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Stereoselective formation of quaternary carbon centers and related functions

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Contents

1. Introduction

The development of efficient asymmetric methods for constructing C–C bonds has enjoyed considerable attention from the organic community in the past 30 years. Among the synthetic challenges that Nature provides, the stereocontrolled construction of quaternary carbon centers is, without a shadow of a doubt, a remarkable task. The need to generate such C–C bonds has provoked the disclosure of several asymmetric methods which have been previously reviewed.[1] In the beginning, most of the reported methods involved the use of chiral auxiliaries to induce enantioselectivity in the newly formed C–C bonds. Despite the stoichiometric use of chiral auxiliaries, this approach still boasts practical aspects. However, efficient enantioselective catalytic methods provide an access to optically active material in large amounts using small quantities of chiral catalysts without the necessity of removing the chiral unit. As a result, research devoted toward the development of enantioselective catalytic methods is gaining in importance and major breakthroughs have recently been achieved.[2] This review presents methods using both stoichiometric and catalytic process for the asymmetric construction of quaternary carbon centers. Since four reviews have been published on this subject in less than 10 years, most of the examples were picked from literature from the years 2000 to 2003 and selected according to their novelty. The examples that have been cited in previous reviews will not be emphasized.

2. Alkylation of enolates

2.1. Application of chiral auxiliaries

The stereocontrolled formation of tetrasubstituted enolates

Keywords: quaternary carbon centers; enantioselective catalytic methods; electrophile.

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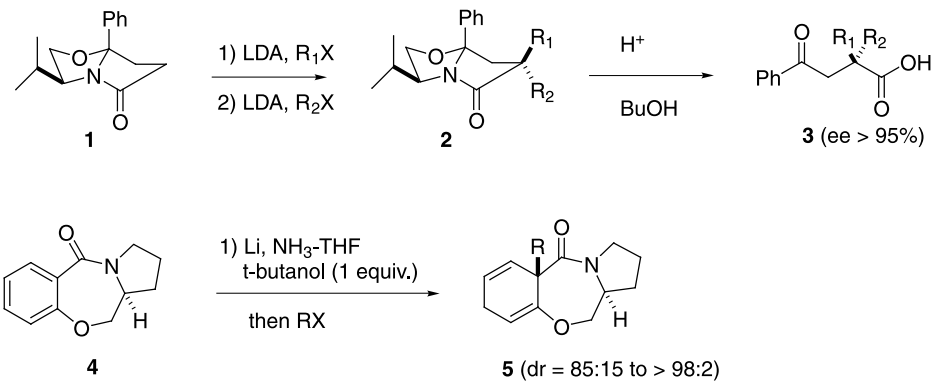
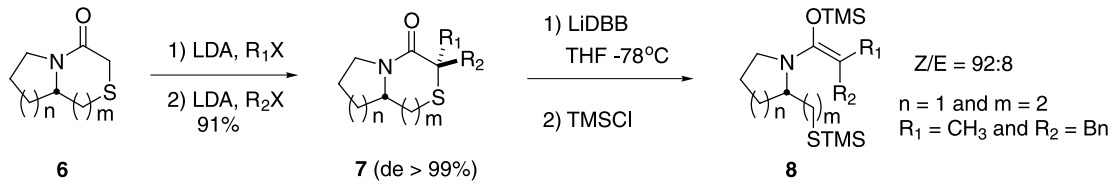


Scheme 1.



Scheme 2.

combined with facially selective addition of an electrophile represents a formidable challenge in organic synthesis. The pioneering work of Meyers[3] and Schultz[4] involving the use of chiral cyclic lactams is one of the important contributions in the asymmetric formation of quaternary carbon centers (Scheme 1). Since 1984, several other research groups have focused their efforts in this area and this work has been the subject of previous reviews.[1b,d]

Recently, Manthorpe and Gleason[5] reported an elegant approach to generate tetrasubstituted enolates **8** in a stereospecific manner using the reductive cleavage of bicyclic thioglycolate lactams **7** (Scheme 2). Their method is based on bicyclic systems that constrain the sulfur to one face of the carbonyl plane (Fig. 1).

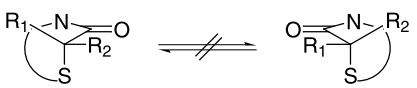


Figure 1.

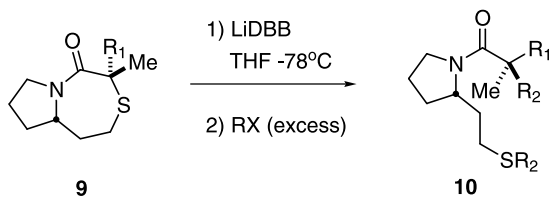
Gleason demonstrated a clear relation between the S–C–C–O dihedral angle in **7** and the enolate geometry (*E*/*Z*) during α,α-disubstituted amide formation. The same group has subsequently reported the synthesis of quaternary centers via the alkylation of the tetrasubstituted enolates with *n*-alkyl iodides (Table 1).[6] In most of the cases, high diastereoselectivity was observed. Interestingly, Gleason's method produces quaternary carbon centers in high selectivities without the use of cyclic chiral enolates or metal chelation.

Highly stereoselective formation of tetrasubstituted enolate is also achieved using camphor-derived lactam auxiliary.[7] Boeckman and co-workers have discovered that the counter anion is important to obtain good chemical yield and high diastereoselectivity. For instance, the lithium *Z*-enolate **12** was trapped with TBSCl to afford the corresponding silyl enol ether **13** (R=*i*-Pr) in quantitative yield (Scheme 3).

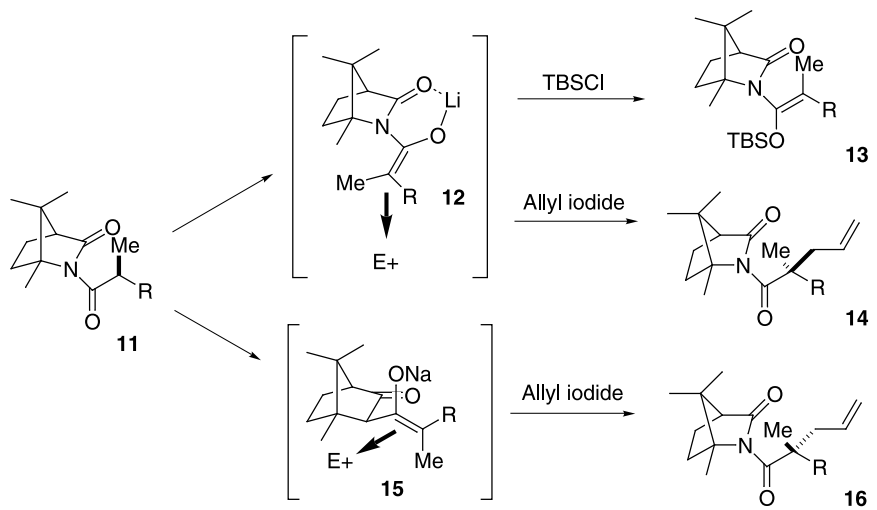
Despite exclusive formation of the enolate **12**, lactam **14a** was obtained in poor selectivity and low chemical yield. Replacement of lithium by a sodium atom led to a more reactive enolate **15** that after treatment with allyl iodide, furnished **16a-b** in high diastereomeric ratio and in good yield (Table 2, entries 2 and 3). The stereochemical outcome is opposite to the one obtained with lithium enolate **12**. This is rationalized on the basis that the sodium enolate is oriented perpendicular to the lactam π system in order to avoid unfavorable electronic interaction (Scheme 3).

Chiral 2,2-disubstituted cyclopentene-1,3-diones are synthetically useful building blocks in the enantioselective synthesis of a variety of natural products such as (+)-madindolines A (**17**) and B (**18**) (Fig. 2). Kobayashi and co-workers reported the enantioselective synthesis of the cyclopentenedione moiety **21** via a stereofacial

Table 1. Alkylation using unactivated electrophile



R_1	R_2X	Yield (%)	de (%)
Bn	EtI	89	93
Bn	*n*BuI	76	>95
*n*Pr	EtI	85	89
*n*Pr	*n*BuI	71	95
*n*Pr	*i*Bu	59	87
Et	*n*PrI	83	>95
Allyl	EtI	84	88
Allyl	BuI	80	91
*n*Bu	*n*PrI	88	>95



Scheme 3.

Table 2. Alkylation with allyl iodide

Entry	Lactam	Temperature (°C)	Product (yield, %)	dr (**16**/**14**)
1	**11a**: R=*i*-Pr	0	**16a**, (36)	13.7:1
2	**11a**: R=*i*-Pr	−30	**16a**, (60)	20.5:1
3	**11b**: R=C(O)Et	−40	**16b**, (67)	99:1

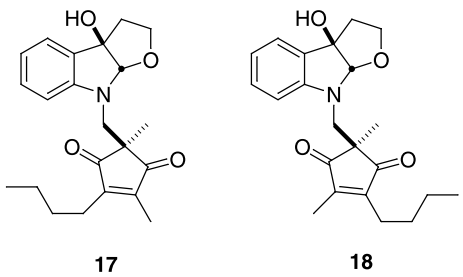
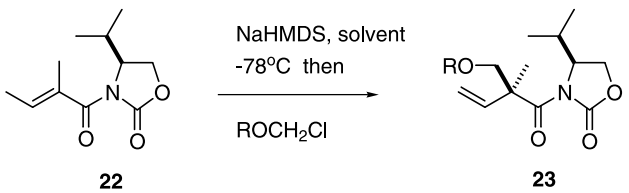


Figure 2.

alkylation of α,β-unsaturated imide **19** with benzyloxymethyl chloride (Scheme 4).[8]

A model study revealed that the α-alkylation of **22** with benzyloxymethyl or methyloxymethyl chloride afforded the imide **23** in diastereomeric ratios ranging from 8:1 to 10:1 (Table 3). Treatment of **22** with NaHMDS followed by addition of TBSCl gave the enol ether **24** in 90% as a single isomer (Scheme 5). In light of this result, they surmised that the electrophilic attack must occur on the less hindered face of the 6-membered ring sodium enolate **25** to produce the quaternary carbon center in **23** possessing the *S*-configuration.

Table 3. α-Alkylation of α,β-unsaturated imide **21**

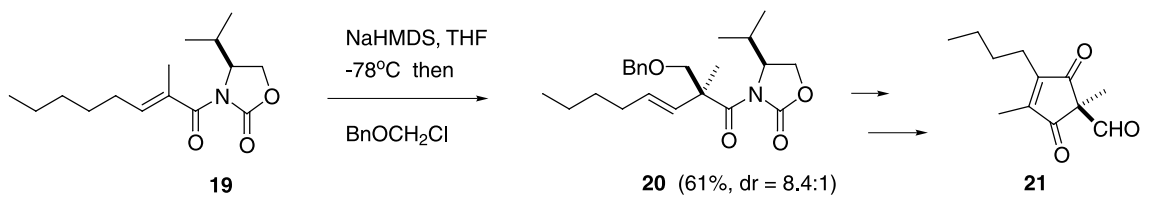


Entry	R	Solvent	Yield (%)	dr
1	Me	THF	37	10:1
2	Me	Toluene	70	8:1
3	Bn	THF	48	11:1
4	Bn	Toluene	67	10:1

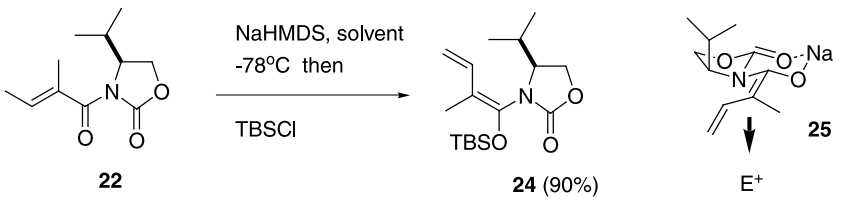
In 2002, Omura and co-workers presented an elegant total synthesis of madindolines A (**17**) and B (**18**) featuring a highly stereoselective acylation as the key step (Scheme 6).[9] The asymmetric induction was a consequence of the formation of a 1,6-lithium chelate **27** that directs the electrophile **28** attack on the less hindered enolate face, i.e. *anti* to the hydoxylindoline moiety.

In 2001, Satoh and co-workers reported the asymmetric synthesis of 4,4-disubstituted 2-cyclopentanones **32** from 1-chlorovinyl *p*-tolylsulfoxides **30** and cyanomethyllithium (Scheme 7).[10] The cyclopentenone ring system thus formed is a versatile and abundant framework for the synthesis of natural products. Exposure of enantiopure 1-chlorovinyl *p*-tolylsulfoxides **30** to 5 equiv. of cyanomethyllithium affords the desired 5,5-disubstituted cyclopentadienes **31** in yields ranging from 93 to 98% (98.5–99.5% ee).

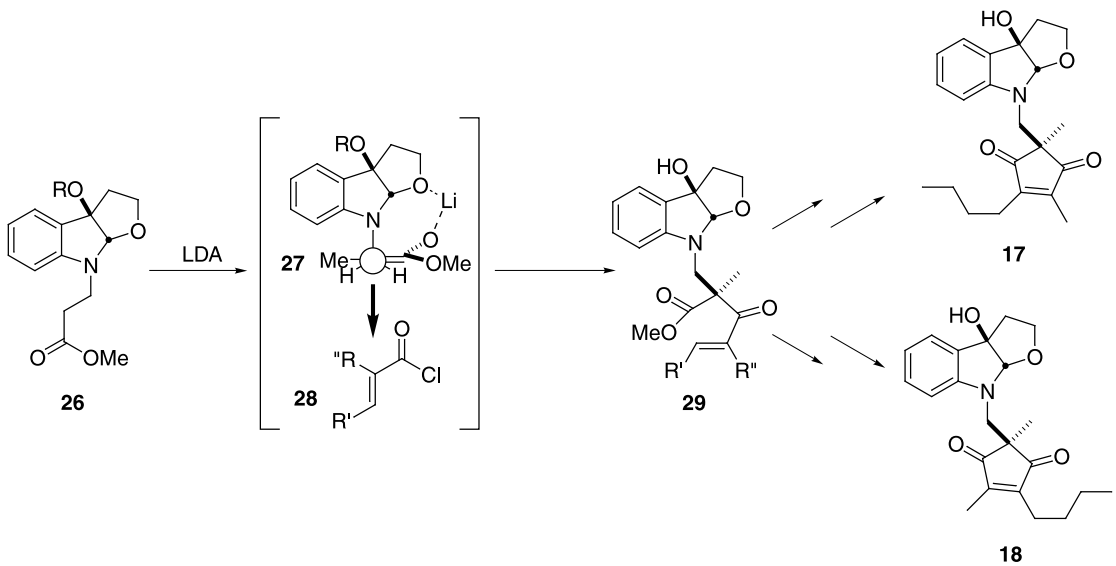
Under acidic conditions, the amines **31** were easily



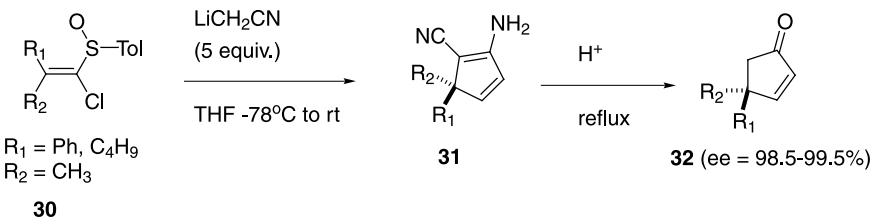
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

transformed into the corresponding enones **32** in excellent yield. The high enantioselectivity could be explained on the basis of the formation of a 5-membered lithium chelate **33** between the sulfoxide oxygen and the chlorine (Fig. 3). This model explains the control of the stereofacial selectivity of the nucleophilic attack.

α,β-Hydroxy acids and 1,2-diol units having quaternary centers are common elements in macrolides and polyether antibiotics. Moreover, their wide utilization as chiral building blocks has created demands to develop practical methodologies aimed at obtaining these chiral units in their pure enantiomeric form. One of the most important practical syntheses is the Sharpless dihydroxylation of substituted olefins.[11] In general, high enantioselectivity is reached with 1,1-di and trisubstituted *E*-olefins giving *syn* 1,2-diol products. Recently, Ley and co-workers reported a practical method to prepare *trans* α,β-dihydroxy acids employing butane-2,3-diacetal (BDA) as the chiral source.[12] BDA (**35**) has been used as a chiral auxiliary in Michael[13] and aldol reactions.[14] Treatment of BDA (**35**) with 1.05 equiv. of LiHMDS in THF at −78°C generated the corresponding enolate which after being exposed to different ketones followed by an acidic treatment, provided the α,β-dihydroxy acid compounds **38** in high chemical and optical yields (Scheme 8 and Table 4).

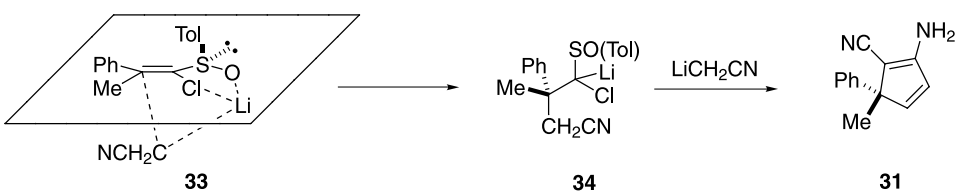
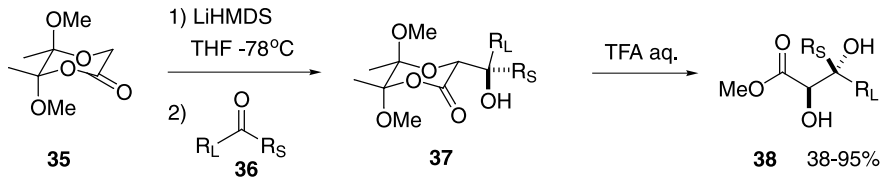
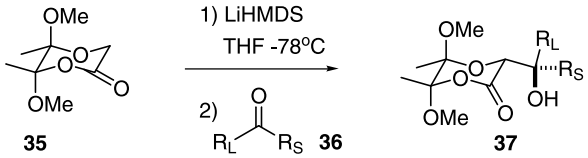


Figure 3.



Scheme 8.

Table 4. Reactions of glycolate **35** with ketones **36a-j** mediated by LiHMDS in THF at −78°C



Entry	Ketone	Product	Yield (%)	de (%)
1	**36a**: R_L=*t*-Bu, R_S=Me	**37a**	32	95
2	**36b**: R_L=*t*-Bu, R_S=CH_2Cl	**37b**	89	95
3	**36c**: R_L=CF_3, R_S=Ph	**37c**	92	17
4	**36d**: R_L=Ph, R_S=Me	**37d**	79	91
5	**36e**: R_L=Ph, R_S=CH_2OMe	**37e**	96	90
6	**36f**: R_L=Ph, R_S=Et	**37f**	76	71
7	**36g**: R_L=Ph, R_S=CH_2Br	**37g**	92	90
8	**36h**: R_L=3-pyridine, R_S=Me	**37h**	93	85
9	**36i**: R_L=2-furan, R_S=Me	**37i**	70	80
10	**36j**: R_L=Ph, R_S=CH=CHPh (*E*)	**37j**	90	82

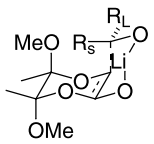


Figure 4.

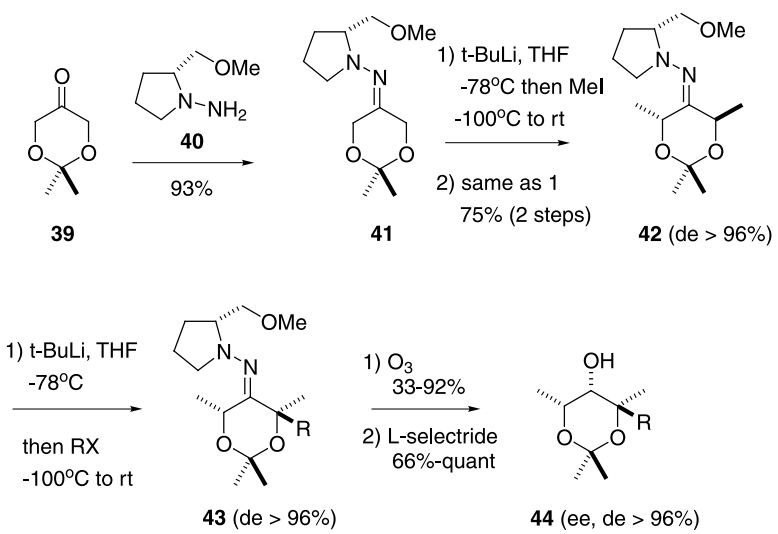
The stereochemical outcome of this reaction can be rationalized using the transition state model illustrated in Figure 4. The axial orientation of the methoxy groups favors electrophile attack on the *re* face thereby avoiding steric interactions. Additionally, lithium chelation imposes a chair-like transition state placing the large group (R_L) in the equatorial position.

The exploitation of the RAMP-hydrazone method in the elaboration of enantiopure 1,2,3 triol motifs possessing quaternary carbon centers was investigated by Enders.[15] The hydrazone **41** was easily prepared by the condensation of protected 2-keto-1,3-diols **39** and (−)-(*R*)-1-amino-2-methoxymethylpyrolidine **40** (Scheme 9).

A double exposure to *t*-BuLi at −78°C followed by addition of MeI provided the α,α′-dimethyl hydrazone **42** in 78% chemical yield (de>96%). The key step to install the quaternary center resided in a third metallation of **42** and alkylation with various halogenated benzyl, allyl and alkyl electrophiles. The results depicted in Table 5 clearly indicate the high transfer of chirality from the RAMP auxiliary provides another efficient synthetic tool for the synthesis of enantiopure 1,3-dihydroxy-2-ketones and 1,2,3-triols bearing quaternary centers.

