Synthetic Methods

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Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and their Applications in Organic Synthesis

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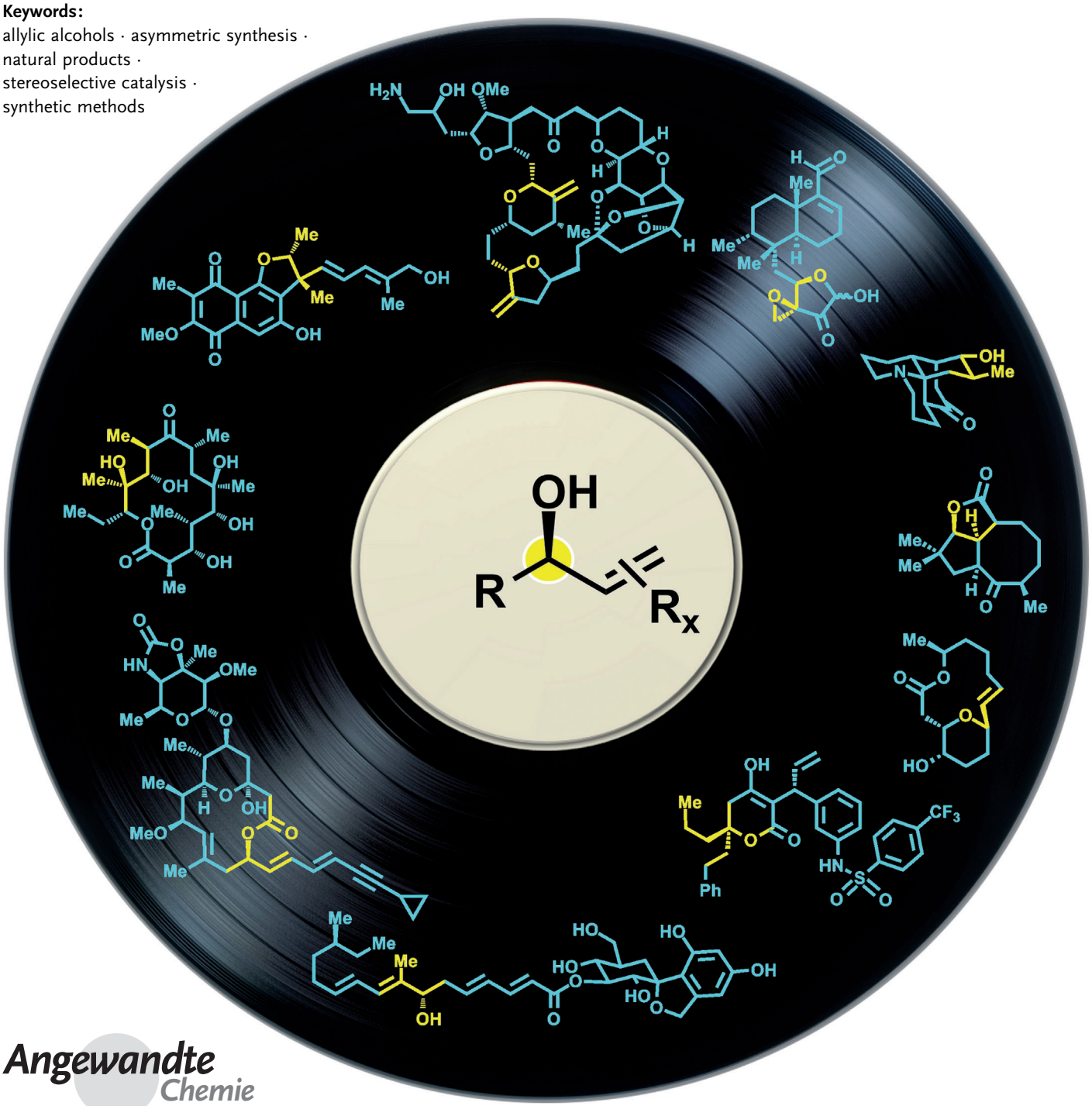
Keywords:
allylic alcohols · asymmetric synthesis · natural products · stereoselective catalysis · synthetic methods



