford the product **A1** in 79% yield and 96% *ee*. However, the related amination afforded the related allylic amine **A2** in 89% yield and only 74% *ee* (Scheme 108).[294]



Scheme 108.

9. Platinum-Catalyzed Enantioselective Allylation

The enantioselective allylic alkylation of sodium malonate with 1,3-diphenyl-2-propenyl acetate **1** using the catalyst system $[\{Pt(\pi\text{-}C_3H_5)Cl\}_4]$/**L28b** afforded the optically active product **A1** in 74% yield and 84% *ee* (see Scheme 108) The analogous reaction with the P,P ligand **L208**, afforded the product **A1** with 95% *ee* and 39% conversion.[295]

10. Conclusion

In summary, metal-catalyzed asymmetric allylation has become a powerful method for the efficient formation of carbon–hydrogen, carbon–carbon, carbon–oxgen, carbon–nitrogen, and carbon–sulfur bonds in a highly enantioselective manner, and has been applied successfully to the total synthesis of many natural products.

Soft nucleophiles are usually used in the Pd-, Mo-, Ir-, Ru-, Rh-, Pt-catalyzed enantioselective allylic substitutions,

while organozinc or magnesium reagents are usually used in the Cu- or Ni-catalyzed asymmetric coupling reactions. Palladium catalysts have been most widely studied. Although it is a challenge to control the regio- and enantioselectivities of palladium-catalyzed allylic substitutions with unsymmetrical allyl substrates, there are already many successful examples. Molybdenum- and iridium-catalyzed reactions occur readily at the more sterically hindered end of unsymmetrical allylic substrates, while the copper-catalyzed reaction proceeds through an S_N2' mechanism to form the branched products. More efficient and a universal metal–ligand combination will need to be pursued to meet the needs of organic synthesis and medicinal chemistry in the near future. The different working models for the regio- and enantioselectivity now available may enable the rational design of new readily available, efficient, and universal ligands.

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