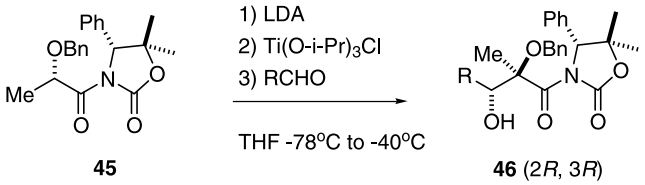
Table 5. Synthesis of α-quaternary hydrazone **43**

Entry	R	X	Yield (%)	de (%)
1	Allyl	Br	99	>96
2	*i*-Pr	I	40	>96
3	*i*-Pr	I	39	>96
4	*n*-Hex	I	89	>96
5	$(R'O)CH(CH_2)_2$	I	81	83
6	$TBSO(CH_2)_3$	I	76	>96
7	Bn	Br	80	>96
8	$BnOCH_2$	Cl	82	>96

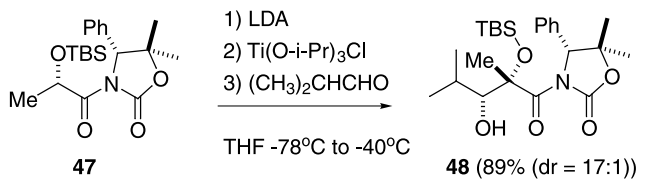


Scheme 9.

Table 6. Preparation of (2*R*,3*R*)-diol



Entry	R	Yield (%)	Selectivity
1	$CH_3CH{=}CH$	85	24:1
2	$(CH_3)_2CH$	96	57:1
3	$CH_3(CH_2)_3CH_2$	93	>99:1



Scheme 10.

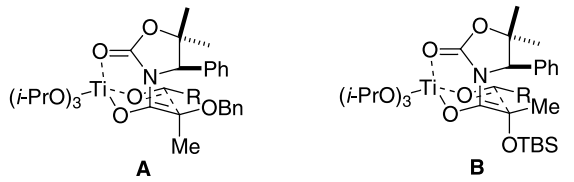


Figure 5.

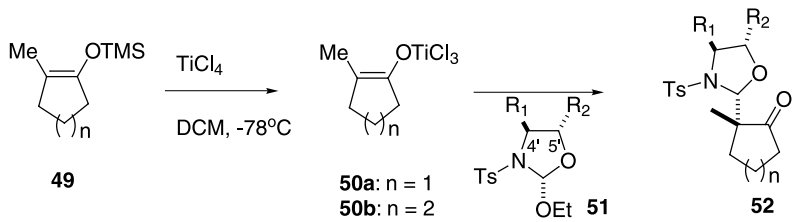
Recently, titanium enolates have been involved in the stereoselective construction of tertiary alcohols.[16] This method, developed by Kobayashi and co-workers, takes advantage of the exclusive *E* or *Z* enolate formation on which a chiral imide auxiliary is attached. The 'Super Quats' derivatives[17] have been used as chiral auxiliaries in order to avoid the formation of keto-carbamate by-products. Kobayashi discovered that the configuration of the newly formed chiral centers is directly dependant on the choice of protecting group. When benzyl ether lactate derivative **45** was used, the exclusive formation the tetrasubstituted *E*-enolate is observed leading to the *anti* 1,2-diol **46** (Table 6).

The tetrasubstituted *Z*-enolate is predominantly formed when *tert*-butyldimethylsiloxy ether imide **47** is employed thereby providing *syn* 1,2-diol **48** in high diastereomeric excess (Scheme 10). Although the mechanism of enolate formation remains unclear, titanium-coordinated transition states **A** and **B**, depicted in Figure 5, can rationally explain the high selectivity of the aldol reaction.

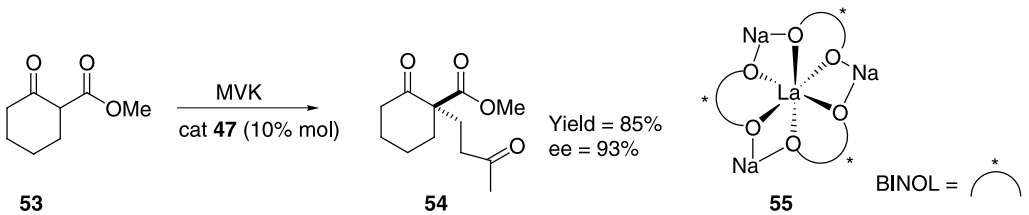
Another example employing titanium enolates was recently reported by Hoppe.[18] In this case, the titanium enolate **50** was prepared from a titanium metal exchange of the corresponding silyl enol ether **49** (Scheme 11). This enolate was condensed with **51** giving ketone **52** in which the facial selectivity was controlled by the electrophile. The diastereoselectivity of the quaternary centers was drastically influenced by the nature of substituents upon both the enolate and chiral 2-alkoxy-3-sulfonyl-1,3-oxazolidine **51**. It was found that the reaction was highly diastereoselective when small groups at C4′ or two *trans*-arranged groups at C4′ and C5′ were installed on the chiral 2-alkoxy-3-sulfonyl-1,3-oxazolidine **51**.

2.2. Metal catalyzed 1,4-addition and aldol reactions

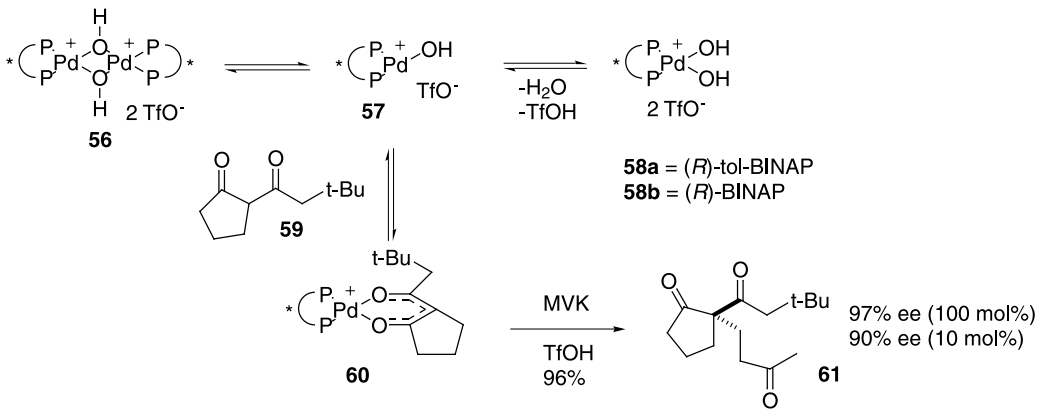
1,4-Conjugate additions of nucleophiles into α,β-unsaturated carbonyl systems is one of the most versatile reactions in the synthetic arsenal for the generation of tertiary and quaternary centers.[19] In the past few years, several research groups have devoted their efforts to establish catalytic enantioselective versions.[1e,20] In this area many groups have achieved significant breakthroughs, notably, Shibasaki and co-workers.[21] They created a new class of chiral heterobimetallic lanthanide, La–Na–BINOL complex (LSB), that has proven to be highly efficient in the enantioselective formation of C–C bonds. They reported that the LSB (**55**)-catalyzed Michael reaction of 1,3-dicarbonyl compounds and different Michael acceptors generates 2-disubstituted-1,3-dicarbonyl products in a highly enantioselective fashion (Scheme 12).



Scheme 11.



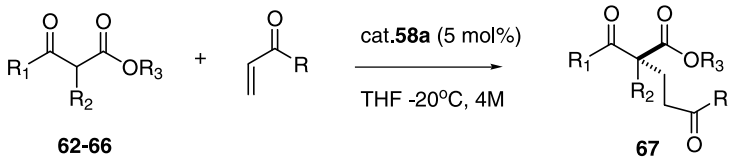
Scheme 12.

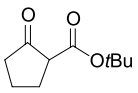
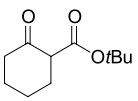
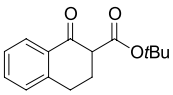
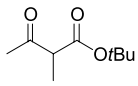
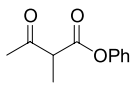
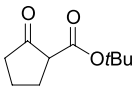
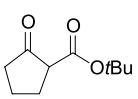
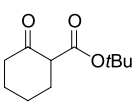


Scheme 13.

Recently, the first example of an enantioselective catalytic Michael addition using a chiral palladium enolate was introduced by Sodeoka et al.[22] Their strategy takes advantage of the palladium hydroxy complex **56** that possesses two distinct chemical behaviors, Lewis acidity and Bronsted basicity (Scheme 13). Clear evidence of palladium enolate **60** formation was observed by ^{1}H NMR when 1,3 diketone **59** was treated with palladium hydroxy

Table 7. Michael reaction using various β-ketoester



Entry	Ketoester		Enone	Time (h)	Yield (%)	ee (%)
1		**62**	R=Me	24	92	92
2[a,b]		**63**	R=Me	72	92	90
3[c,d]		**64**	R=Me	48	88	89
4[a,b,c]		**65**	R=Me	72	88	90
5[b,c]		**66**	R=Me	72	69	93
6[e]		**62**	R=Me	40	93	93
7[a]		**62**	R=Et	20	84	88
8[a,b]		**63**	R=Et	72	89	86

[a] Catalyst **58b** was used.
[b] The reaction was conducted at 0°C.
[c] 10 mol% of Pd catalyst was used.
[d] 1 M.
[e] 2 mol% of catalyst **58b** was used.

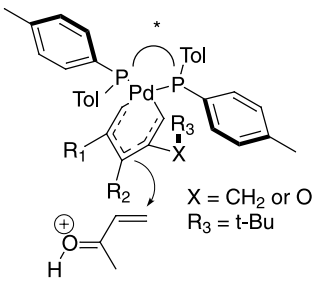
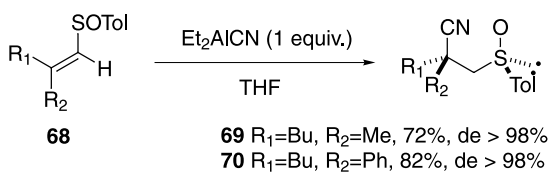


Figure 6.

complex **57**. Methyl vinylketone (MVK) and triflic acid were then added to the reaction mixture to provide **61** in high enantiomeric excess. This result clearly demonstrates the potential of this method in organic synthesis (Table 7). During the elaboration of this method, Sodeoka found that a bulky ester group was crucial for obtaining high ee's. This observation can be rationalized by the transition state model depicted in Figure 6. In this model, the bulky group R_3 is oriented in such manner to avoid severe steric interactions with the tolyl group. The *si* face is thus blocked and the electrophile attacks preferentially on the *re* face of the palladium enolate.

Highly stereoselective hydrocyanation of alkenyl sulfoxide **68** with Et_2AlCN was demonstrated by Ruano and Ramos (Scheme 14).[23] Taking into the account that the cyano and sulfinyl groups in **69** and **70** can be easily transformed to



Scheme 14.

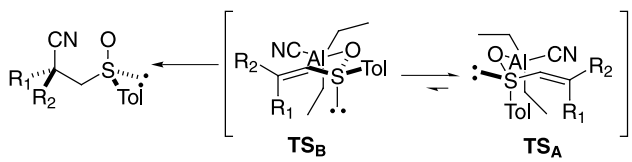


Figure 7.

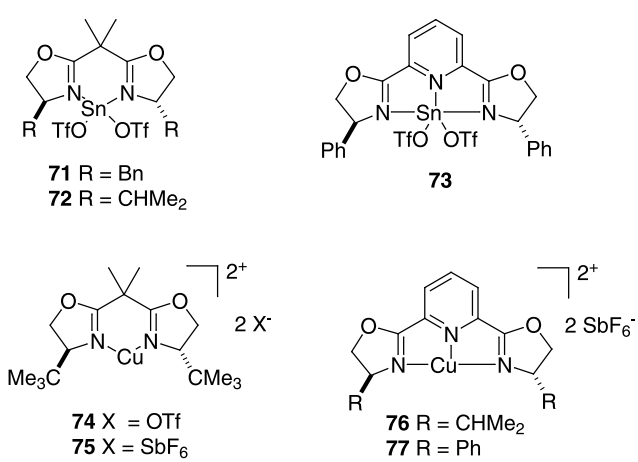


Figure 8.

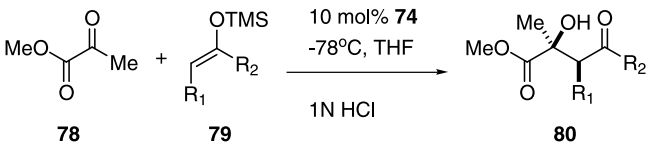
other functional groups, this method becomes attractive in preparing optically pure quaternary carbon center.

Ruano and Ramos have proposed that the reaction can undergo via two possible transition state models, TS_A and TS_B (Fig. 7). According to this model, TS_A is higher in energy then TS_B due to unfavorable steric interaction between the tolyl and ethyl groups. The high stereoselectivity of the hydrocyanation process is thus explained.

Bidendate bis(oxazolinyl) (box)- and tridendate bis(oxazolinyl)-pyridine (pybox)-Cu(II) and tin (II) complexes **71**-**77** exhibit effective catalysis of Diels–Alder, carbonyl-ene, Michael and aldol reactions (Fig. 8).[24]

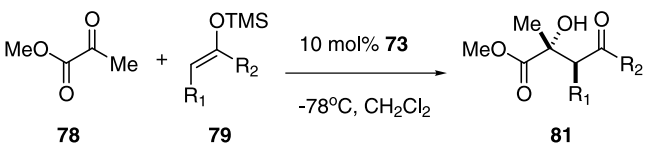
In the case of the aldol reaction, Evans reported[25] that complexes **73** and **74** catalyzed the union of trisubstituted silyl enol ethers **79** and pyruvate ester derivative **67** to form essentially enantiopure aldol adducts **80** and **81** bearing a tertiary alcohol (Tables 8 and 9).

Table 8. Catalyzed enantioselective aldol reactions



Entry	R_1	R_2	Enol silane geometry	*syn/anti*	ee (%)	Yield (%)
1	Me	*t*-BuS	*Z*	94:6	96	96
2	Me	*t*-BuS	*E*	95:5	98	88
3	Me	EtS	*Z*	94:6	93	90
4	Me	EtS	*E*	98:2	98	91
5	*t*-Bu	EtS	*Z*	90:10	93	88

Table 9. Catalyzed enantioselective aldol reactions

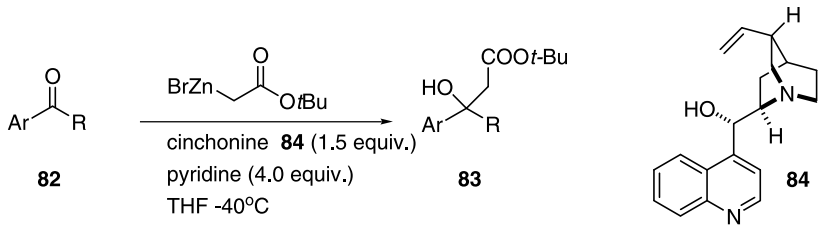


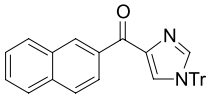
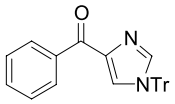
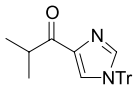
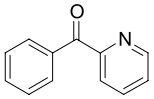
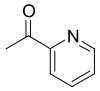
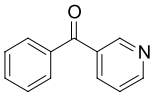
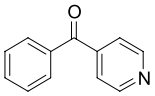
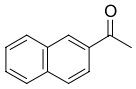
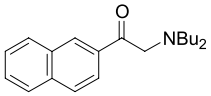
Entry	R_1	R_2	Enol silane geometry	*syn/anti*	ee (%)	Yield (%)
1	Me	*t*-BuS	*Z*	99:1	99	94
2	Me	*t*-BuS	*E*	99:1	96	84
3	Et	*t*-BuS	*Z*	98:2	97	84
4	*i*-Bu	*t*-BuS	*Z*	99:1	99	81
5	Me	EtS	*Z*	95:5	92	91
6	Et	EtS	*Z*	99:1	97	94
7	*i*-Bu	EtS	*Z*	99:1	97	76

2.3. Miscellaneous

The asymmetric Reformatsky reaction is a facile approach to produce β-hydroxyesters and in the past decades, a panoply of methods has been generated.[26] Recently, Ojida and co-workers proposed the creation of enantiopure tertiary alcohols **83a-i** using cinchona alkaloids as the chiral ligand (Table 10).[27] Different ligands were tested and it was found that cinchonin (**84**) provided the highest enantioselective excess. They noted that the addition of pyridine significantly improved the rate and

Table 10. Asymmetric Reformatsky reaction with ketones and related compounds



Entry	Substrate	Product	Yield (%)	ee (%)
1	 **82a**	**83a**	97	97 (*S*)
2	 **82b**	**83b**	99	97
3	 **83c**	**83c**	73	94
4	 **82d**	**83d**	98	90 (*S*)
5	 **82e**	**83e**	94	86
6	 **82f**	**83f**	27	28
7	 **82g**	**83g**	41	13
8	 **82h**	**83h**	42	15
9	 **82i**	**83i**	99	0

the enantioselectivity of the Reformatsky process. The authors discovered that chelation of zinc with the sp^2-nitrogen adjacent to the carbonyl was essential to obtain the quaternary centers in high enantioselectivity (entries 7–9).

The stereoselective construction of quaternary spirocyclic centers is a considerable challenge in organic synthesis. The level of difficulty can be substantially increased if the asymmetry of the carbon center is issued from a group located far from the spiro center as featured in the structure of Fredericamycin A (Fig. 9).

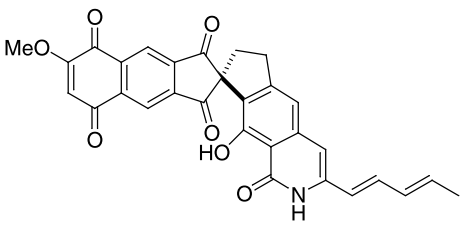
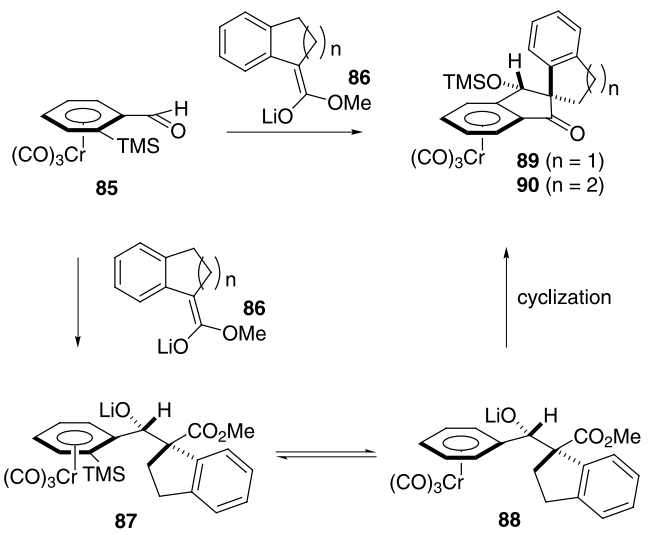


Figure 9. Structure of Fredericamycin.

Recently, Moser et al. reported an efficient method involving a [3+2] cycloaddition for the stereocontrolled synthesis of spirocyclic ketones **89** and **90** (Scheme 15).[28] This cycloaddition can be dissected into a cascade process of aldol condensation/Brook rearrangement/cyclization involving arene chromium complex **85** and tetrasubstituted enolates **75**. This tandem reaction provides the spirocycles **89** and **90** in good yields as single diastereomers.

Konopelski et al.[29] have demonstrated that aryllead(IV) tricarboxylates **91**-**93** are excellent arylation reagents to construct sp^2-sp^3 bonds bearing quaternary carbon centers



Scheme 15.

(Table 11). They proposed that the high diastereoselectivity originates from a carbanion stabilization by a distal siloxy group (Scheme 16).

This interaction is thought to direct the silyloxy group to the axial position thereby orienting the aryllead (IV) triacetate complex to attack *anti* to the siloxyether group furnishing α,α-disubstituted β-ketoester **95** in high diastereomeric excess (entries 2–4 and 7–8)

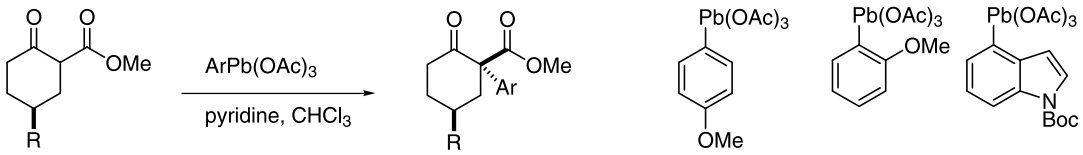
3. Radical reactions

The asymmetric formation of C–C bonds via radical reactions has enjoyed increasing attention in the recent years.[30] However, few examples related to the asymmetric construction of quaternary carbon centers have been described. In 1995, Guindon and co-workers reported a highly diastereoselective chelation-controlled allylation reaction of α-halo-β-alkoxy ester **97** and allyltrimethylsilane or allyltributyltin (Scheme 17).[31]

Treatment of tertiary α-halo-β-alkoxy esters **97a-c** with allyltrimethylsilane or allyltributyltin (2 equiv.), $MgBr_2$–OEt_2 (1–3 equiv.) and triethylborane (20 mol%) in dichloromethane at −78°C provided the corresponding β-alkoxyesters **98a-c** in 35–80% yield in a diastereoisomeric ratio of >100:1 (Table 10). Higher yields were obtained when allyltributyltin was employed (Table 12). This constitutes the first example of Lewis acid bidentate complexation to control facial selectivity in atom transfer reactions.[32]

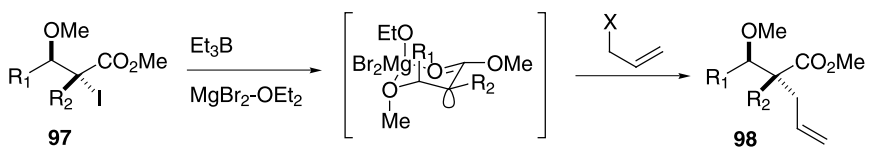
Zard and co-workers achieved the total synthesis of

Table 11. Arylation result for 5-substituted β-ketoester **94a-j**



Entry	β-Ketoester R=	$ArPb(OAc)_3$	Yield (%)	dr
1	*t*-Bu **94a**	91	96	9:1
2	OTBS **94b**	91	97	20:1
3	OTBS **94c**	92	98	30:1
4	OTBS **94d**	93	98	30:1
5	OAc **94e**	91	64	4:1
6	OPiv **94f**	91	68	6:1
7	OTIPS **94g**	91	92	15:1
8	OTBDPS **94h**	91	95	99:1
9	OMe **94i**	91	96	4:1
10	OBn **94j**	91	85	6:1

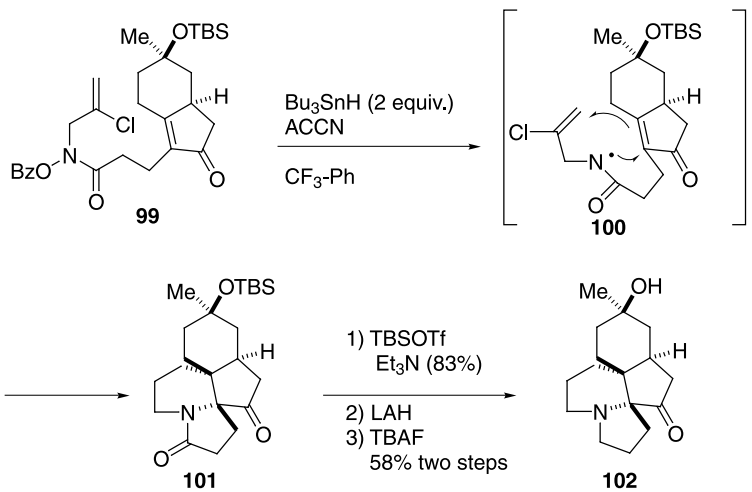
Scheme 16.