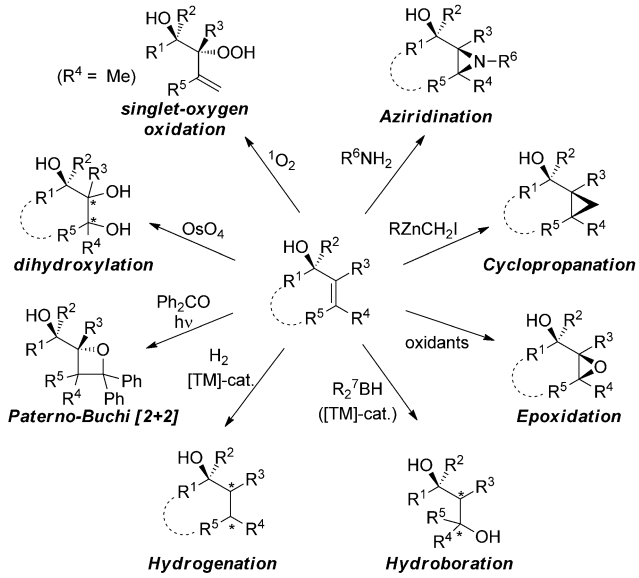
Allylic alcohols represent an important and highly versatile class of chiral building blocks for organic synthesis. This Review summarizes the plethora of methods developed for the catalytic asymmetric synthesis of enantioenriched allylic alcohols. These include: dynamic kinetic resolution (DKR/DKAT), nucleophilic 1,2-addition to carbonyl groups, allylic substitution, oxidation of C–H bonds, the addition of O nucleophiles to π systems, reduction of unsaturated carbonyl compounds, and an alternative route from enantioenriched propargylic alcohols. Furthermore, these catalytic asymmetric processes are exemplified by their applications in the syntheses of complex molecules such as natural products and potential therapeutic agents.

From the Contents

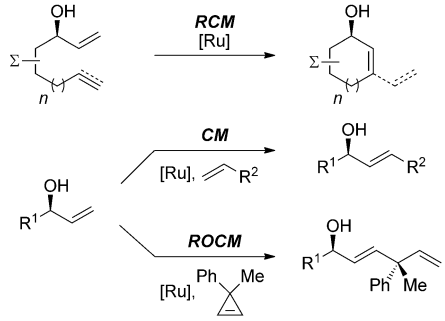
1. Introduction

Allylic alcohols are an important class of versatile building blocks for organic synthesis, since they permit a wide range of subsequent transformations, including carbon–carbon bond-forming reactions, in addition to numerous possibilities for the manipulation and introduction of functional groups. When enantiopure allylic alcohols are employed, a variety of highly diastereoselective reactions can be used to form building blocks with up to three contiguous stereocenters (Scheme 1). In many of these transformations the alcohol (or alkoxide) serves as a directing group and ensures a high level of selectivity.[1] Examples include aziridination,[2,3] Simmons–Smith-type cyclopropanation,[4,5] epoxidation,[6] hydrogenation,[7,8] Paterno–Büchi reaction,[9] dihydroxylation,[10] and singlet oxygen-mediated oxidation (Scheme 1).[11]

Furthermore, the allylic hydroxy group can also direct a variety of olefin metathesis reactions such as ring-closing metathesis (RCM), cross-metathesis (CM), and ring-opening cross-metathesis (ROCM), which enhance both the selectivity and the rate of reaction (Scheme 2).[12,13] These effects were ascribed to hydrogen bonding between the alcohol and the chloride atom of the ruthenium catalyst.



Scheme 1. Diastereoselective transformations of secondary and tertiary allylic alcohols. TM = transition metal.



Scheme 2. Directed olefin metathesis.