Scheme 17.

Table 12. Radical allylation under chelation control

Entry	Substrate	Product	Ratio *anti/syn*	Yield (%) X=TMS	Yield (%) X=$SnBu_3$
1	**97a**: R_1=Ph, R_2=Me	**98a**	>100:1	39	76
2	**97b**: R_1=Me, R_2=Me	**98b**	>100:1	35	65
3	**97c**: R_1=Et, R_2=Me	**98c**	>100:1	40	80



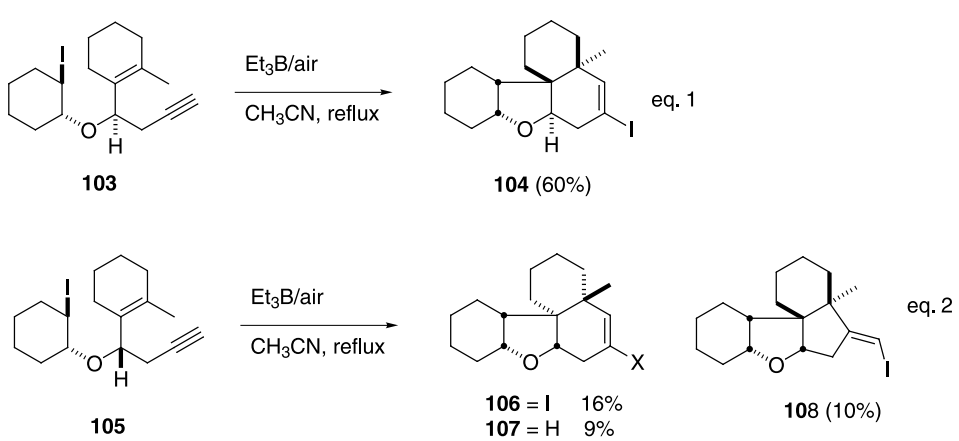
Scheme 18.

13-deoxyserratine (**102**), a complex lycopodium alkaloid, in 10 steps (Scheme 18).[33] The corner stone of this elegant synthesis resided in a stereoselective tandem radical cyclization of amidyl radical **100** generated from hydroxylamine **99** thereby creating a tetracyclic fused-ring **101** bearing two vicinal quaternary carbon centers. A chlorine atom was purposely installed on the olefin to disfavor a 5-*exo* mode closure without hindering the 6-*endo* trigonal cyclization. The chlorine atom was then removed by reduction with a second equivalent of tributyltin hydride. This transformation solved a significant problem in the synthesis of the serratine skeleton.

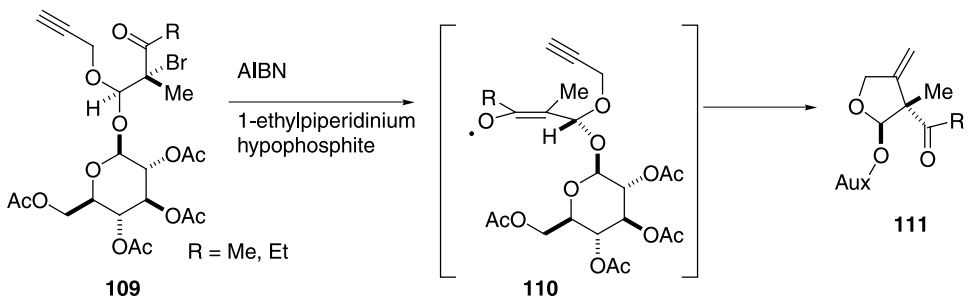
Hoffmann et al.[34] reported a single step synthesis of complex polycyclic compounds possessing vicinal quaternary centers in a radical-mediated cascade cyclization (Scheme 19). This elegant strategy proceeded first through a radical 5-*exo-trig*-cyclization followed by a 6-*endo-dig* cyclization. It was remarkable that in the second step (Eq. (1)), the unusual 6-*endo-dig* cyclization (**104**) dominated over the 5-*exo-dig* cyclization. In Eq. (2), the second 5-*exo-dig* cyclization (**108**) competes with the 6-*endo-dig* pathway (**106** and **107**). Ring strain could be invoked to explain these results.

Control of the absolute configuration of C–C bonds formed via radical reactions can be possible when temporary linked chiral auxiliaries are employed.[28a] For instance, the treatment of **109** bearing a glucopyranosyl based auxiliary with AIBN and a source of hydrogen such as 1-ethyl-piperidium hypophosphite gave **111** in quantitative chemical yield and diastereomeric excess of 96% (Scheme 20).[35]

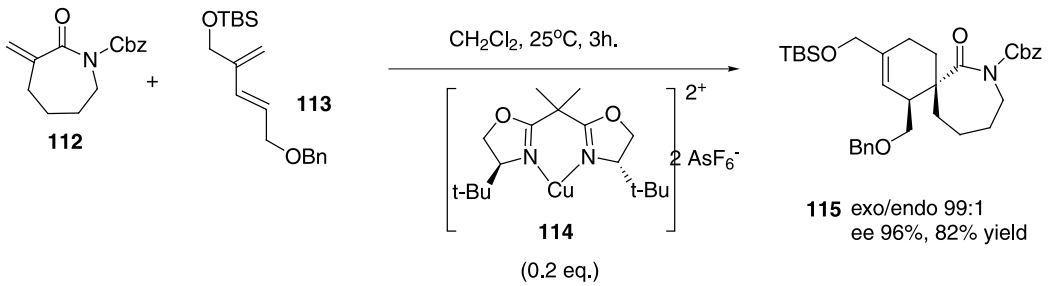
The high stereochemical outcome of the radical process could be explained by considering allylic strain in **110** which dictates the facial selectivity during the cyclization. According to Stoodley, this method can be employed in



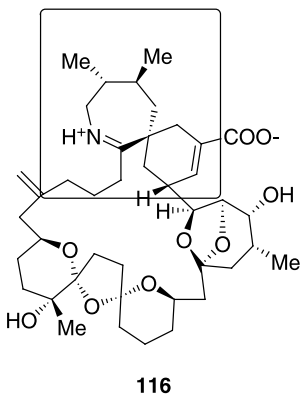
Scheme 19.



Scheme 20.



Scheme 21.



116

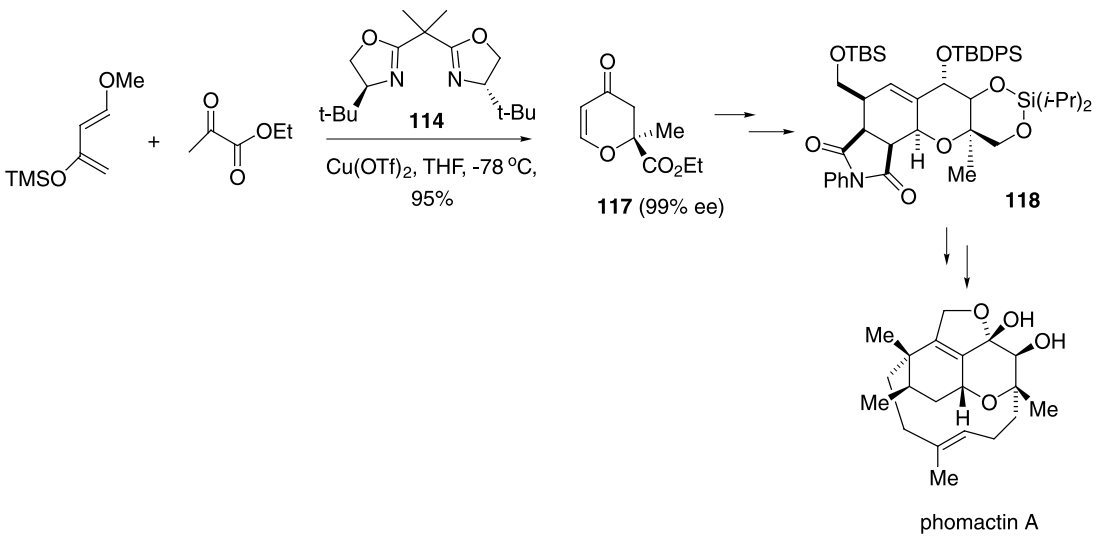
Figure 10. Pinnatoxin A.

the preparation of multigram quantities of lactone possessing α-quaternary carbon centers.

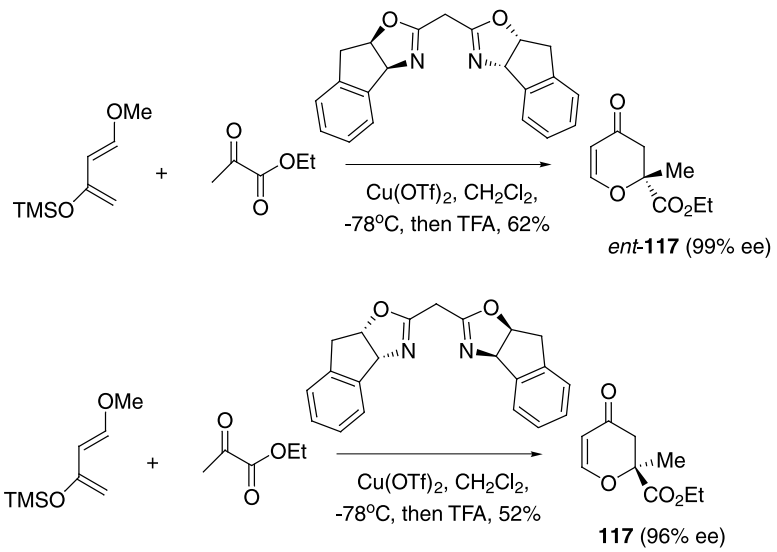
4. Cycloadditions

4.1. Enantioselective Diels–Alder reaction

The Diels–Alder reaction is one of the most versatile tools in the arsenal of the organic chemist. When α-substituted enones and enals are used as dienophiles, the reaction gives rise to cycloadducts bearing a quaternary carbon center (Scheme 21).



Scheme 22.



Scheme 23.

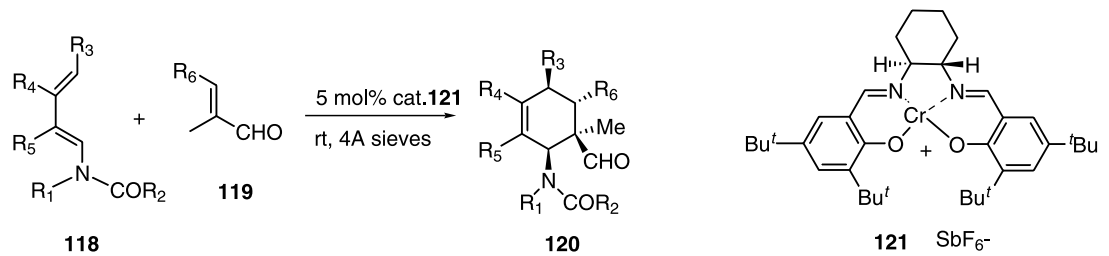
As a result of continuous efforts to develop effective catalytic process for the enantioselective Diels–Alder reaction, novel chiral catalysts for the asymmetric Diels–Alder reaction are emerging. For example, the copper/BOX complexes, namely (*S*,*S*)-*t*-BuBOX/Cu (**114**), originally developed by Evans,[22,36] has been utilized as a chiral Lewis acids in the Diels–Alder reaction to construct an azaspiro[5.6]dodec-9-ene system **115** that is found in the marine natural toxin pinnatoxin A (**116**) (Fig. 10) (Scheme 21).[37]

In 1998 Jorgensen reported[38] that the same catalyst can be employed to catalyze hetero-Diels–Alder reactions of various α-dicarbonyl dienophiles and Danishefsky type dienes. The reactions furnished 2,3-dihydro-4-pyranones possessing a quaternary carbon center at C5 in excellent chemical and optical yields. This method of producing 2,3-dihydro-4-pyranones such as **117** was further applied by Danishefsky in the enantioselective synthesis of the Phomactin A oxadecalin core **118** (Scheme 22).[39]

Ghosh et al. demonstrated that the conformationally constrained *cis*-aminoindan-2-ol-derived bis(oxazoline)/copper complex was also a very effective catalyst for the hetero-Diels–Alder reaction with a high transfer of chirality (Scheme 23).[40]

Though a number of catalysts proved to be highly efficient in catalyzing Diels–Alder reactions, the usual catalyst loading still remains high. Most of the catalysts are effective at 5–20 mol% loading. For instance, in order to perform a highly enantioselective metal-catalyzed [4+2] cycloaddition with various substituted 1-carbamate-1,3-butadienes **118** and methacrolein derivatives **119**, 5 mol% of the Jacobsen's chiral catalyst[41] **120** was needed (Table 13).[42]

Table 13. Enantioslective Diels–Alder reaction with various 1-aminobutadienes (**118**) in the presence of Cr(III)–salen complex **120**



Entry	R_1	R_2	R_3	R_4	R_5	R_6	Time	Yield (%)	ee (%)
1	Bn	MeO	H	H	H	H	21 h	99	93
2	Alkyl	MeO	H	H	H	H	24 h	95	89
3	Me	MeO	H	H	H	H	22 h	96	79
4	Bn	*t*-BuO	H	H	H	H	23 h	99	92
5	Bn	Me	H	H	H	H	25 h	85	91
6	Bn	MeO	Me	H	H	H	22 h	94	93
7	Bn	MeO	Ph	H	H	H	5 d	63	93
8	Bn	MeO	H	Me	H	H	15 h	93	95
9	Bn	MeO	H	H	Me	H	4 d	81	95
10	Bn	MeO	Me	H	Me	H	9.5 h	40	92
11	Bn	MeO	H	H	H	Me	8 d	62	93

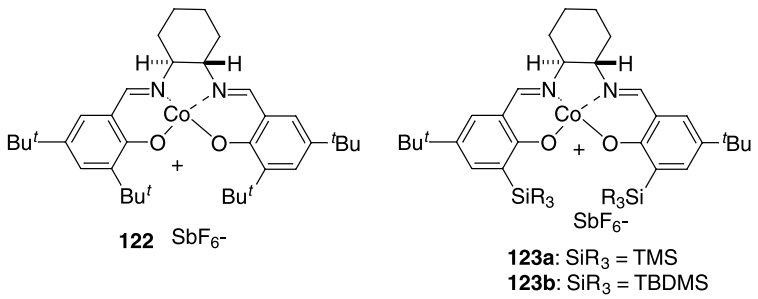
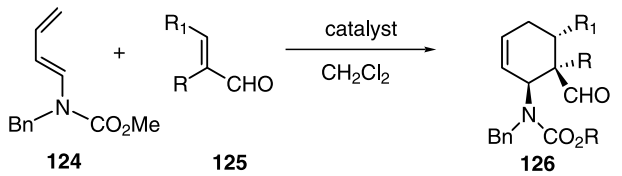


Figure 11. New chiral Co(III)–salen catalysts.

Table 14. Enantioselective Diels–Alder reaction between diene **124** and various acroleins **125** catalyzed by Co(III)–salen complexes



Entry	R	R_1	Catalyst	Loading (mol%)	Time	Yield (%)	ee (%)
1[a]	Me	H	**122**	5	2 h	93	95
2	Me	H	**123a**	0.05	3 d	93	98
3	Me	H	**123a**	0.1	16 h	98	98
4	Et	H	**123a**	0.1	30 h	93	>97
5	TBSO(CH_2)$_2$	H	**123a**	0.5	18 h	100	>97
6	–(CH_2)$_4$–		**123a**	2.0	3 d	78	>95
7[a]	Me	H	**123b**	0.1	20 h	100	98

[a] 4 Å molecular sieves were used.

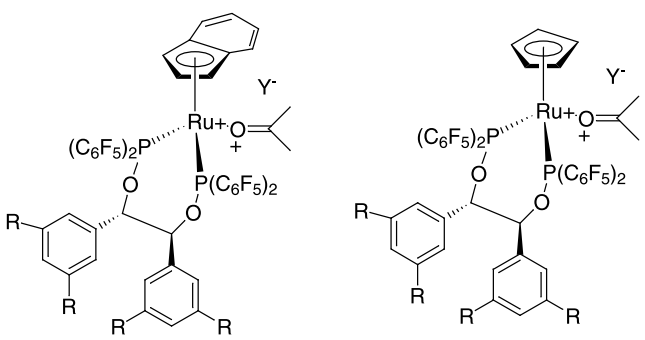


Figure 12.

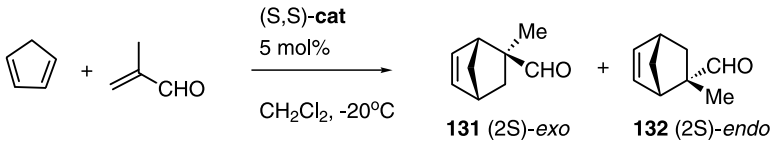
Further studies by Rawal on metal–salen complexes have shown that the Co(III)–salen complex **122** (Fig. 11) was an effective catalyst for the reaction between 1-carbamate-1,3-butadiene and methacrolein (entry 1, Table 14).[43] After 2 h at room temperature and with 5 mol% of the catalyst, the reaction was completed and the cycloadduct **126** was obtained in an enantiomeric excess of 95%.

O-Silyl substituted salen cobalt(III) complexes **123a** and **123b** have been applied to the same diene–dienophile system. These catalysts are more effective in comparison to the original Co(III)–salen complex (**122**). Moreover, the enantioselectivity (ee=98%) of the reaction was maintained even at 0.05 mol% catalyst loading (entry 2, Table 14). It is noteworthy that these catalysts are also active at room temperature and below and do not require inert atmospheres.

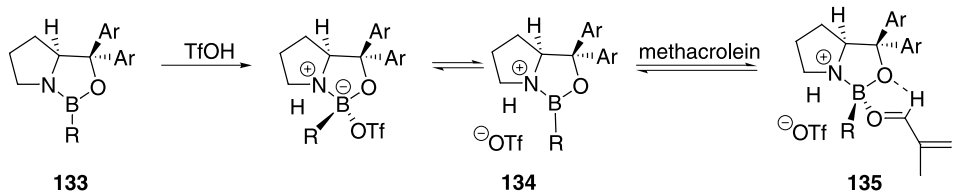
Another example of a chiral Lewis acid catalyst is an indenyl ruthenium (biphop-F) cationic complex developed by Kündig (Fig. 12).[44] The reaction of methacrolein and cyclopentadiene in the presence of 5 mol% of the catalyst gave almost exclusively the *exo*-product **131** in excellent enantiomeric excesses (Table 15). It was found that the rate of the cycloaddition reaction was dependant on the catalyst counter anion. The reaction with the indenyl catalyst was faster than with its cyclopentadienyl analogue (Fig. 12).

Corey and co-workers have recently reported asymmetric Diels–Alder reactions catalyzed by a triflic acid activated chiral oxazaborolidine.[45] Treatment of oxazaborolidine **133** with anhydrous triflic acid in dichloromethane produces a Lewis superacid **134** which then acts as a catalyst in a reaction forming an organized complex **135** with an α,β-unsaturated aldehyde (Scheme 24).

Table 15. Enantioselective Diels–Alder reaction of cyclopentadiene and methylacrolein



Entry	Catalyst	Time (h)	Yield (%)	*exo*/*endo*	ee (%)
1	**127a**	5	87	99.8:0.2	89
2	**129b**	22	91	97:3	92
3	**130b**	22	87	97:3	97
4	**127b**	2.5	85	99.7:0.3	88
5	**128b**	4	80	99.8:0.2	95



Scheme 24.

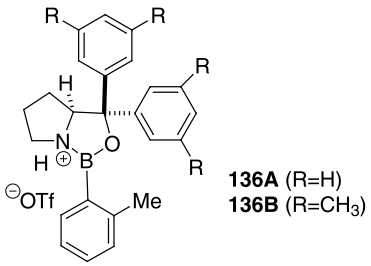
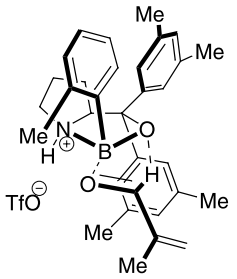


Figure 13.



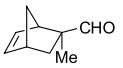
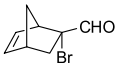
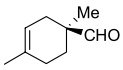
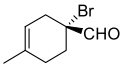
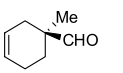
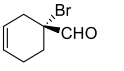
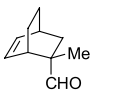
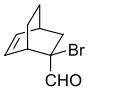
145

Figure 14. Pre-transition state assembly of an aldehyde–LA complex **145**

The best enantioselectivity was achieved with aryl substituents on the boron, namely, *o*-tolyl (Fig. 13). Various dienes were subjected to the reaction with 2-methacrolein or 2-bromoacrolein to afford cycloadducts bearing a quaternary center in high yields and excellent enantioselectivities. Even non-activated dienes such as butadiene (entries **5** and **6**) reacted in the presence of the catalyst (Table 16). The enantioselectivity of the transformation was rationalized by a pre-transition state assembly of an aldehyde–Lewis acid complex **145** depicted in Figure 14.