If the directing effect of the alcohol is too weak to achieve sufficient levels of selectivity, directing groups can be installed to permit further elaboration.[14] Such directing groups include diphenylphosphine or the removable *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) group, which have been employed to efficiently direct hydroboration[15] and hydroformylation[16,17] reactions, thereby furnishing *syn*-1,2-diols and *anti*-aldolates, respectively, with excellent selectivity. Allyl vinyl ethers or allylic carbamates have been used to

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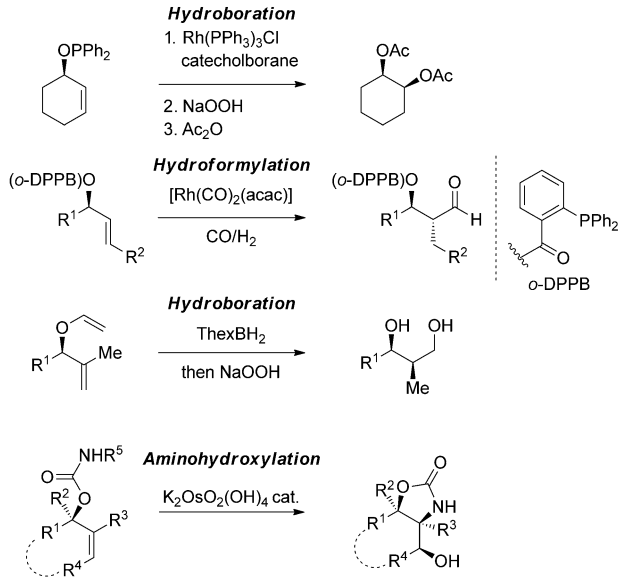
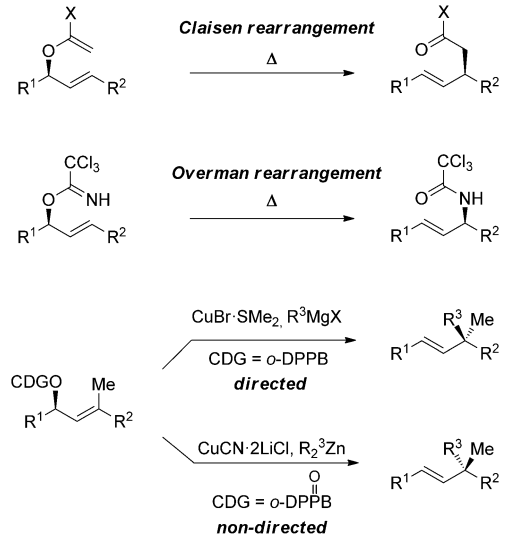


Scheme 3. Directed reactions of allylic alcohol derivatives. acac = acetylacetonate, Thex = thexyl.

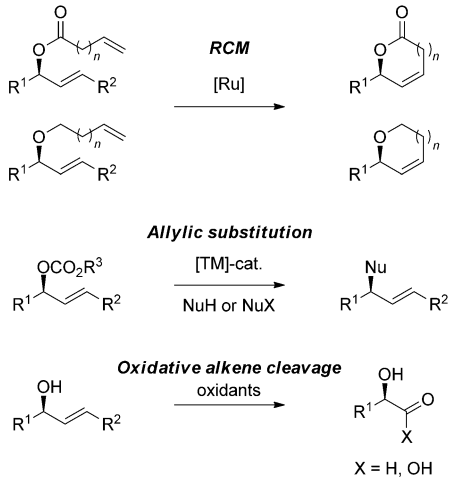


Scheme 4. [3,3]-Sigmatropic rearrangement and related transformations with [1,3]-chirality transfer.

direct intramolecular hydroboration[18] and aminohydroxylation[19] reactions (Scheme 3).

[3,3]-Sigmatropic rearrangements of enantioenriched allylic alcohols and their derivatives have been intensively studied and widely used in organic synthesis, for example the Claisen[20] and Overman[21] rearrangements that proceed with high levels of chirality transfer (Scheme 4).[22] Perfect 1,3-chirality transfer was also obtained for copper-mediated directed allylic substitution[23] reactions involving *o*-DPPB esters (Scheme 4).[14,24] This transformation enables the stereospecific construction of tertiary and quaternary carbon centers. The directing power of the *o*-DPPB group can be controlled by an "oxidative on/off switch", which allows the preparation of both optical antipodes of the substitution product from a single substrate enantiomer.

As previously mentioned, olefin metathesis is an important application for enantioenriched allylic alcohols. "Non-directed" ring-closing metathesis of enantioenriched allylic esters and ethers has been widely used, since it allows the formation of valuable cyclic ethers and (macro)lactones (Scheme 5).[25] Other transformations include enantiospecific allylic substitution of terminal allylic alcohols[26] and oxidative cleavage to α-hydroxy acids or α-hydroxy aldehydes.[27] The latter can be further elaborated, for example, by Wittig olefination or stereoselective nucleophilic additions. It is



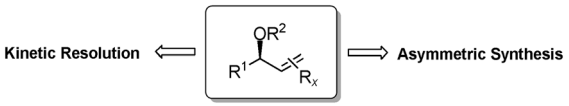
Scheme 5. Miscellaneous reactions. Nu = nucleophile.

Alexandre Lumbroso studied chemistry at the University of Nantes, France. He completed his PhD under the supervision of Professor Jean-Paul Quintard in 2009, working on the utilization of organostannanes for the stereoselective synthesis of imino sugar derivatives. He is currently a postdoctoral researcher in the group of Prof. Bernhard Breit at the Albert-Ludwigs-Universität Freiburg, Germany. His research focuses on the development of new atom-economic regio- and stereoselective reactions using homogeneous catalysis.

Michael Cooke studied chemistry at the University of Southampton and completed his PhD at the University of Cambridge with Prof. Matthew J. Gaunt, focusing on the development of copper-catalyzed C–H functionalization reactions. In 2011 he joined the group of Prof. Bernhard Breit at the Albert-Ludwigs-Universität Freiburg, Germany, where he is undertaking postdoctoral research into the development of atom-economic, catalytic asymmetric reactions.

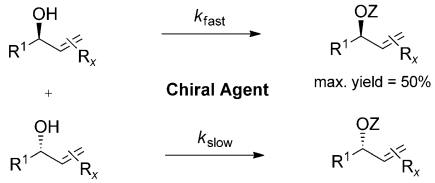
important to note that chiral allylic alcohols and their derivatives are also present as structural motifs in various natural products and/or potential therapeutic agents.

As a consequence of their utility in a broad range of transformations and their role as a structural motif in many complex molecules, the development of rapid and efficient methods to access enantioenriched allylic alcohols has drawn considerable interest. Such methods can be grouped into two main areas (Scheme 6).



Scheme 6. Approaches to enantioenriched allylic alcohols.

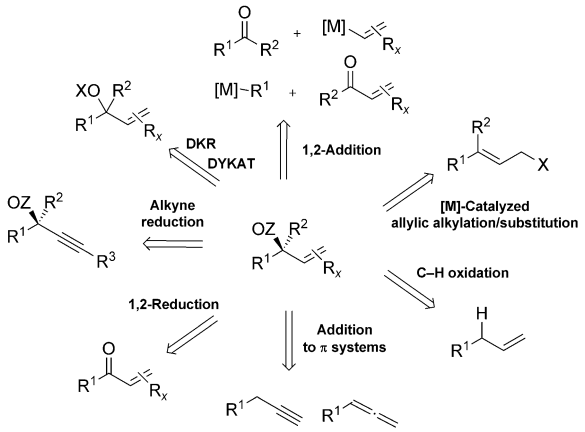
The kinetic resolution of racemic allylic alcohols promoted by chiral agents is a common approach (Scheme 7). A large number of procedures have been developed for this transformation, including enzymatic[28] and non-enzymatic



Scheme 7. Access to enantioenriched allylic alcohols by kinetic resolution.

resolutions.[29] Although practical methods have been developed, they are limited by a maximum theoretical yield of 50%, thus making this approach unattractive with regard to atom economy and will, therefore, not be discussed in this Review. Dynamic kinetic resolution reactions (DKR/DYKAT) have been described that overcome this limitation, which makes them attractive for the preparation of enantioenriched allylic alcohols and their derivatives.