The use of a chiral diene constitutes another approach to induce chirality into Diels–Alder products. Recently, Rawal has described the synthesis and the application of

Table 16. Diels–Alder reaction of 1,3-diene with 2-methacrolein or 2-bromoacrolein (CH_2Cl_2) catalyzed by chiral Lewis acid

Entry	Diene	Product	Catalysis[a]	Conditions	Yield (%)	*exo*/*endo*	ee (%)
1		 **137**	**136a** **136b**	−95°C, 1 h	99 97	91:9 91:9	91 96
2		 **138**	**136a** **136b**	−95°C, 1 h	99	91:9	92 96
3		 **139**	**136b**	−78°C, 13 h	96		97
4		 **140**	**136a** **136b**	−95°C, 1 h	98		97
5		 **141**	**136b**[b]	−78°C, 24 h	85		94
6		 **142**	**136a** **136b**	−95°C, 2 h	95 97		96
7		 **143**	**136a**[b] **136b**[b]	−78°C, 24 h	91 58	5:95 6:94	92
8		 **144**	**136a** **136b**	−95°C, 2 h	81 85	6:94 7:93	92

[a] 6 mol%.
[b] 20 mol%.

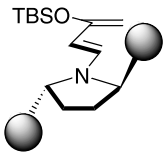
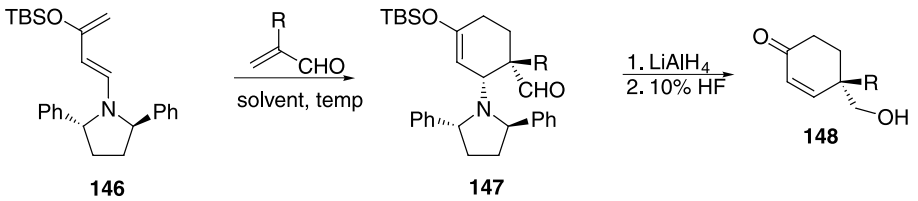


Figure 15.

Table 18. Asymmetric [4+2] cycloadditions of chiral 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes with methacrolein and ethylacrolein

Entry	R	Diene	Yield of **148** (%)	ee (%)
1	Me	**149a**	67	91
2	Me	**149b**	54	79
3	Me	**149c**	49	96
4	Et	**149a**	65	92



Scheme 25.

chiral 1-amino-3-siloxy-1,3-butadienes in Diels–Alder reactions.[46] It was found that a diene with a C_2-symmetric *trans*-2,5-diphenylpyrrolidine unit was efficient in the reaction with methyl and ethyl α-substituted acroleins (Fig. 15). The chiral diene **146** reacted with methacrolein to give the corresponding *endo*-diastereomer cycloadduct **147** containing the requisite quaternary center (Scheme 25). The removal of the chiral auxiliary unit was accomplished using a LAH reduction followed by HF hydrolysis to afford the 4,4-disubstituted cyclohexenones **148** in good enantiomeric excess (Table 17). A similar outcome was obtained in the case of ethylacrolein as the dienophile (entry 4).

Table 17. Asymmetric [4+2] cycloadditions of chiral amino siloxy diene **146** with substituted acroleins

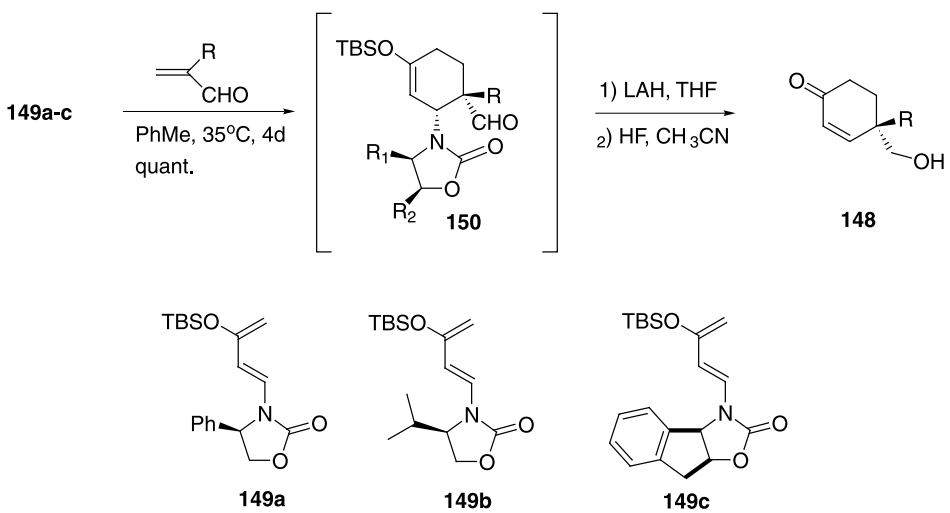
Entry	R	Solvent	Temperature (°C)	Yield of **147** (%)	Enone **148** (%)	ee (%)
1	Me	THF	20	85	72	86 (*S*)
2	Me	CH_3CN	20	52	56	76 (*S*)
3	Me	PhMe	−10	71	79	88 (*S*)
4	Et	PhMe	20	86	87	88 (*S*)

Chiral 3-siloxy-1,3-butadienes **149a-c** bearing various oxazolidinone auxiliaries at C-1 were also investigated (Scheme 26).[47] The cycloaddition of these dienes with methacrolein and ethylacrolein resulted in the exclusive formation the *endo*-diastereomer adducts **150a-c**. As previously mentioned above, the chiral auxiliary unit was removed to give the corresponding cyclohexenones **148** possessing a quaternary carbon center at C4 in enantiomeric excesses ranging from 79 to 96% (Table 18).

A close examination of the proposed transition states **A** and **B** reveals that the carbonyl group of the chiral auxiliary adopts a conformation which is *anti* to the diene moiety (Fig. 16). In transition state **A**, the auxiliary substituent blocks one face of the diene favoring the attack of the dienophile *anti* to the substituents. The high diastereoselectivity of the cycloaddition process reaction is thus readily explained using this model.

4.2. [2+3] Cycloadditions

Highly diastereoselective multicomponent syntheses of substituted imidazolines with quaternary carbon stereo-centers



Scheme 26.

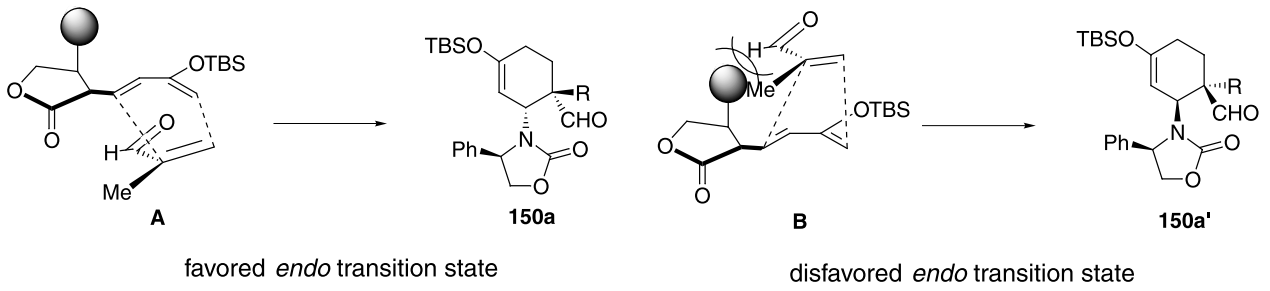
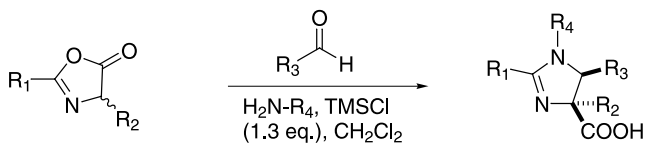
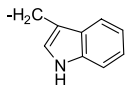


Figure 16. Two possible *endo* approaches of the dienophile toward a chiral diene.



Scheme 27. Highly diastereoselective multicomponent synthesis of unsymmetrical imidazolines.

Table 19. Highly diastereoselective multicomponent synthesis of unsymmetrical imidazolines

Entry	R_1	R_2	R_3	R_4	Yield (%)
1	Ph	Me	Ph	Bn	75
2	Ph	Me	*p*-OMe–Ph	Bn	78
3	Ph	Me	Pyridine	Bn	76
4	Ph	Me	CO_2Et	*p*-F–Ph	72
5[a]	Ph	Me	Ph	$-(CH_2)_2-CO_2Et$	51
6	Ph	Me	Ph	$-CH_2-CO_2Me$	70
7	Ph	Me	Ph	*p*-F–Ph	74
8	Me	Me	*p*-OMe–Ph	Bn	60
9	Ph	Ph	Ph	Bn	65
10	Ph		Ph	Bn	68
11	Ph	$-(CH_2)_2-CO_2Me$	Ph	Bn	60

[a] A mixture of two diastereoisomers was obtained in 3:1 ratio (*trans*/*cis*).

have been developed by Tepe (Scheme 27).[48] It was found that the reaction of oxazolones **151** and imines in the presence of TMSCl as a Lewis acid gave various imidazolines **152** in good yields as single diastereomers (Table 19). Tepe et al. suggested that the reaction occurred via a 1,3-dipolar cycloaddition (Fig. 17). The formation of only one diastereomer was explained by the steric repulsion between the R_3 group and the R_2 group during the cycloaddition step.

As in the case of the Diels–Alder reaction, asymmetric 1,3-dipolar cycloadditions can be performed using a chiral Lewis acid catalyst. The use of chiral Lewis acids to catalyze 1,3-dipolar cycloaddition reactions between nitrones and alkenes has been extensively investigated.[49] Activation of the dipolarophiles and nitrones is necessary for a normal electron demand cycloaddition to proceed. However, a catalytic system was developed for dipolarophiles with two points of binding. Monodentate substrates such as α,β-unsaturated aldehydes must compete with a nitrone for the coordination site of the catalyst. The catalyst coordinates much more strongly with nitrones, thus shutting down the catalytic cycle of the reaction. The problem can be solved by the appropriate choice of chiral Lewis acid. The first asymmetric 1,3-dipolar cycloaddition reaction between nitrones and α,β-unsaturated aldehydes has recently been reported by Kündig.[50] The authors used (cyclopentadienyl) iron (biphop-F) **153** and (cyclopentadienyl) ruthenium (biphop-F) **154** cationic complexes, which have also been

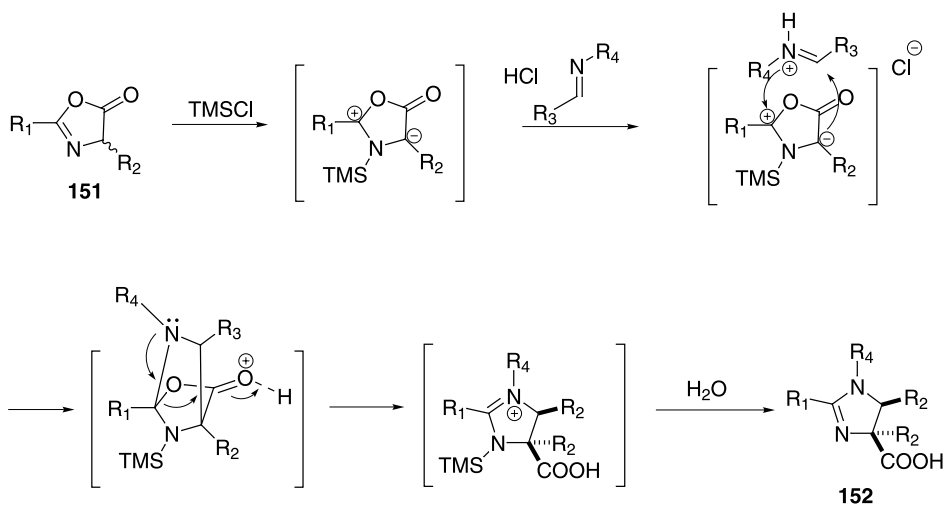
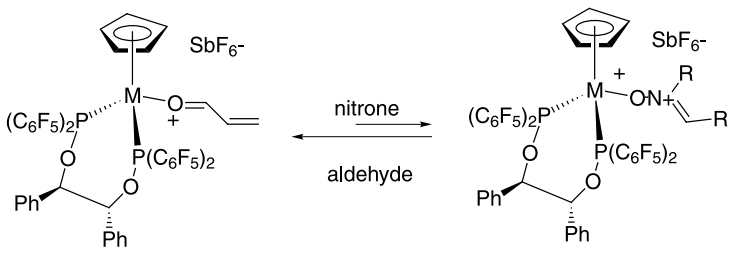


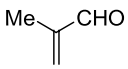
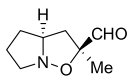
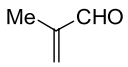
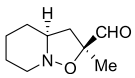
Figure 17. Proposed mechanism of 1,3-dipolar cycloaddition.



153 M = Fe
154 M = Ru

Figure 18.

Table 20. (*R*,*R*)-Fe-Lewis acid **153** catalyzed enantioselective 1,3-dipolar cycloadditions (5 mol%)

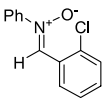
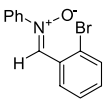
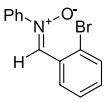
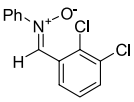
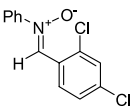
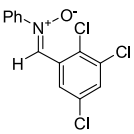
Nitrone	Enal	Yield (%)	Product	ee (%)
		92		96
		71		>96

used to catalyze the Diels–Alder reaction (see Table 15). Detailed mechanistic studies depict a clear portrait of the chiral environment when aldehydes are complexed on the metal (Fig. 18). The catalytic process could be rationalized by the preference of the catalyst to coordinate with the aldehydes or to coordinate with the nitrones in a reversible manner.

The results have shown that the reaction of methacrolein with various nitrones **155**-**156** was most effective in the presence of the iron catalyst **153**. Slow addition of the nitrone to an excess of a methacrolein/catalyst mixture was required in order to achieve a good enantioselectivity and to avoid the non-catalyzed background reaction. High yields and enantioselectivity were observed (Table 20).

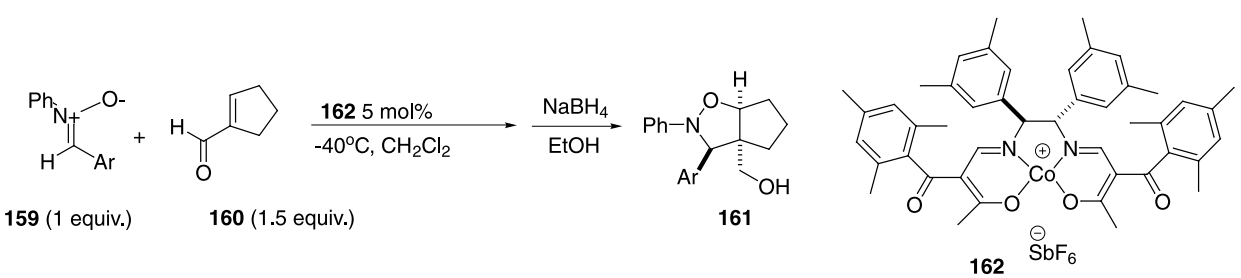
Yamada and co-workers have described an enantioselective cycloaddition of nitrones **159** to 1-cyclopentene-1-carbaldehyde **160** catalyzed by chiral cationic cobalt (III) complex **162** (Scheme 28).[51] The corresponding isoxazolidines **161** were obtained in a very good yield, excellent *endo*/*exo* selectivity and high enantioselectivity (Table 21).

Table 21. Asymmetric 1,3-dipolar cycloaddition reaction of various nitrones **159a-f** and 1-cyclopentene-1-carbaldehyde **160**

Nitrone		Time (h)	Yield (%)	*endo*/*exo*	ee (*endo*) (%)
	**159a**	96	96	99/1	80
	**159b**	96	85	99/1	85
	**159c**	96	18[a]	>99/1	91
	**159d**	96	Quant.	>99/1	87
	**159e**	60	Quant.	>99/1	83
	**159f**	96	93	>99/1	85 (100[b])

[a] Reaction temperature was −78°C.
[b] After a recrystallization from ethanol.

The high diastereo and enantioselectivity were explained by the approach of the nitrone from the least hindered direction to the axially coordinated aldehyde (Fig. 19). It was also postulated that the improvement in enantioselectivity was due to the coordination of the halogen atom in *ortho* position of the nitrone with the metal complex.



159 (1 equiv.) **160** (1.5 equiv.) **161** **162**

Scheme 28.

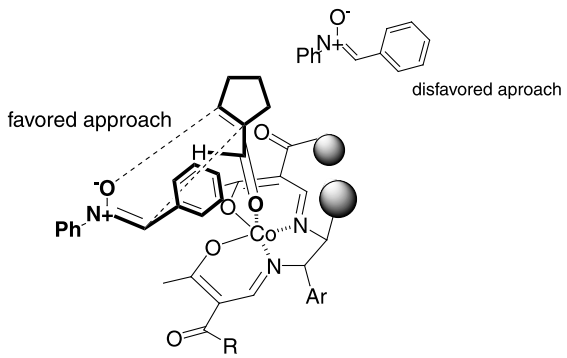
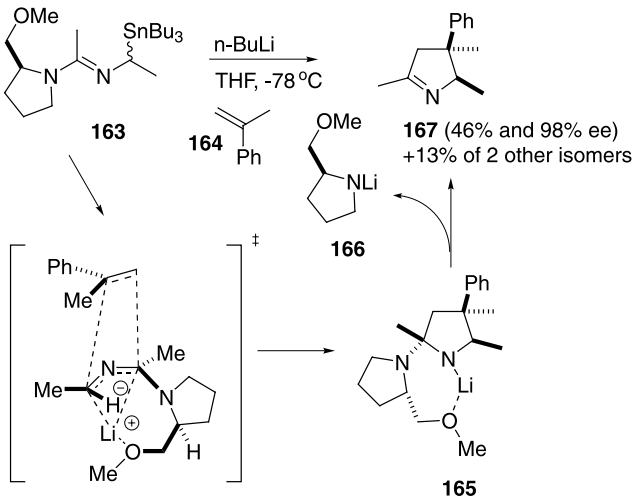
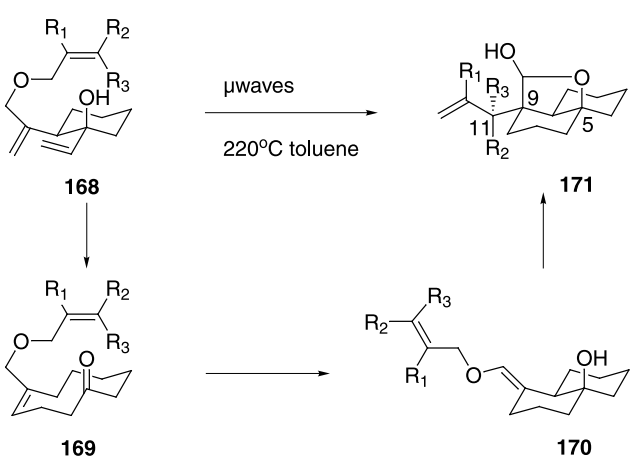


Figure 19. Approach of the nitrone toward a coordinated aldehyde.



Scheme 29.

The first example of an asymmetric cycloaddition of a 2-azaallyllithium with an alkene was published by Pearson (Scheme 29).[52] Originally, a chiral lithium base such as (−)-sparteine was employed to induce chirality but no selectivity was detected. To solve this problem, a chiral auxiliary unit was then attached to the allyl anion precursor **163** and after the addition of 1-methyl styrene **164**, the [2+3] cycloadduct **167** bearing a quaternary carbon center was formed in moderate yield (46%) but with an enantiomeric excess of 98%.



Scheme 30.

5. Sigmatropic rearrangements

Claisen and oxy-Cope rearrangements are important reactions for the multiple construction of carbon–carbon bonds.[53] Barriault and Denissova[54] have reported highly diastereoselective microwave accelerated oxy-Cope/ene/Claisen cascade reactions generating decalin skeletons possessing quaternary carbons at C-9 and C-5 (Scheme 30). The cascade process starts with a thermal oxy-Cope reaction of **168** producing in situ the corresponding enol that rapidly tautomerizes to afford the macrocyclic ketone **169**. The latter undergoes a transannular carbonyl-ene reaction leading to the 1,5-hexadiene enol ether **170**, which is poised for a subsequent Claisen rearrangement to give the bicyclic lactol **171**.

The tandem process proved to be highly diastereoselective (de>98%) (Table 22). Depending on the substitution pattern of the allyl ether **168**, additional stereogenic centers can be introduced at C11 (entries 2 and 3). The high diastereoselectivity can be rationalized using the proposed mechanism depicted in Figure 20. The transannular ene reaction can adopt two transition states **A** and **B** leading to enol ethers *E* **189** and *Z* **190**, respectively. A close examination of the transitions states reveals that the allyl ether group develops severe steric interactions with the ring. Conversely in **A**, the ring has steric interactions with H_2. Transition state **A** is thus favored over **B** and the exclusive formation of lactol **180** occurs. In the propargyl ether series (entries 6 and 7), the tricyclic allenes **184** and **185** were obtained in high yields. Interestingly, the heating of propargyl ether **178** resulted in the exclusive formation of tetracyclic acetals **186**. This is explained by the subsequent addition of the lactol hydroxyl moiety onto the allene.

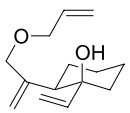
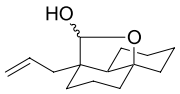
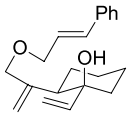
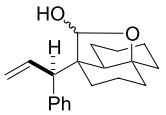
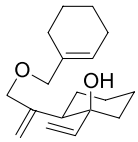
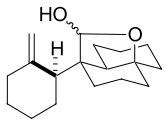
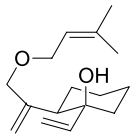
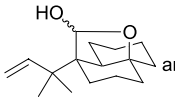
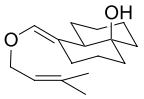
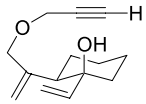
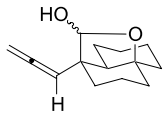
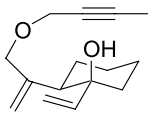
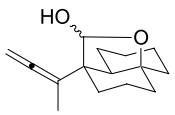
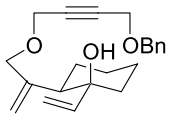
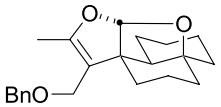
Stoltz et al. reported a new tandem process in which quaternary carbon centers are created in good chemical yields and high diastereoselectivity.[55] The tandem process generates the allyl ether **195** in situ via rhodium-mediated 1,2-hydride migration which rearranges via a subsequent aliphatic Claisen rearrangement to afford the aldehyde **196** (Scheme 31).

The diastereoselectivity was improved by cooling the reaction mixture to −40°C and adding Me_2AlCl or DIBAL. Interestingly, the rearrangement of geranyl and neryl ethers **197** and **198** produced the cyclohexanols **199** and **200** through a final Lewis acid catalyzed ene reaction (entries 1 and 2, Table 23). In the presence of DIBAL at −40°C, the ene reaction was suppressed and the rearrangement of geranyl and neryl ethers **197** and **198** gave the corresponding alcohols **201** and **202** (entries 3 and 4).

Recently, Buchwald and co-workers described a domino copper-catalyzed C–O coupling/Claisen rearrangement reaction.[56] In this process, allyl vinyl ethers **206** were prepared in situ by the coupling of a vinyl halide **204** and an allylic alcohol **203** with complete retention of double bond geometry (Scheme 32).

Once being formed, the allyl ethers underwent a subsequent thermal Claisen rearrangement. Compounds containing a tertiary carbon center vicinal to a quaternary one (entries

Table 22. Tandem oxy-Cope/ene/Claisen reaction of 1,2-divinylcyclohexanols allyl and propargyl ethers[a]

Entry	Substrate		Product		Yield (%) (de, %)
1		**172**		**179**	75 (>98)
2		**173**		**180**	75 (>98)
3		**174**		**181**	60 (>98)
4		**175**	 and  **182** **183**		76 (>98) and 15 (**183**)
6		**176**		**184**	98 (>98)
7		**177**		**185**	68 (>98)
8		**178**		**186**	81 (>98)

[a] All reactions were performed in toluene with 2 equiv. of DBU. The solutions were irradiated at 600 W for 1 h in a quartz cell.

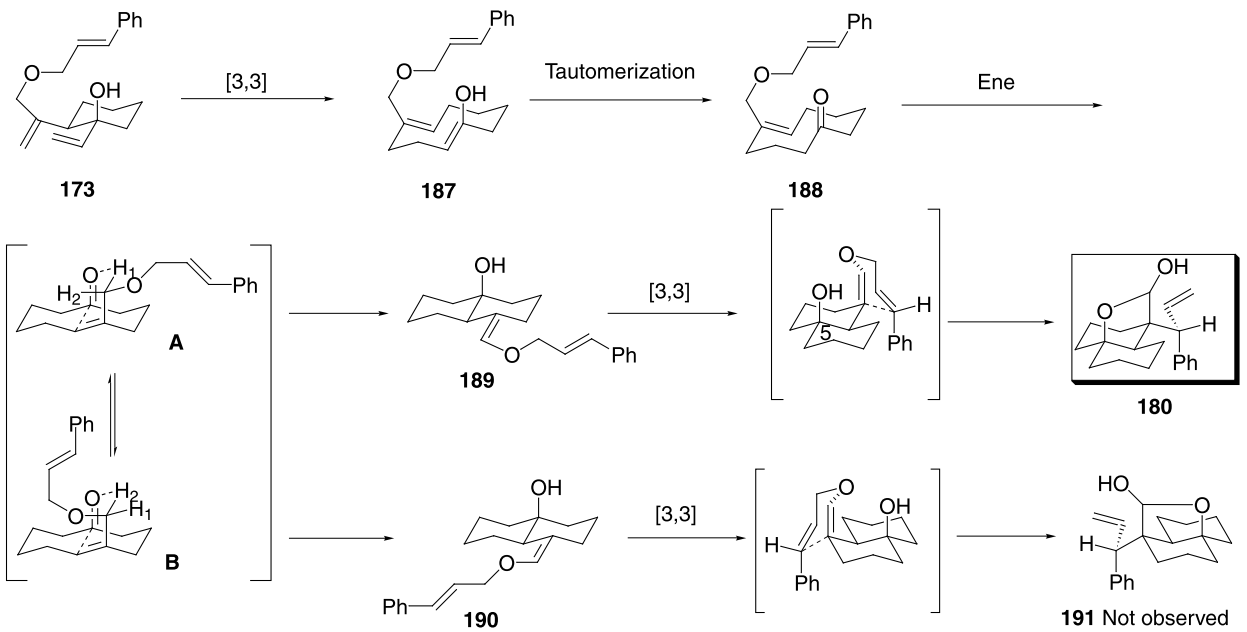
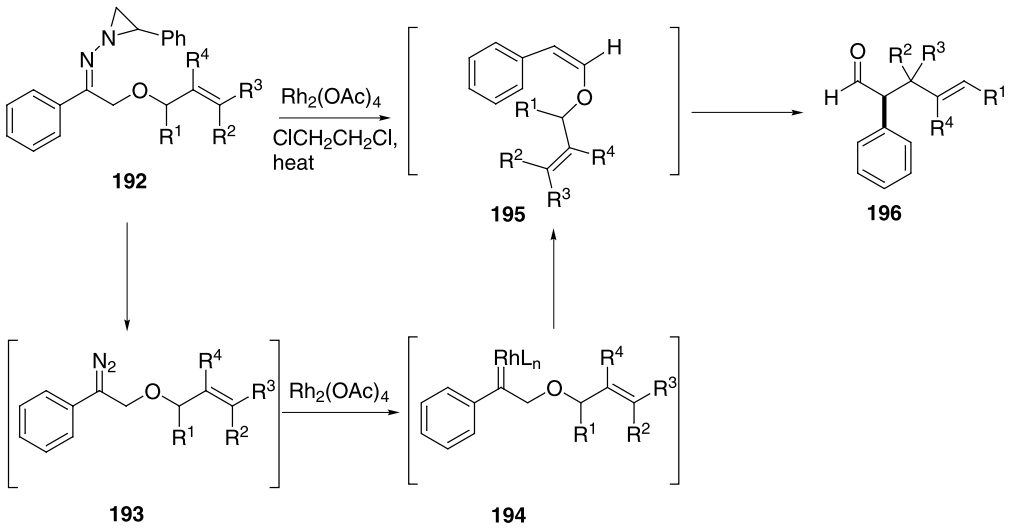
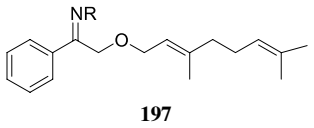
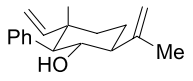
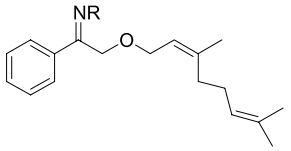
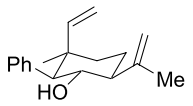
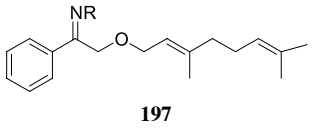
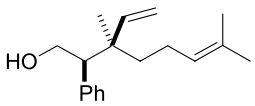
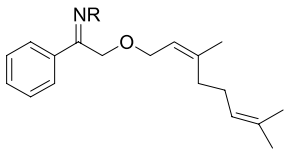
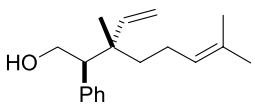


Figure 20. Proposed mechanism of the tandem oxy-Cope/ene/Claisen reaction.

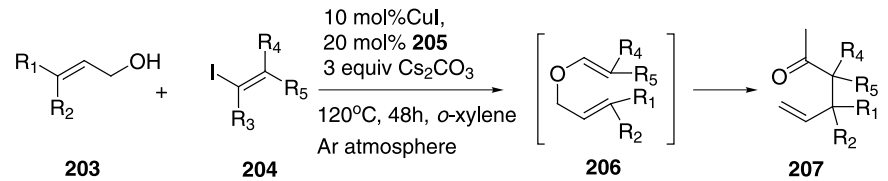


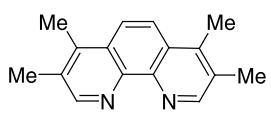
Scheme 31.

Table 23. Tandem rodium mediated 1,2-hydride shift/Claisen reaction

Entry	Substrate[a]	Product[b]	Yield (%) (dr)
1	 **197**	 **199**	68 (>20:1)[c]
2	 **198**	 **200**	63 (>20:1)[c]
3	 **197**	 **201**	88 (>20:1)[d]
4	 **198**	 **202**	78 (>20:1)[d]

[a] R=NCH_2CHPh.
[b] Reaction conditions: $Rh_2(OAc)_4$ (1 mol%), $ClCH_2CH_2Cl$, 130°C, 2–8 h.
[c] Subsequent treatment with Me_2AlCl at −40°C.
[d] Subsequent treatment with DIBAL at −40°C.

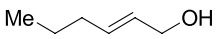
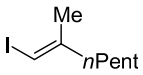
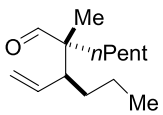
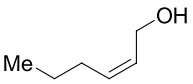
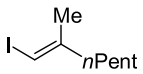
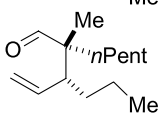
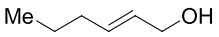
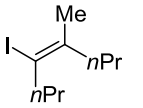
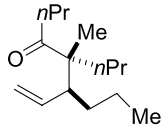
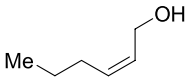
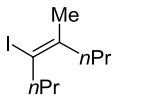
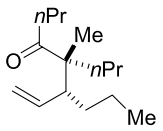
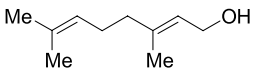
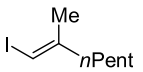
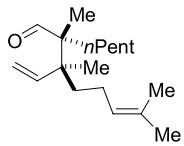
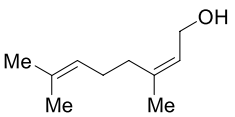
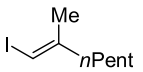
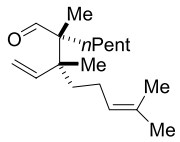
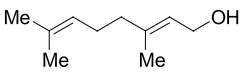
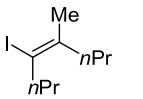
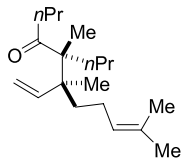
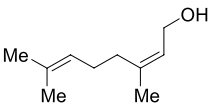
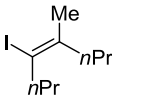
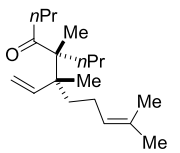




205

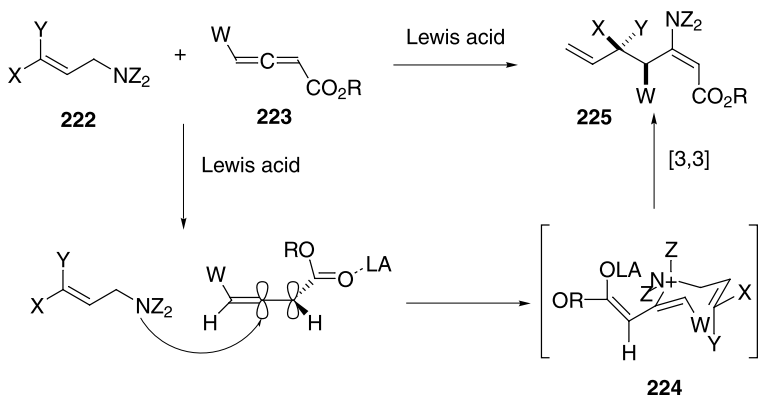
Scheme 32. C–O bond formation—Claisen rearrangement tandem reaction.

Table 24. C–O bond formation—Claisen rearrangement tandem reaction

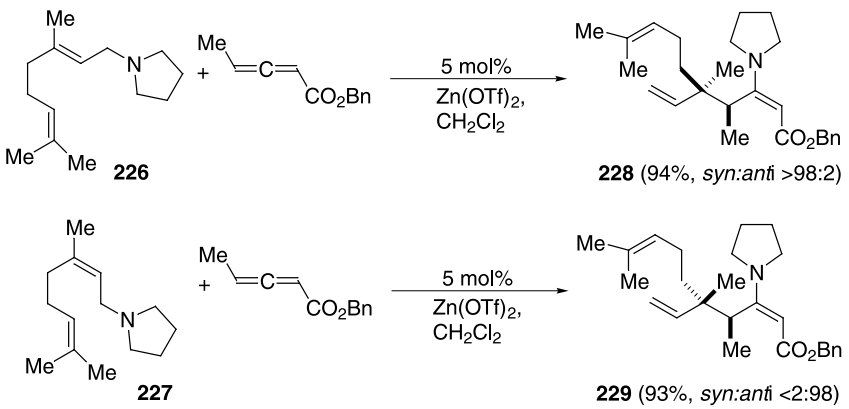
Entry	Alcohol		Vinyl halide		Product		Yield (%)	dr
1		**208**		**212**		**214**	55	92:8
2		**209**		**212**		**215**	68	5:95
3		**208**		**213**		**216**	59	88:12
4		**209**		**213**		**217**	–	9:91
5		**210**		**212**		**218**	77	92:8
6		**211**		**212**		**219**	77	6:94
7		**210**		**213**		**220**	62	87:13
8		**211**		**213**		**221**	69	12:88

1–4) or with two adjacent quaternary centers (entries 5–8) were synthesized in diastereomeric ratio ranging from 87/13 to 92/8 (Table 24). The lower diastereoselectivities observed in entries 3, 7 and 8 were attributed to the lower stereochemical purity of the corresponding vinyl iodides (Table 24).

Advances in Lewis acid catalyzed Claisen rearrangements

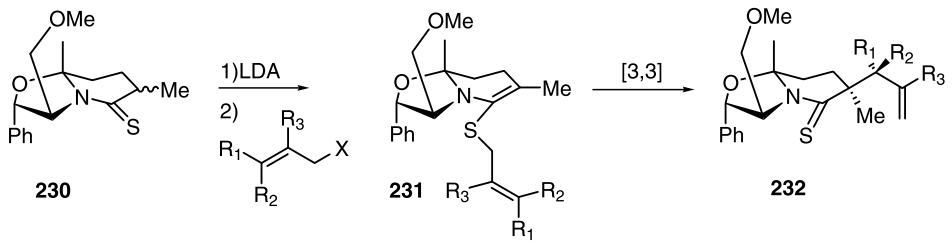


Scheme 33.



Scheme 34.

Table 25. Diastereoselective thio-Claisen rearrangements

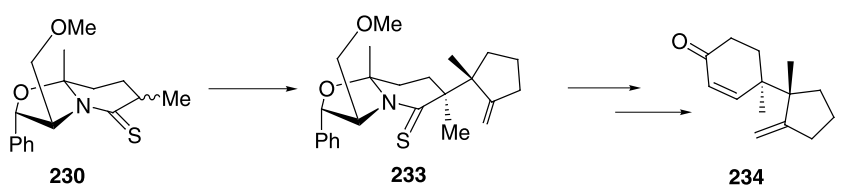


Entry	Allyl halide				T (°C)[a]	Yield (%)	dr
	R_1	R_2	R_3	X			
1	H	H	Me	Cl	25	71	3:1
2	Me	H	H	Br	25	79	91:9
3	Ph	H	H	Br	140	48	>99:1
4	Me	Me	H	Br	140	68	>99:1
5[67]	Me	Me	H	Br	65[b]	65	>20:1

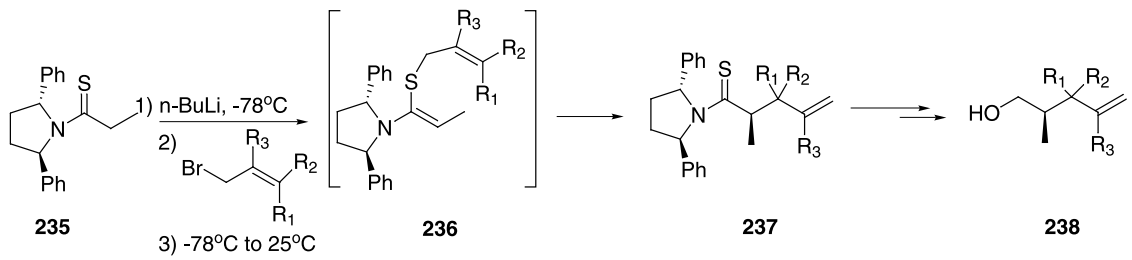
[a] Rearrangements at room temperature were carried out in THF; at 140°C, xylene was the solvent employed.
[b] $PdCl_2(MeCN)_2$ was used as catalyst.

have been recently reported by MacMillan and co-workers.[57] Various *E* allyl-vinylammonium species **224** were generated in situ via the Lewis acid catalyzed 1,4-conjugated addition of tertiary amines **222** to allenic esters **223** (Scheme 33). The presence of $Zn(OTf)_2$ proved to be essential to engage the subsequent Claisen rearrangement. This method displays a broad tolerance toward modification of the allyl amines as well as the allenoate structures. The use of γ-disubstituted allyl amines **226** and **227** afforded compounds **228** and **229** in good yields and excellent selectivities. The stereochemical outcome of the vicinal quaternary and tertiary carbon centers was directly dependent of the geometry of the allyl amines (Scheme 34).

In 1994, Meyers et al.[58] reported an asymmetric thermal [3,3]-sigmatropic rearrangement of the *S*-allylthioenamines **231** which are readily obtained from S-allylation of chiral bicyclic thiolactams **230** using various allylic halides (Table 25). It was demonstrated that the diastereoselectivity as well as the reaction conditions were dependent on the allylic halide substitution pattern (Table 4). The Claisen rearrangement proceeded over the top face of the bicyclic system affording the desired product **232** in diastereomeric ratios ranging from 3:1 to >99:1. The same group has recently demonstrated that the presence of palladium(II) or nickel(II) catalysts in the reaction mixture allow the reaction to proceed at room temperature while maintaining the high



Scheme 35. Application for the synthesis of (−)-trichodiene.



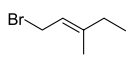
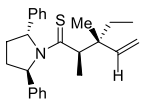
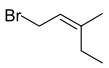
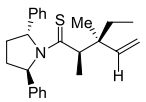
Scheme 36. Thio-Claisen rearrangement using chiral auxiliary.

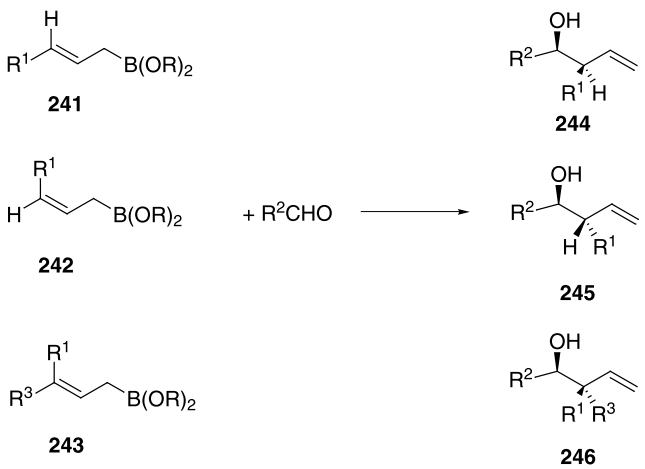
diastereoselectivity of the quaternary carbon center formation (entry 5).[59]

This method was further applied to the enantioselective synthesis of (−)-trichodeine (**234**)[60a,68b] and to cyclohexenones with spiro-connected cyclopentenes (Scheme 35).[68c]

The thio-Claisen rearrangement using C_2-symmetric pyrrolidines as removable chiral auxiliaries was studied by Rawal.[61] In Meyer's examples shown above, the diastereofacial selectivity arouse from a rigid bicyclic thiolactam framework preventing rotation around the C–N bond. In the case of C_2-symmetric pyrrolidine, rotation around the C–N bond gives identical rotamers thus solving the rotation issue in a different manner. The tertiary thioamides **235** were deprotonated with *n*-BuLi and treated with various allylic bromides to form *N*,*S*-ketal intermediates **236**, which upon refluxing in THF rearranged to give the corresponding thio-Claisen products **237** in high chemical yields (Scheme 36). Thioamides **239** and **240**, possessing vicinal tertiary and quaternary centers, were obtained with excellent diastereoselectivities (Table 26).

Table 26. Thio-Claisen rearrangement using chiral auxiliary

Entry	Substrate	Conditions	Product	Yield (%)	de (%)
1		Reflux, 9 h	 **239**	81	>99
2		Reflux, 9 h	 **240**	88	>99



Scheme 37.

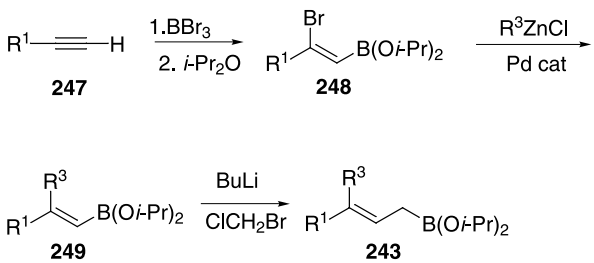
6. Allylation of aldehyde

6.1. Allylboronates

The reaction of γ- monosubstituted allylboronates **241** and **242** with aldehydes has been extensively used to generate homoallylic alcohols **244** and **245** with tertiary centers (Scheme 37).[62] This reaction is believed to proceed via a cyclic Zimmerman–Traxler chair like transition state originating from boron complexation to the oxygen of the carbonyl giving *syn*- or *anti*- products with high and predictable enantio and diastereoselectivity.

In the same way, the reaction of γ- disubstituted allylboronates **243** with aldehydes are expected to yield the corresponding homoallylic alcohols **246** bearing a quaternary carbon center. However, for a long time the application of **243** has been limited due to its difficult accessibility as a pure *Z* or *E* isomer. There are only a few examples in the literature concerning the synthesis and reactivity of γ- disubstituted allylboronates.