Alternatively, asymmetric synthesis can be used to construct the enantioenriched allylic alcohol directly. Numerous highly stereoselective transformations that yield structurally diverse enantioenriched allylic alcohols have been reported, and the most efficient enantioselective catalytic methods are presented in this Review, as well as their applications in organic synthesis (Scheme 8). These include: 1) stereoselective C–C bond-formation reactions, such as nucleophilic 1,2-



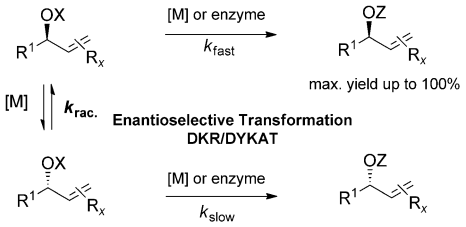
Scheme 8. Catalytic asymmetric access to enantioenriched allylic alcohols.

addition to carbonyl compounds and allylic alkylation, 2) stereoselective C–O bond-forming reactions, such as allylic substitutions, and 3) C–H bond oxidation and the addition of O nucleophiles to π systems. Also discussed are stereoselective C–H bond-forming reactions, that is, the reduction of unsaturated carbonyl compounds as well as an alternative means of access from enantioenriched propargyl alcohols. With the exception of some special examples, only methods involving catalytic amounts of the chiral inductor are reported. The reduction of α-halo epoxides, nucleophilic additions to enantioenriched epoxides, desymmetrization of *meso*-epoxides, oxidation of chiral allylic selenides, asymmetric dihydroxylation of dienes, and elimination reactions of iodo ketals and cyclic allylic carbonates will not be discussed, as they have been summarized in detail in the review by Hodgson and Humphreys in 2007,[30] and no significant improvements in these methods have been made.

2. Dynamic Kinetic Resolution of Racemic Allylic Alcohols and Derivatives

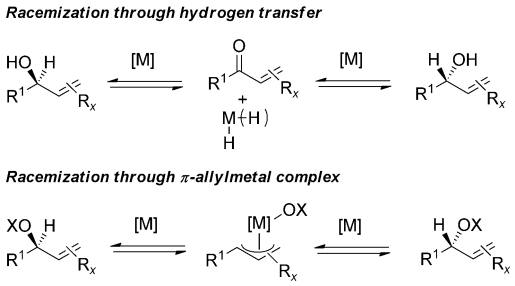
The major limitation of kinetic resolutions—the maximum theoretical yield of 50%—can be overcome by in situ racemization of the starting materials (Scheme 9). Dynamic kinetic resolution (DKR) or dynamic kinetic asymmetric transformation (DYKAT) is, therefore, a powerful method for the preparation of optically active allylic alcohols, as in theory a quantitative yield of the desired enantiomer can be obtained.[31] Among the different racemization methods classified by Zwanenburg (enzyme-catalyzed, acid-catalyzed, base-catalyzed etc.),[32] racemization catalyzed by transition metals is the method of choice for the preparation of enantioenriched allylic alcohols.[31a,b,d,g]

Bernhard Breit studied chemistry at the University of Kaiserslautern, Germany, where he obtained his PhD in 1993 with Prof. Regitz. After postdoctoral research with Prof. Trost at Stanford University, he completed his habilitation in 1998 in Marburg with Prof. R. W. Hoffmann. In 1999 he was appointed as an Associate Professor at the University of Heidelberg. Since 2001, he has been a Full Professor of Organic Chemistry at the Albert-Ludwigs-Universität Freiburg. His research interests include the development of new concepts and methods for organic synthesis.



Scheme 9. Dynamic kinetic resolution (DKR).

The two general transition-metal-catalyzed racemization processes are depicted in Scheme 10. The first proceeds



Scheme 10. Racemization processes in DKR.

through hydrogen transfer via metal (di)hydrides and ketones as intermediates,[33] which was introduced by the research groups of Williams[34] and Bäckvall[35] in 1997 through the use of rhodium and ruthenium complexes, respectively. The second employs π-allylmetal complexes as intermediates, as pioneered by Allen and Williams.[36] Palladium is the metal used most widely for this purpose.