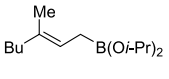
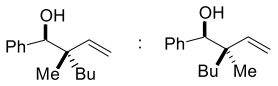
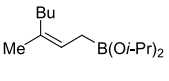
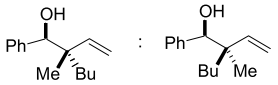
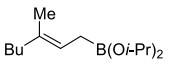
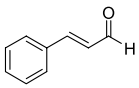
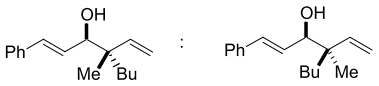
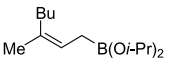
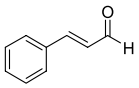
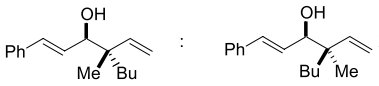
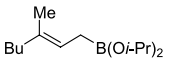
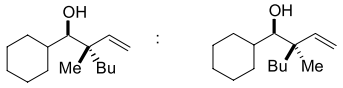
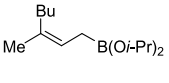
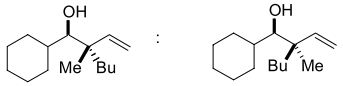
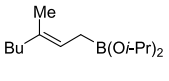
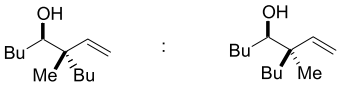
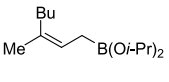
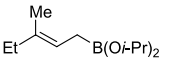
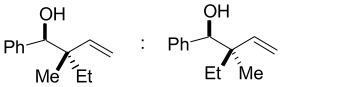
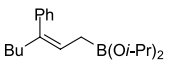
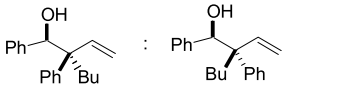
In 1993, Suzuki and co-workers published an approach to generate selectively *E* or *Z* γ-disubstituted allylboronates.[63] These allylboronate esters **243** were synthesized from the haloboration of 1-alkynes **247** followed by a cross-coupling reaction with different alkyl zinc reagents and a subsequent carbon homologation (Scheme 38).



Scheme 38.

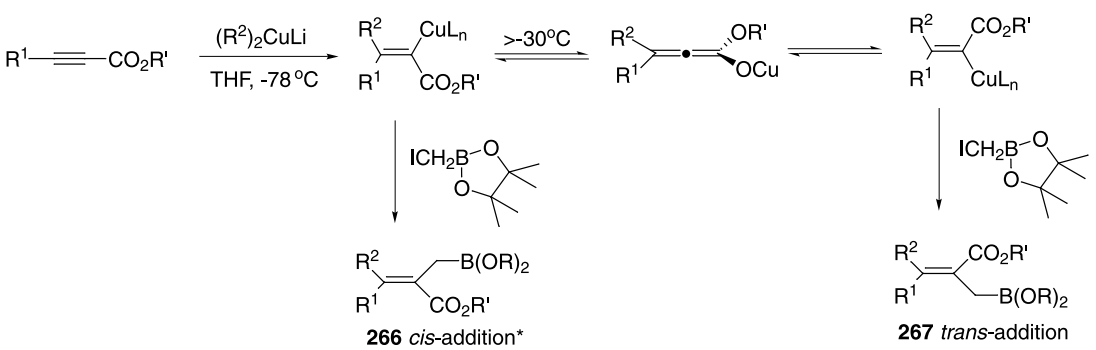
E isomers (purity >95%) reacted with various aldehydes to give homoallylic alcohols bearing asymmetric quaternary carbon centers (Table 27). High diastereoselectivity (≥95%) was observed in all cases in addition to very

Table 27. Reaction of 3,3-disubstituted allylborane derivatives with aldehydes

Entry	Borane	Aldehyde	Product (dr)	Yield (%)
1	 **250**	 **254**	 **255** (97:3)	95
2	 **251**	 **254**	 **255** (12:88)	96
3	 **250**	 **256**	 **257** (95:5)	96
4	 **251**	 **256**	 **257** (10:90)	95
5	 **250**	 **258**	 **259** (95:5)	84
6	 **251**	 **258**	 **259** (11:98)	82
7	 **250**	 **260**	 **261** (95:5)	89
8	 **251**	 **260**	 **261** (11:89)	81
9	 **252**	 **262**	 **263** (95:5)	90
10	 **253**	 **264**	 **265** (95:5)	92

good chemical yields (entries 1, 3, 5, 7, 9, and 10). Since the isomeric purity of *Z* isomers was lower (85%) than that of *E* isomers, lower diastereomeric ratios were observed (entries 2, 4, 6, and 8). An enantioselective version of this method using γ-disubstituted allylboronate tartrate ester derivatives was later reported by the same group.[64] Despite excellent diastereomeric ratios (>95%), the enantioselectivity of the reaction was moderate with enantiomeric excess varying from 62 to 80%.

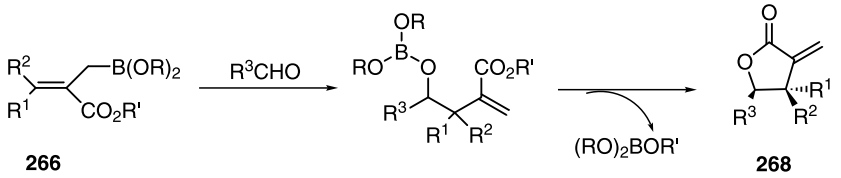
Almost 10 years later, Hall and Kennedy reported an efficient synthesis of tetrasubstituted 2-alkoxycarbonyl



* Note, that use of HMPA as an additive is essential for a good *cis*-selectivity

Scheme 39.

Table 28. Stereoselective synthesis of γ-lactones with quaternary centers in the β position



266 **268**

Entry	Boronate (R^1,R^2)	Aldehyde (R^3)	Conditions[a]	Yield of **268** (%)[b]	dr[c]
1	Et, Me	C_6H_5	A	89	>20:1
2	Et, Me	*p*-MeO–C_6H_4	B	70	19:1
3	Et, Me	*p*-MeO–C_6H_4	C	55	20:1
4	Et, Me	*p*-NO_2–C_6H_4	B	81	>20:1
5	Bu, Me	*p*-NO_2–C_6H_4	B	76	>20:1
6	Me, Bu	*p*-NO_2–C_6H_4	D	67	>20:1
7	Et, Me	C_9H_{19}	A	68	18:1
8	H, Me	C_6H_5	B	60	>20:1
9	Me, *s*Bu	*p*-NO_2–C_6H_4	A	26	15:1[d]
10	Me, *i*Bu	*p*-MeO–C_6H_4	C	65	>20:1
11	Me, allyl	*p*-MeO–C_6H_4	C	48	[3,3] rear
12	$POCH_2$, MeP=*t*-$BuPh_2Si$	*p*-NO_2–C_6H_4	B	75	>20:1

Methods A: toluene, rt, >12 d; B: toluene, 80°C, 16–120 h; C: toluene, 110°C, 16–24 h; D: CH_2Cl_2, 40°C, 48 h.
[a] Reaction scale: 1 mmol.
[b] Unoptimized yields.
[c] Measured by HPLC or ^{1}H NMR.
[d] 1:1 Mixture of epimers at the *s*-butyl side chain center.

boronate esters **266** generated as pure isomers (Scheme 39; HMPA used as an additive is essential for a good *cis*-selectivity).[65]

The allylboration reaction with **266** and various aldehydes results in the diastereoselective formation of α-exomethylene γ-lactones **268** possessing stereogenic quaternary carbon centers (Table 28). The geometry of the isomeric allylboronate esters **266** was transferred to the corresponding lactones **268** without the lost of stereochemical information (entries 5 and 6).

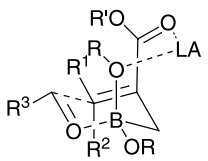
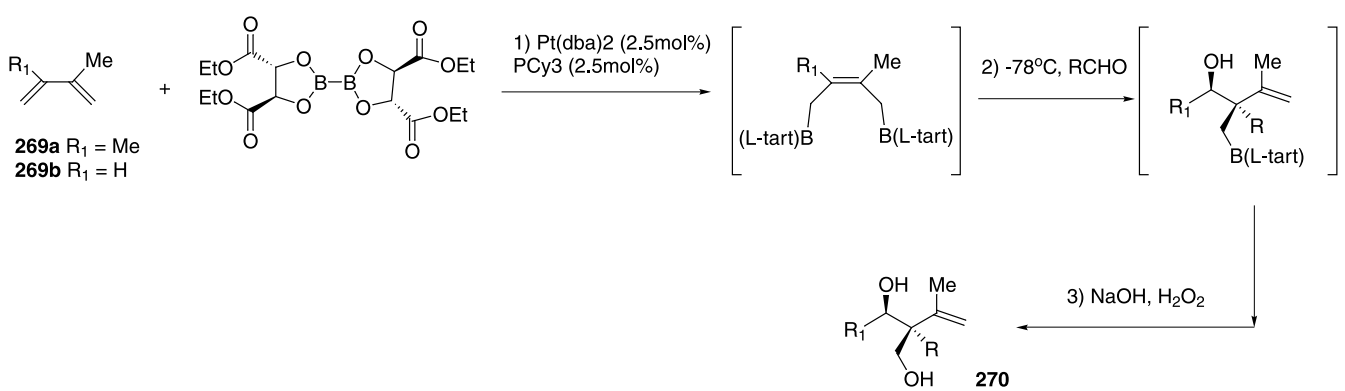


Figure 21.

Their approach was further improved by the introduction of a Lewis acid as a catalyst to enhance the reaction rate.[66] A large rate increase was noticed (6–24 h vs. 12 days) as well as an improvement in the reactivity towards otherwise non-reactive aldehydes such as cyclohexanecarboxaldehyde. Among the tested Lewis acids, $Cu(OTf)_2$ and $Sc(OTf)_3$ were the most effective in dichloromethane, whereas $Yb(OTf)_3$ was found to be efficient in THF and toluene.

Hall et al. proposed that the complexation of the metal on the carboxyester and one of the boronate oxygens could increase the acidity of boron, thereby strengthening its bond with the aldehyde moiety (Fig. 21).

Another interesting example of an asymmetric allylboronation reaction generating a quaternary carbon center was reported by Morken and Morgan.[67] They have developed a tandem platinum catalyzed diboronation/allylation procedure which provides an access to nonracemic functionalized 1,3-diols (Scheme 40). (*Z*)-selective 1,4-addition

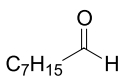
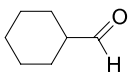
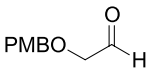
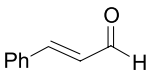
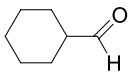
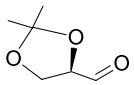
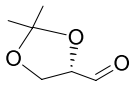


269a R_1 = Me
269b R_1 = H

270

Scheme 40.

Table 29. Asymmetric allylboronation of various aldehyde

Entry	R_1	RCHO	Yield % of **270**[a]	ee (%)
1	Me		68	70
2	Me		72	74
3	Me		58	66
4	Me		59	40
5	Me		65	33
6	H		65	74[b]
7	Me	 ***(R)***	71	[c]
8	Me	 ***(S)***	66	[d]

[a] Step 1: 1 equiv. of diene, 1 equiv. of diboron tartrate, benzene, rt, 12 h. Step 2: Add toluene, 4 Å mol. sieves, 1 equiv. of aldehyde, −78°C, 3 h. Step 3: 50°C, 3 h.
[b] Same procedure except that 5% $(PPh_3)_2Pt$(ethylene) was used for 24 h at 80°C in step 1.
[c] >95% of stereoisomer purity.
[d] 1:1 Mixture of stereoisomers.

of commercially available bis(diethyl-L-tartrateglycolacto)-diboron across 1,3-dienes **269a-b** catalyzed by $Pt(dba)_2$ in the presence of PCy_3 in benzene, resulted in a formation of bis-boronates. After an oxidative workup, the desired 1,3-diols **270** containing a quaternary center were obtained in good yields and enantioselectivities ranging from 33 to 74% depending on the nature of the aldehyde (Table 29). The enantioselectivity dropped substantially when aromatic and α,β-unsaturated aldehydes were employed (entries 4 and 5).

In the case of enantiomerically pure aldehydes (entries 7 and 8), bis-boronates show matched and mismatched stereoselection. In all cases, the allylboration reaction led to the exclusive formation of the *syn*-product (>19:1 *syn/anti*).

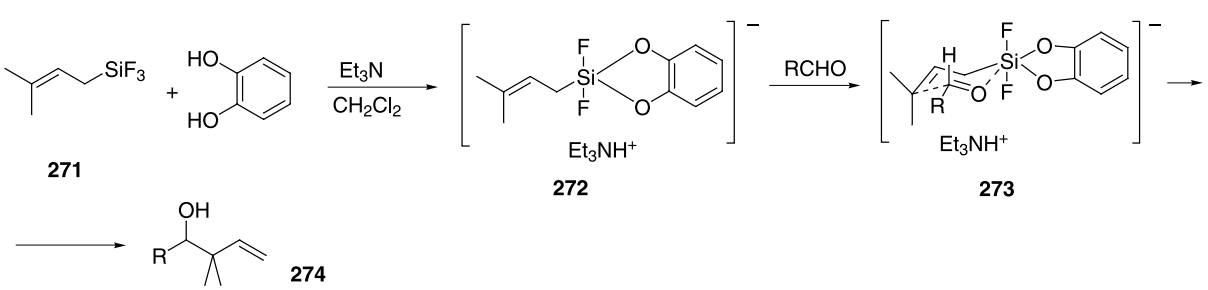
6.2. Allylsilanes

As opposed to allylboration, the reactions of allylic trichlorosilanes with aldehydes are known to proceed through an open transition state, making the diastereoselectivity more difficult to control.[68] Lewis acids are normally required to activate the carbonyl group to promote these reactions. In the majority of examples reported in the literature, chiral Lewis acids were used to induce the enantioselectivity.[69] However, this approach is less applicable in the case of γ- substituted allylic species. Lower selectivities were observed in most cases reflecting an open-transition state.

To address this problem, the conversion of an open-transition state to a closed one was envisaged. Over the past 20 years, the addition of allylic trichlorosilanes to aldehydes catalyzed by Lewis bases has been studied. The idea behind the use of Lewis bases is founded on the following concept. If a silicon atom carries highly electronegative and sterically compact ligands such as fluorine or chlorine, the coordination number of the silicon can expand from 4 to 5 or even to 6 giving negatively charged penta- or hexacoordinated compounds. Even though the silyl group formally becomes electron rich, the negative charge is delocalized into the electronegative ligands therefore making the silicon atom rather electron deficient. As a result, the silicon atom acquires a significant Lewis acid character and becomes capable of complexing with a carbonyl group thereby creating an opportunity for a cyclic transition state.

Sakurai et al. have contributed to the development of highly regiospecific and stereoselective allylations of aldehydes with allyltrifluoro and allyltrichlorosilanes activated in the presence of triethylamine. Catechol (Scheme 41), proline, 3-amino-propan-1ol and even methanol have been used as Lewis bases to accelerate these reactions.[70]

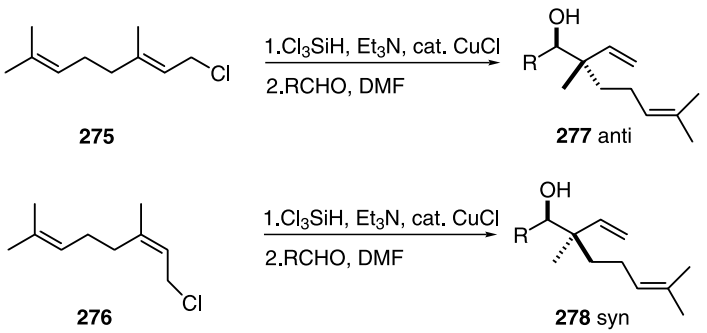
The allylation reaction involves the formation of a pentacoordinated silicate intermediate **272**. Due to its increased Lewis acidity, **272** can bind to the carbonyl of the aldehyde giving rise to the corresponding hexacoordinate complex **273** which decomposes to provide the homoallylic alcohol **274**. The enhanced nucleophilicity of

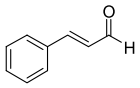
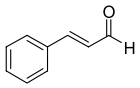


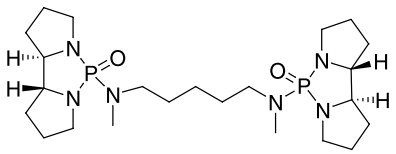
271 **272** **273** **274**

Scheme 41.

Table 30. Synthesis of homoallylic alcohols with quaternary centers from allyl halides



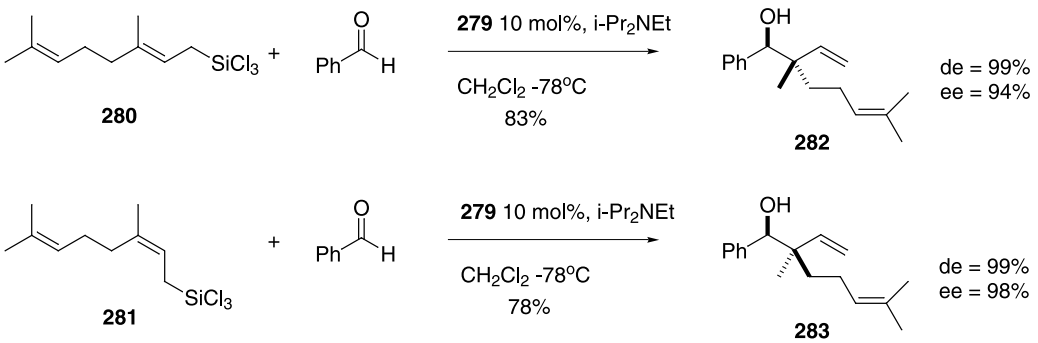
Entry	Allylic halide	Aldehyde	Product ratio, *syn*/*anti*	Yield (%)
1	**275**	PhCHO	<1/99	82
2		$Ph(CH_2)_2CHO$	<1/99	91
3			<1/99	97
4	**276**	PhCHO	>99/1	92
5		$Ph(CH_2)_2CHO$	>99/1	87
6			>99/1	93



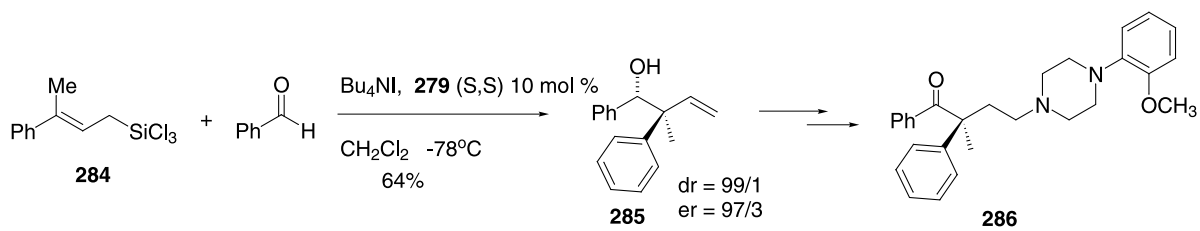
279

Figure 22.

the γ-carbon (due to electron donation from the hypervalent silicon atom into the allyl π-system) accounts for the high regioselectivity of the allylation process. This is believed to proceed via a six-membered chair-like transition state. Interestingly, this reaction can occur even in the presence of water and moreover, the reagent system can discriminate linear alkanals from α-branched alkanals. It was noticed that discrimination between aromatic and aliphatic aldehydes is



Scheme 42.



Scheme 43. Application of a chiral Lewis base catalyst in a total synthesis of serotonin antagonist LY426965 (**286**).

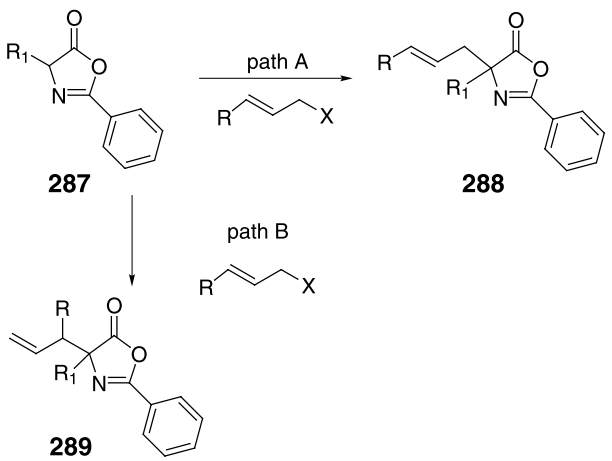


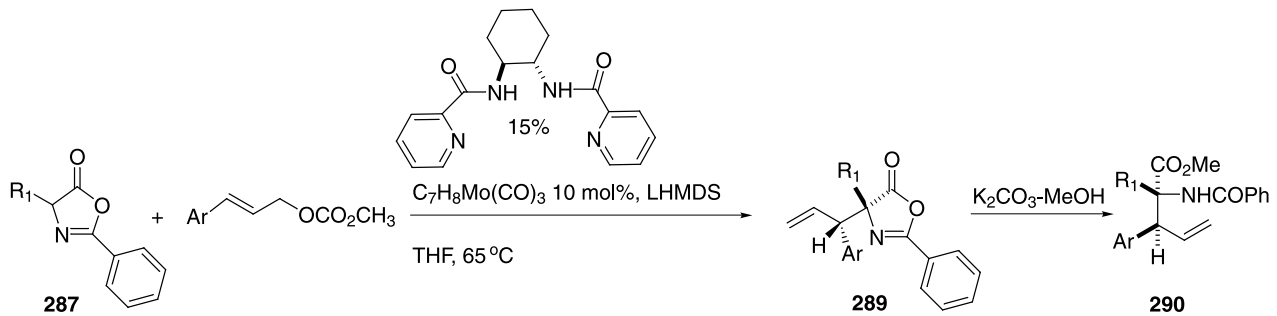
Figure 23.

also possible. This depends on the substituents on the pentacoordinate silicate intermediates.

Kobayashi has shown that DMF as a solvent also promotes the addition of allyl trichlorosilanes with excellent diastereoselectivity.[71a] The hypothesis that DMF coordinates to the silicon forming a hypervalent silicate was supported by ^{29}Si NMR studies. Kobayashi developed a protocol to generate in situ allylsilanes from the allyl chlorides **275** and **276**, which then react smoothly with aldehydes to form exclusively *anti* or *syn* homoallylic alcohols **277** and **278** (Table 30).[67b]

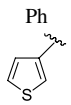
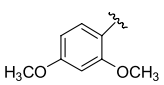
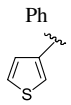
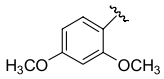
Asymmetric allylation employing various chiral Lewis bases,[72] such as phosphoramides, formamides, *N*-oxides, ureas and diamines have been investigated by several groups.[73] In 2001, Denmark et al. introduced 2,2′-bis-pyrrolidine-based bisphosphoramide **279** (Fig. 22) as a catalyst for the enantioselective formation of quaternary centers.[74] The new catalyst promotes a diastereo- and enantioselective addition of γ-disubstituted trichloroallylsilanes **280** and **281** to unsaturated aldehydes (Scheme 42).

They proposed that the reaction proceeds through a closed hexacoordinate cationic siliconate transition state.[75] This



Scheme 44.

Table 31. Mo-catalyzed formation of 1,1-disubstituted azalactones **289**

Entry	Ar	R_1	Time (h)	Isolated yield (%)		ee (%)	dr
				Branched (path B)	Linear (path A)		
1		CH_3-	3	92	0	99	97:3
2		CH_3-	3	84	0	91	96:4
3		CH_3-	4	84	4	92	>98:2
4		CH_3-	3	89	0	90	>98:2
5		$PhCH_2-$	3	92	0	67	>98:2
6		$PhCH_2-$	3	86	0	94	>98:2
7		$PhCH_2-$	3	90	0	94	>98:2
8	Ph	$CH_3S(CH_2)_2-$	4	86	6	92	>98:2
9	Ph	$(CH_3)CHCH_2-$	4	85	5	96	>98:2
10	Ph	CH_2CHCH_2-	3	82	6	97	>98:2
11	Ph	$(CH_3)_2CH-$	6	76	11	96	>98:2

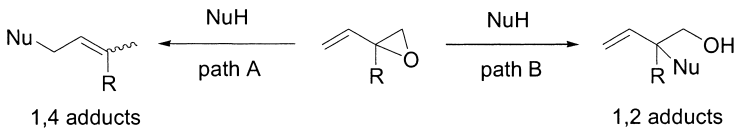
method was further applied to the synthesis of the serotonin antagonist LY426965 (**286**) (Scheme 43).[76]

7. Metal catalyzed carbon–carbon formation

7.1. sp^3–sp^3 Carbon–carbon bond

In 1998, Trost and co-workers reported that palladium catalyzed asymmetric allylic alkylation reaction with azalactones **287** provided an efficient route to quaternary amino acids (path A). The nucleophilic attack occurs from the least substituted terminus of the aryl-substituted allyl system (Fig. 23).[77]

The same group has recently disclosed that Mo catalysts can be used to generate chiral quaternary amino acids via path B[78] in a one-pot process (Scheme 44).[79] The reaction



Scheme 45.

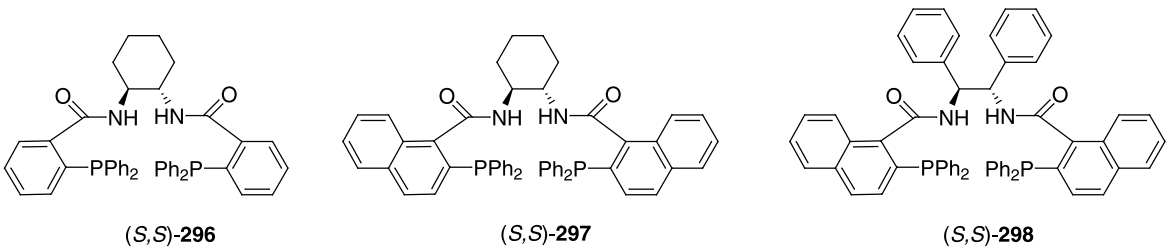
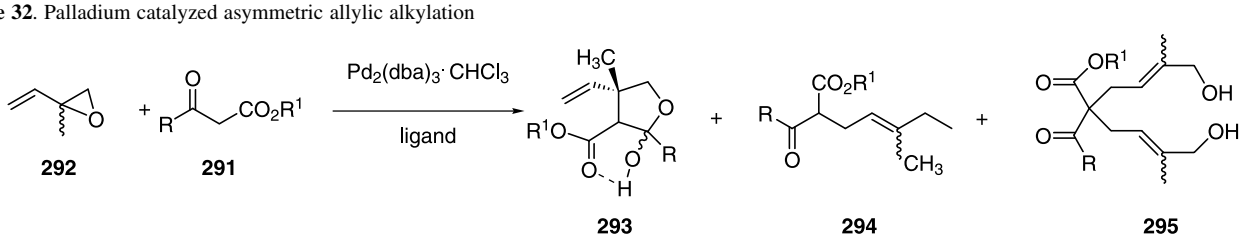
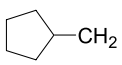
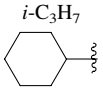


Figure 24.

Table 32. Palladium catalyzed asymmetric allylic alkylation



Entry	Ester		Method [a]	Time (h)	Ratio[b] **293/293/294**	Yield (%) **293**	ee (%)[c]
	R	R^1					
1	CH_3	C_2H_5	A	1.2	79:17:4	70	96
2	CH_3	n-C_4H_9	A	1	82:14:4	65	97
3	CH_3	t-C_4H_9	A	24	77:17:6	65	95
4	CH_3	$PhCH_2$	A	2.5	72:19:9	61	95
5	C_2H_5	C_2H_5	A	4	80:17:3[d]	71	96.5
6	$CH_2{=}CH(CH_2)_8$	C_2H_5	B	2.5	80:13:7[d]	71	95
7	$PhCH_2$	C_2H_5	A	2	n.d.	71	93.5
8		C_2H_5	B	2.5	80:13:7[d]	70	98
	i-C_3H_7	C_2H_5	B	2.3	81:17:2[d]	74	97
9							
10		C_2H_5	B	11	90:10:–	74	99
11		C_2H_5	B	11	90:10:–	80	97
12	Ph	C_2H_5	A	1.25	77:23[d]	59	98.5[e]
13	p-O_2N–C_6H_4	C_2H_5	B	<5 min	n.d.	57	95[e]

All reactions conducted on 0.5 mmol scale in 5 mL of solvent using 1 mol% $Pd_2dba_3{\cdot}CHCl_3$ and 3 mol% ligand.
[a] Method A: (*S*,*S*)-**298** and 1 mol% TBAT in PhH at 40°C. Method B: (*S*,*S*)-**296** in CH_2Cl_2 at rt (no additive).
[b] Determined by ^1H NMR on crude mixture unless indicated otherwise.
[c] Determined after dehydration of the initial adduct.
[d] Determined after treatment with TBAF.

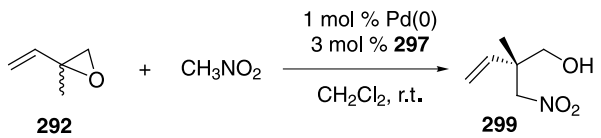
conditions have shown a high tolerance to a number of substituents Ar and R_1. In all cases, high enantio- and diastereoselectivity were observed (Table 31).

Interestingly, the formation of linear products (path A) was detected in 6–11% yields when alkyl groups longer than methyl or branched alkyl substituents were used (entries 8–11).

Metal-catalyzed addition of pronucleophiles to vinyl epoxides can follow two pathways (Scheme 45), from which 1,2 type addition route (path B) leads to formation of adducts bearing quaternary carbon centers, if a carbon-centered pronucleophile is employed.

While heteroatom pronucleophiles were previously reported to follow a 1,2-addition pathway due to their ability to make hydrogen bonds or to coordinate to oxygen of an epoxide, thus delivering the nucleophile to the adjacent carbon, carbon-centered pronucleophiles would be less likely to participate in this type of bonding or coordination.[80] Therefore, these nucleophiles would be expected to discriminate less between path A and path B. Trost and Jiang have investigated an addition of β-ketoesters **291** to isoprene monoepoxide **292** catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence chiral ligands (Fig. 24 and Table 32).

They have found that, if properly selected, a chiral ligand can control the regioselectivity as well as the enantioselectivity, thus favouring the formation of the 1,2-adduct. The use of TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate) as an additive also improved the regioselectivity. The authors found that with enantiopure ligand and racemic epoxide, two diastereomeric π-allyl palladium complexes



292 **299**

Scheme 46.

Table 33. Double cyclization reaction between substituted cyclohexadiene–$Fe(CO)_3$ complex **303** and conjugated diene chain

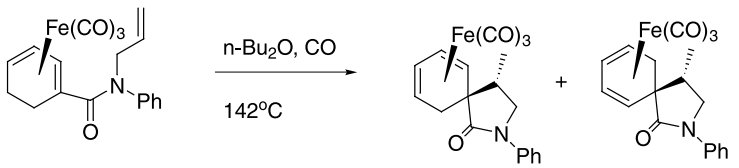
Entry	R_1	R_2	Time (h)	Concentration (M)	Yield (%)
1	H	Me	10	0.02	75
2	OMe	Me	24	0.004	54
3	H	CO_2Me	12	0.004	51
4	OCH_3	CO_2Me	24	0.004	34

were formed. One favours an attack of the nucleophile from the least substituted allyl terminus, resulting in the formation of 1,4-adduct, while the other diastereomer gives rise to the 1,2-adduct. Enhancing the rate of interconversion of the diastereomeric complexes increases the regioselectivity of the reaction.

A number of β-ketoesters were tested. In all cases, the compounds with a quaternary carbon center (1,2-adduct) were formed as major products in a good ratio and enantioselectivities ranging from 93.5 to 99%. The size of R^1 did not seem to affect the regioselectivity, whereas increasing of the size of R did improve it (entries 10 and 11). The method is not restricted to the use of β-ketoesters as pronucleophiles. For instance, nitromethane reacted with the epoxide **292** to give a corresponding 1,2-adduct in 51% yield and 97% ee (Scheme 46).

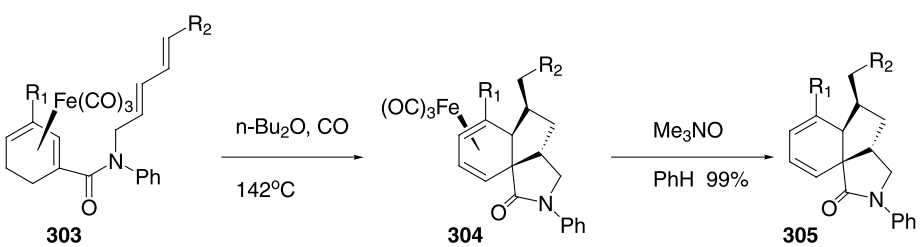
In 1989, Pearson reported the formation of spirocycles via thermal intramolecular coupling of a cyclohexadiene-$Fe(CO)_3$ complex **300** with a terminal olefin (Scheme 47).[81] A 1:1 mixture of epimers **301** and **302** was formed resulting from thermal rearrangement of the diene–$Fe(CO)_3$ complex.

Recently, a double cyclization reaction between substituted cyclohexadiene–$Fe(CO)_3$ complex **303** and the conjugated diene chain has been published by the same group (Scheme 48).[82] This new process creates angular fused tricyclic products **304** containing four contiguous asymmetric centers that include a quaternary carbon center. This



300 **301** **302**

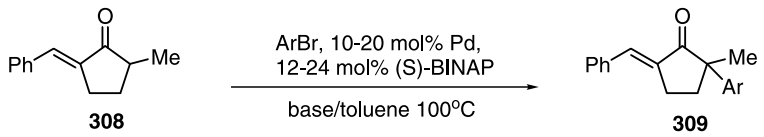
Scheme 47.



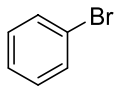
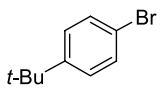
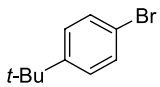
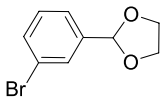
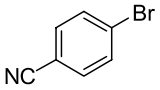
303 **304** **305**

Scheme 48.

Table 34. Asymmetric palladium catalyzed the arylation of tetralone derivatives

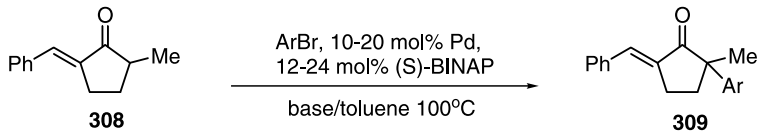


308 **309**

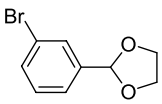
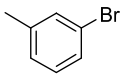
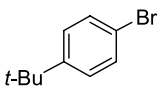
Entry	R	ArBr	ee (%)	Yield (%)
1	H		73	66
2	H		88	73
3	MeO		77	56
4	H		84	74
5	H		61	40[a]

[a] The reaction was carried out at 70°C using 5 equiv. of halide and 5 equiv. of NaO*t*-Bu

Table 35. Asymmetric palladium catalyzed arylation of cyclopentanone derivatives



308 **309**

ArBr	Conditions	Yield (%)	ee (%)
	NaHMDS, 10 mol% $Pd_2(dba)_3$/BINAP	86	95
	NaO*t*Bu, 20 mol% $Pd(OAc)_2$/BINAP	80	94
	NaO*t*Bu, 20 mol% $Pd(OAc)_2$/BINAP	75	98

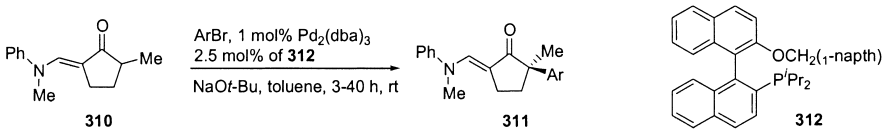
metal-catalyzed process involving two consecutive ene reactions is highly stereoselective (Table 33). In each example, only one isomer was isolated.

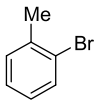
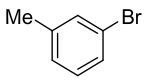
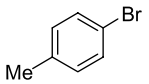
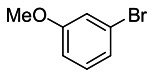
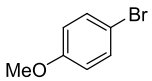
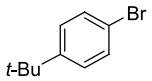
7.2. sp^2–sp^3 Carbon–carbon bond

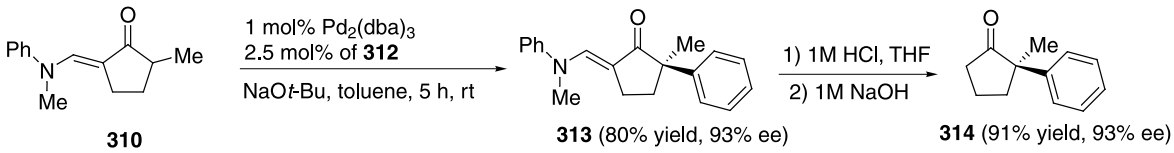
Buchwald and co-workers reported an asymmetric palladium catalyzed arylation of ketone[83] and lactone[84] enolates as a method to generate a quaternary carbon center in the α-position. The enolates of α-methyl substituted tetralones **306** react with various aryl bromides in the presence of a palladium/(*S*)–BINAP complex to afford enantiomerically enriched α-disubstituted tetralones **307** with enantioselectivities ranging from 61 to 88% (Table 34).[85] The enantioselectivity of the reaction was improved significantly when α′-blocked α-methyl cylopentanone **308** was used as starting material (Table 35).

One of the shortcomings of the reaction was the high catalyst loading and elevated temperature. Also, the benzylidene α′-blocking group was impossible to remove from the product. In order to optimize the conditions, new catalytic system has been introduced.[86] The benzylidene α′-blocking group was replaced by a 2-methyl-5-*N*-methyl-anilinomethylene moiety affording ketone **310**. Arylation of the latter, catalyzed by the (*S*)-BINAP/Pd

Table 36. Asymmetric palladium catalyzed arylation of cyclopentanone derivatives



Entry	ArBr	Yield (%)	ee (%)
1		43	22
2		85	94
3		84	93
4		80	89
5		80	94
6		84	93

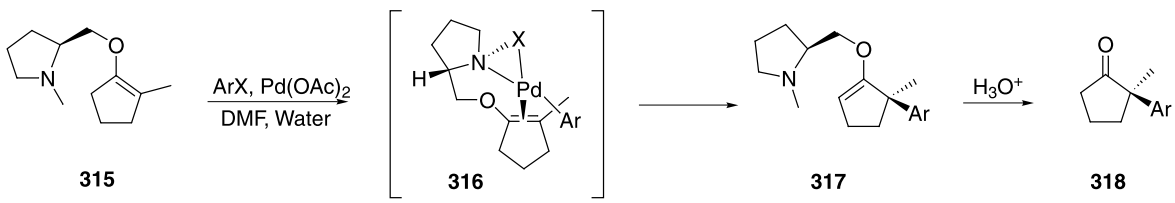


Scheme 49.

complex, occurs to give **311** with ee's varying from 43 to 89%. A series of ligands was evaluated to improve the enantioselectivity. Ligand **312** was found to be the most efficient in catalyzing the arylation of **310** raising the enantiomeric excess up to 94% (Table 36).

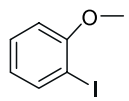
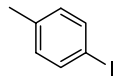
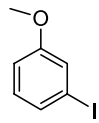
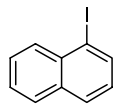
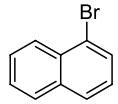
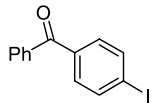
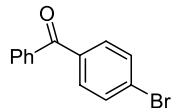
The reactions were carried out at room temperature with catalyst and ligand loading of 1 and 2.5 mol% respectively. The blocking group was successfully removed by acid hydrolysis followed by a retro-Mannich reaction under basic conditions to provide ketone **314** (Scheme 49).

The enantioselective Heck reaction is a powerful method for the construction of new C–C bonds.[87] Its utility in the preparation of several natural product frameworks bearing quaternary carbons has been reported on several occasions. A novel asymmetric Heck arylation generating a quaternary stereocenter was reported by Hallberg and co-workers.[88] The method is based upon a palladium-coordinating chiral auxiliary that directs the oxidative aryl addition to one face of the vinyl ether **315** forming cyclopentanone **318** with an α-quaternary carbon center (Scheme 50). Various 2,2-di-substituted cyclopentanones **318** were produced using different aryl iodides and bromides in 45 to 78% yield with ee's ranging from 90 to 98% (Table 37). The origin of the high stereoselectivity could be rationalized by the formation of an *N*-chelated π-complex (e.g. **316**).



Scheme 50.

Table 37. Asymmetric controlled-Heck arylation

Entry	Aryl halide	Conditions[a]	Yield (%)	ee (%)
1		70°C, 24 h	67	98
2		70°C, 18 h	54	93
3		80°C, 30 h	50	94
4		70°C, 68 h	61	94
5		70°C, 18 h	68	93
6		80°C, 48 h	45	90
7		100°C, 48 h	49	91
8		80°C, 24 h	47	97
9		100°C, 24 h	78	94

[a] All components (1.3 equiv. of **315**, 1 equiv. of ArX, 3% of Pd catalyst) were added to aqueous DMF, the vessel was sealed under air and heated for 18–68 h.

Yoshida and Ihara described a stereoselective synthesis of α-disubstituted cyclopentanones **320** via a palladium catalyzed rearrangement of allenylcyclobutanol **311** in the presence of aryl halides.[89] The results are summarized in Table 38. It was shown that heating was required to enhance the diastereoselectivity. The reaction tolerated electron withdrawing (entries 5 and 6) as well as electron donating (entries 2–4) substituents on the aryl group. The use of aryl bromides (entries 7 and 8) resulted in longer reaction times and poorer yields. In the case of α-bromostyrene (entry 9), compound **314** was isolated. Allenylcyclobutanols **323**-**325** reacted under the same conditions to give the respective product as single diastereomers (Table 39).

8. Miscellaneous

Fu and Mermerian have recently reported an enantioselective synthesis of quaternary centers via intermolecular C-acylation of silyl ketene acetals with acetic anhydride catalyzed by iron complex (I).[90] A number of silyl ketene acetals **329** derived from lactones were successfully acylated in the presence of 5 mol% of the catalyst **330** at room temperature to give the expected lactones **331** in good yield and high enantiomeric excess (Table 40). In the absence of the catalyst no reaction was observed after 60 h at room temperature. It was shown that the catalyst could be recovered in almost quantitative yield. The reaction tolerated a wide range of substituents (R) varying in their electronic and steric properties, including heteroaromatic groups (entries 5 and 6).

This new method is not limited to cyclic silyl acetals. The acylation of silyl acetal **332** (2:1 mixture of *E* and *Z* isomers) with acetic anhydride afforded the desired β-ketoester **333** in 82% yield and 91% ee (Scheme 51). Interestingly, a mixture of isomers of **332** has been efficiently converted into the same enantiomer.

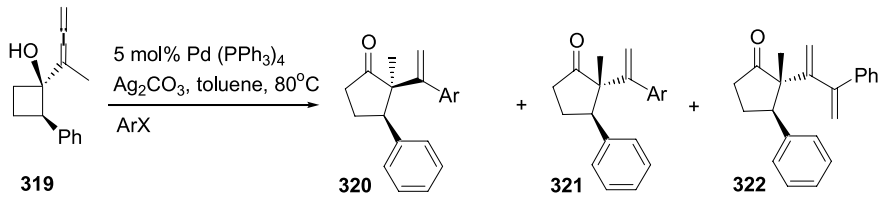
A plausible reaction pathway is outlined in Scheme 52. The authors have proposed that the catalyst initially reacts with acetic anhydride, resulting into the formation of an acylpyridinium ion **334**, which should be more reactive as an acylating agent. It further complexes with the Lewis acidic silicon of the acetal, thus forming an enolate. The activated species of the new ion pair then couple to yield **331** possessing a quaternary carbon center and regenerate the catalyst **330**.

Garcia-Garibay and co-workers have reported an interesting strategy toward enantiospecific synthesis of vicinal tertiary and quaternary carbon centers via photodecarbonylation of α,α′-substituted ketone in solid state (Scheme 53).[91] Enantiopure and racemic samples of (2*R*,4*S*)-2-carbomethoxy-4-cyano-2,4-diphenyl-3-butanone **335** were subjected to photo-irradiation in solution and its two enantiomorphous crystal forms. Solid state reaction occurred with retention of configuration of the original stereocenters. The desired compound containing adjacent quaternary and tertiary centers was synthesized in enantiomerically pure and racemic forms. No loss of enantiomeric purity was observed when the enantiomerically pure ketone **335** was used. A slight loss in diastereomeric excess (de>95%) was attributed to the small percentage of inversion at either one of the two stereocenters, probably due to the reaction occurring at the crystal surface or at the defect sites of the crystal. The mechanism is proposed as follows; upon a photo irradiation a α-cleavage assisted by radical stabilizing substituents occurs, thus generating CO and a radical pair configurationally trapped in the crystal lattice. Then the radicals recombine together to provide the desired product **336**.

Notably, photo-irradiation of enantiomerically pure and racemic ketone in solution resulted into a complex mixture of products.

Shibasaki and co-workers used a catalytic enantioselective Reissert type reaction to construct chiral quaternary centers.[92] Series of 1-substituted isoquinolines were subjected to a reaction with TMSCN, vinyl chloroformate and 2.5 mol% of **339** as a catalyst to afford **338** in good chemical yields and enantiomeric excess ranging from 73 to 95% (Table 41). The reaction turned out to be not very sensitive

Table 38. Palladium catalyzed rearrangement of allenylcyclobutanol **319**



319 **320** **321** **322**

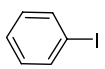
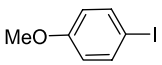
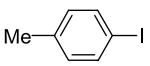
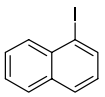
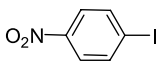
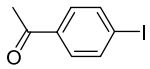
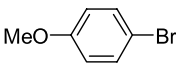
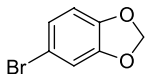
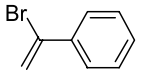
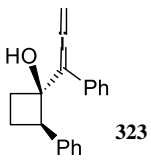
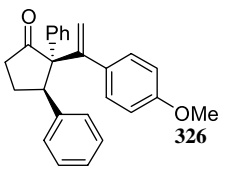
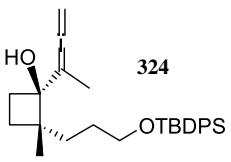
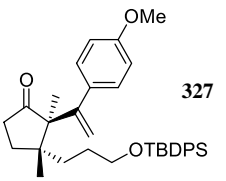
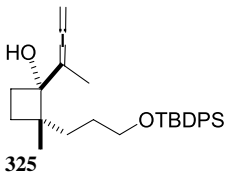
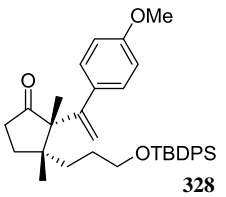
Entry	ArX	Time (h)	**320/321** ratio	Yield (%)
1		3	**320** only	80
2		1.5	**320** only	72
3		1	94:6	89
4		3	84:16	79
5		1.5	**320** only	66
6		4	**320** only	77
7		30	**320** only	37 (52)
8		24	84:16	26
9		30	**322** only	26

Table 39. Palladium catalyzed rearrangement of allenylcyclobutanol **323-325**

Entry	Allenylcyclobutanol	Product	Yield (%)
1	 **323**	 **326**	20
2	 **324**	 **327**	81
3	 **325**	 **328**	91

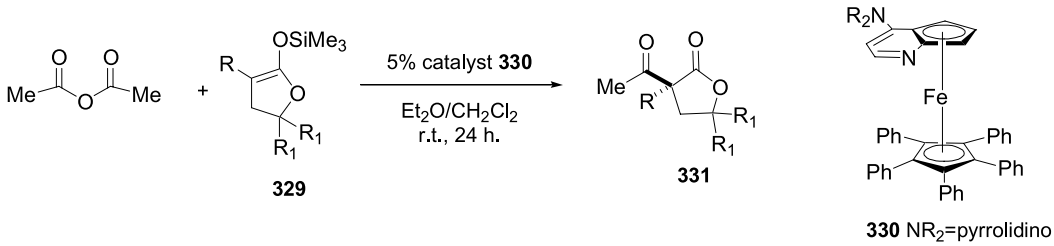
In all cases 5 mol% $Pd(PPh_3)_4$ and Ag_2CO_3 in toluene at 80°C.

to the size of the substituent at the 1-position of quinolines. In some cases, the catalyst loading was reduced to 1 mol% (entries 8 and 10). The mechanistic model depicted in Figure 25 suggests that in the course of the reaction, the acyl isoquinilinium gets activated by the Lewis acid part of the catalyst and the TMSCN by the Lewis base part of **339**.

Van Vranken and co-worker have employed the Moore ring contraction of azidoquinones to install a quaternary carbon center in the course of the total synthesis of (±)-Madindolines A (**17**) and B (**18**).[93] Quinone **340** was treated with sodium azide to produce the corresponding azidoquinone **341** (Scheme 54). The latter upon heating at 100°C gave 1,3-cyclopentanone **342** through the Moore ring contraction reaction.

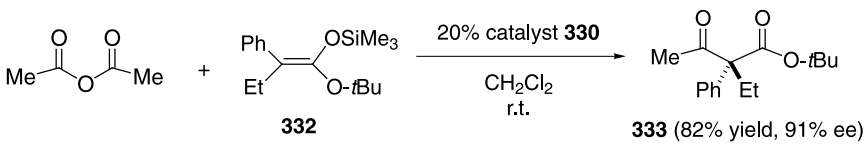
The catalytic asymmetric ring-closing metathesis (ARCM) constitutes a powerful method for the enantioselective synthesis of five and six-membered carbo[94] and heterocycles.[95] In 2002, Hoveyda and co-workers reported an efficient route to prepare optically enriched seven-membered siloxanes ethers employing chiral Mo-based catalysts (Table 42).[96] In all cases, the ARCM of trienes

Table 40. *C*-Acylation of silyl ketene acetals catalyzed by iron complex (I)

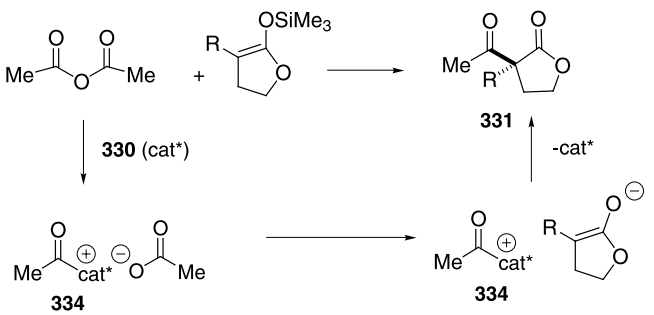


Entry	R	R_1	Yield (%)[a]	ee (%)
1	Ph	Me	80	90
2	4-(MeO)C_6H_4	Me	78	95
3	4-(F_3C)C_6H_4	H	84	90
4	*o*-Tolyl	Me	89	95
5	1-Napthyl	Me	82	99
6	2-Thienyl	Me	84	76
7	3-Thienyl	Me	86	87
8	3-Thienyl	H	73	80
9	3-(*N*-methylindolyl)	Me	92	94

[a] Average of two runs.



Scheme 51.

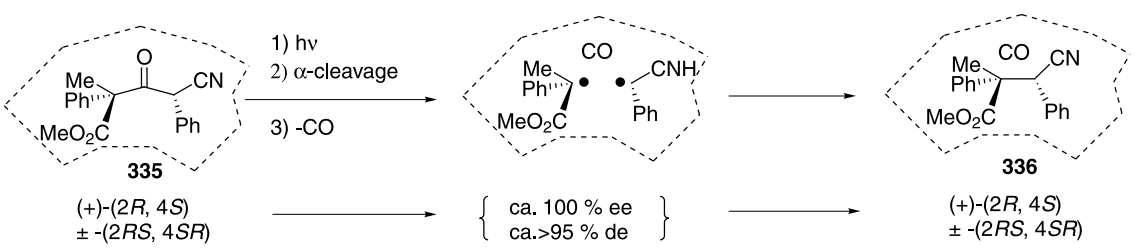


Scheme 52.

343a-f produced the corresponding seven-membered ring ether **344a-f** in 87 to 98% isolated yields and ee ranging from 47 to 94%. Interestingly, the ARCM can be performed in large scale without the use of solvents thereby providing a practical and cost-effective method for the synthesis of medium-ring heterocycle (Scheme 55).[97]

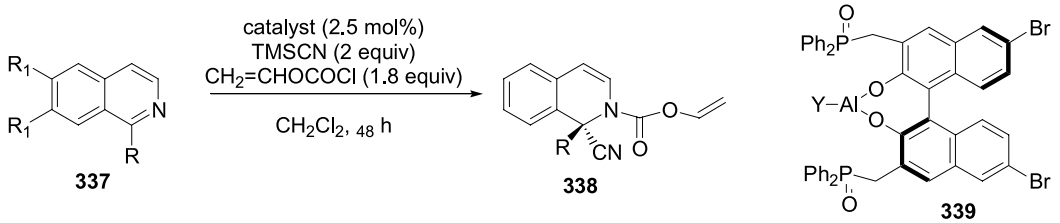
Zr-catalyzed cyclization of various trisubstituted 1,6-dienes provide a novel synthetic route to the construction of cyclopentanes bearing a quaternary carbon center.[98] Treatment of dienes **347**-**349** with 10 mol% of zirconocene dichloride and 5 equiv. of *n*-BuMgCl in THF at 70°C afforded the corresponding 3-vinylcyclopentanes **350**, **352** and **354** along with carbonyl adducts **351** and **353** (Table 43). In most cases, the reaction proves to be highly diastereoselective. High enantioselectivity was achieved when 10 mol% of (*R*)-(ebthi)Zr-binol **360** was used as catalyst (Fig. 26). The unusual formation of aldehyde **351** and ketone **353** can be rationalized by the mechanism depicted in Scheme 56.

Hoveyda and co-workers propose, in one hand, that the cleavage of C–Zr bond in **355** would lead to the formation of the bis-metallic intermediate **357** (pathway 1). The latter would undergo a Zr-alkoxide elimination to give **358** which, after quenching with water, affords the desired compound **350**. On the other hand, the metallocyclopentane **355** could



Scheme 53.

Table 41. Catalytic enantioselective Reissert type reaction



Entry	R_1	R	Y	Temperature (°C)	Yield (%)[a]	ee (%)[b]
1	H	Me	OTf	−60	88	89
2	H	Et	OTf	−60	98	88
3	H	$-CH_2Ph$	OTf	−60	95	92
4	H	$-CH_2OCH_3$	OTf	−60	84	73
5	H	$-CH{=}CH_2$	OTf	−60	80	84
6	H	(*E*)-$CH{=}CHCH_3$	OTf	−60	88	87
7	H	Ph	OTf	−40	95	95
8[c]	H	Ph	OTf	−50	88	95
9	H	*o*-Br−C_6H_4	OTf	−40	62	95
10[c,d]	H	*o*-Br−C_6H_4	OTf	−40	59	93
11	PhCOO	Me	Cl	−60	94	94

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] 1 mol% catalyst was used.
[d] The reaction time was 72 h.

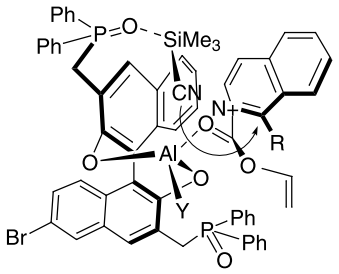
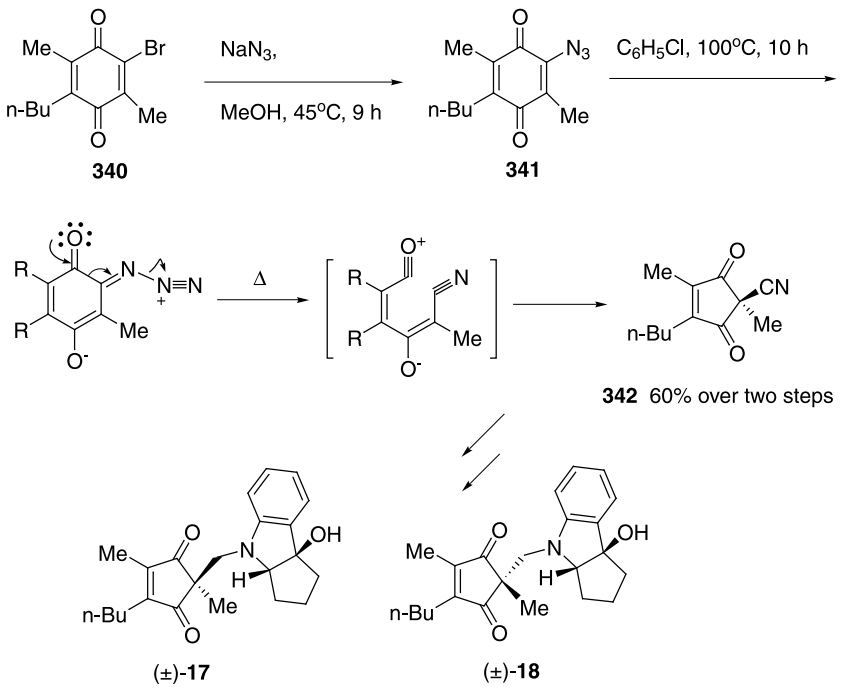
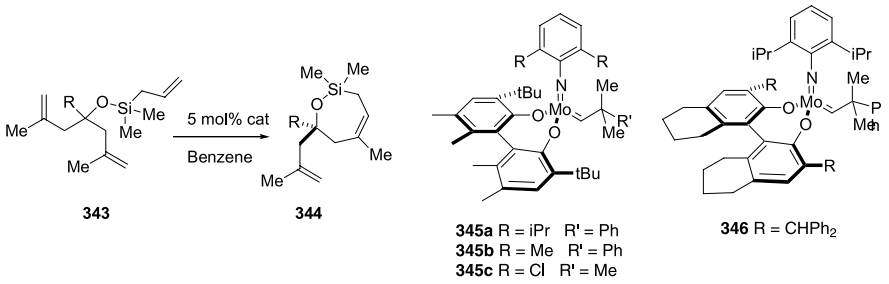


Figure 25.

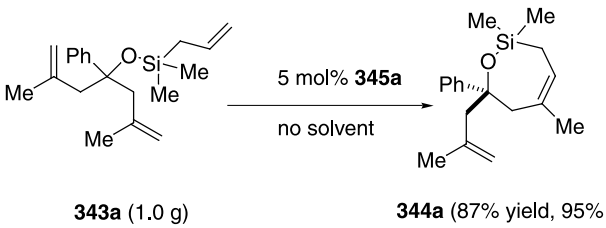


Scheme 54.

Table 42. Mo-catalyzed asymmetric construction of seven-membered ring siloxanes

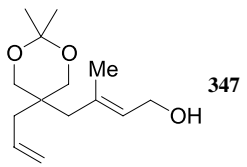
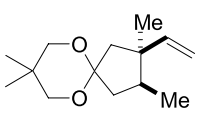
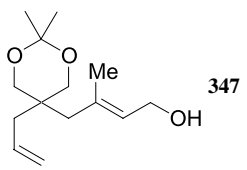
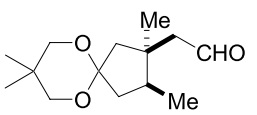
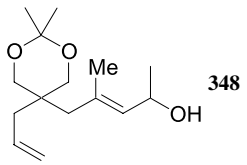
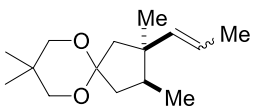
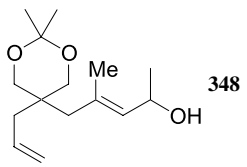
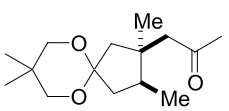
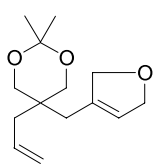
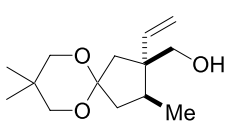


Entry	R	Catalyst	Yield (%)	ee (%)
1	Ph	**345a**	92	93
2	*p*-BrPh	**345c**	98	94
3	Cy	**345a**	91	83
4	*i*-Pr	**345a**	92	90
5	*n*-Bu	**345b**	87	66
6	Me	**346**	90	47



Scheme 55.

Table 43. Zr-Catalyzed intramolecular cyclization of 1,6-dienes

Entry	Substrate	Product	Yield (%)[a]	dr[a]	ee (%)[b]
1	 **347**	 **350**	35 (20)[b]	>25:1 (10:1)[b]	>98
2	 **347**	 **351**	60 (28)[b]	>25:1 (1:1)[b]	>98
3	 **348**	 **352**	65 (12)[b]	>25:1 (>25:1)[b]	58
4	 **348**	 **353**	20 (26)[b]	>25:1 (>25:1)[b]	>98
5	 **349**	 **354**	89 (81)[b]	4:1 (1:1)[b]	>98

[a] 10 mol% $ZrCp_2Cl_2$, 5 equiv. *n*-BuMgCl, THF, 70°C, 12 h.
[b] 10 mol% (*R*)-(ebthi)Zr-binol **360**, 5 equiv. *n*-BuMgCl, THF, 70°C, 12 h.

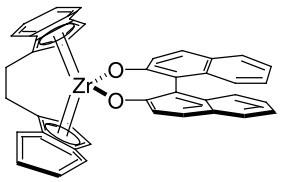


Figure 26.

be opened via pathway 2 to probide intermediate **356**. A Mg–Zr exchange would lead to **357** in which a hydride abstraction of the terminal dialkylzirconocene at C8 (formation of the methyl) and a β-hydride elimination (secondary dialkylzirconocene at C2) would generate enol **359**. The latter is quenched with water to produce the aldehyde **351**.

9. Summary

A large number of new methods and strategies for the asymmetric construction of quaternary stereocenters has been imagined and published in recent years. It follows from this review that the generation of quaternary carbon centers from chiral tetrasubstituted enolates is the most popular approach. Methods involving radical chemistry and catalytic transformations are still in their infancy. Metal-catalyzed approaches are now emerging. Despite the large repertoire of methods, the scope remains limited. Problems associated with the production of these reactions on large scale, reagent costs, ready access to chiral auxiliaries and versatility are noticed. Catalytic asymmetric reactions provide new options to create quaternary centers that are of great value in the construction of architecturally complex molecules.

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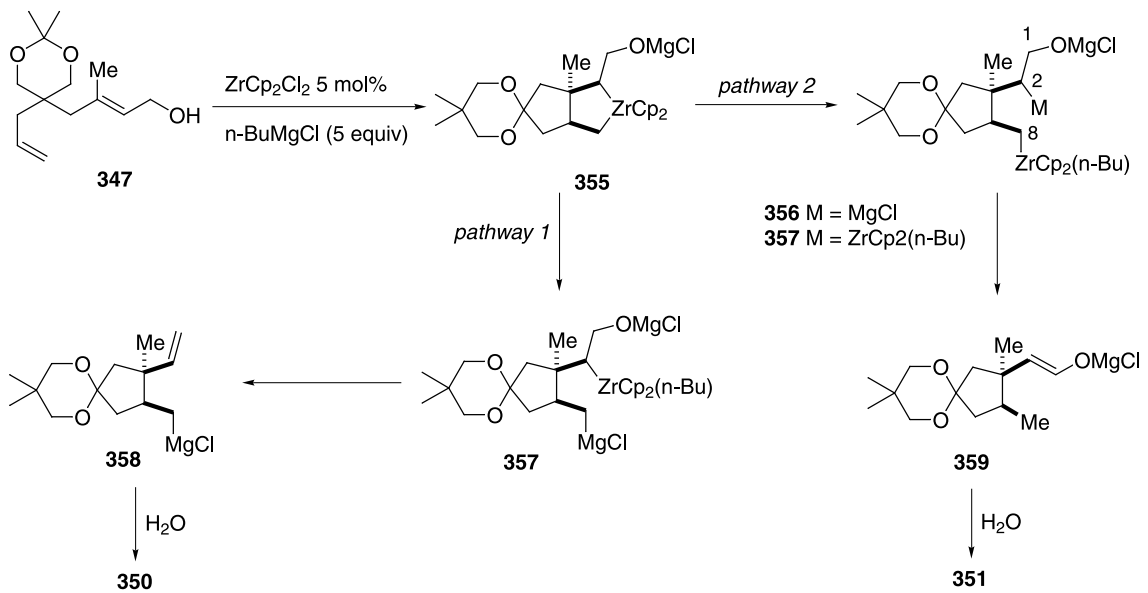

Scheme 56.

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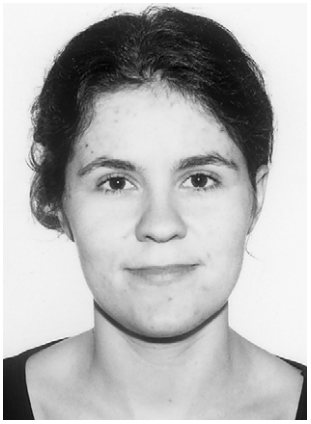
Biographical sketch



Irina V. Denissova was born in 1976 in Moscow Region, Russia and obtained her Diploma of Chemistry in 1998 at Moscow State University. She then worked for a year at Rhone-Poulenc Rorer (now Aventis) Representative Office in Moscow in the marketing department. In September 1999 she moved to Canada to pursue her PhD degree in organic chemistry under the supervision of Professor Louis Barriault at the University of Ottawa.

Louis Barriault was born in 1970, Armagh (Québec). In 1993, he obtained his BSc in chemistry from the University of Sherbrooke. He pursued his PhD at the same institution under the guidance of Professor Pierre Deslongchamps. After completing his doctorate in 1997, he joined the group of Professor Leo A. Paquette at the OSU as a FCAR postdoctoral fellow where he completed the total synthesis of (−)-polycarvernoside A. In May 1999, he accepted a position as Assistant Professor at the University of Ottawa where he has been promoted to Associate Professor (2003). Professor Barriault's research involves the development of novel strategies using tandem pericyclic reactions to construct complex bioactive natural products. Recently, Professor Barriault received the John Polanyi Award in Chemistry (2000), Ontario Innovation Trust Award (2000), Premier's Research Excellence Award (2002), Ottawa Life Science Michael Smith Award (2002) and the Boehringer Ingelheim Young Investigator Award (2002).