The nature of the enantioselective transformation (DKR/DYKAT) falls into one of two categories: 1) chemoenzymatic DKR processes, as introduced by Allen and Williams (see above),[36,37] which involve the use of an achiral transition-metal complex for the racemization reaction[38] in conjunction with an enzyme that acts as the enantioselective catalyst (**1**–**8**, Figure 1),[31a–i] and 2) the chemical DKR or DYKAT process in which both the racemization and enantioselective transformation are catalyzed by a single, chiral transition-metal complex (**9**–**13**, Figure 2).[31a,39] In this Review, chemoenzymatic DKR and chemical DKR will be described separately.

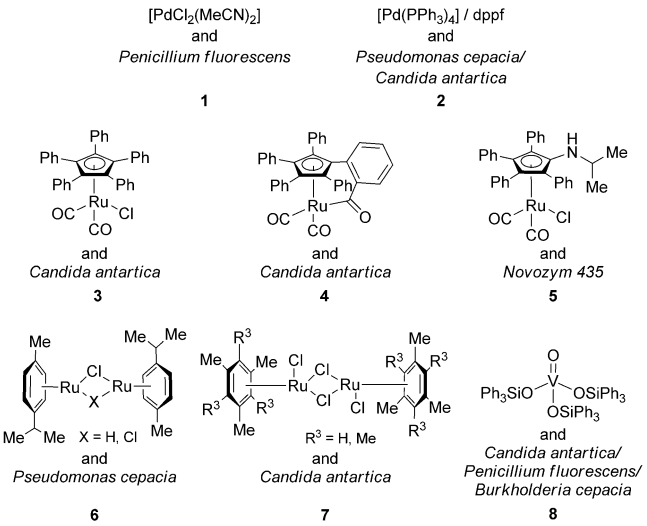


Figure 1. Achiral transition-metal complexes and enzymes used in the chemoenzymatic DKR of allylic alcohols. dppf = 1,1′-bis(diphenylphosphoranyl)ferrocene.

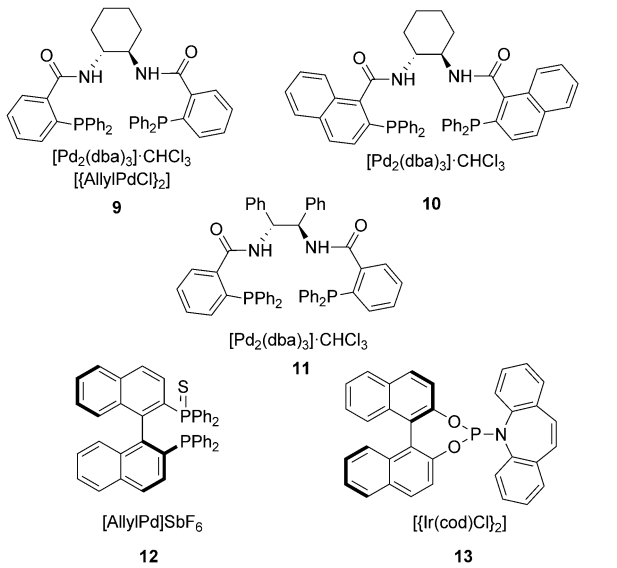


Figure 2. Chiral transition-metal complexes used in the chemical DKR of allylic alcohols.

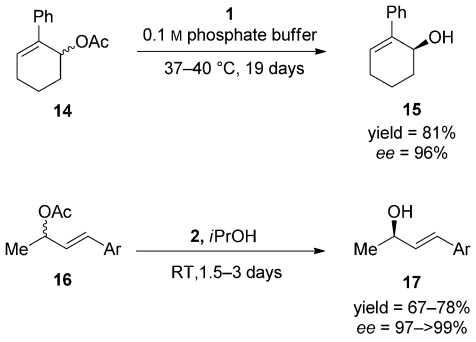
2.1. Chemoenzymatic Dynamic Kinetic Resolution

2.1.1. Palladium-Catalyzed Reactions

In 1996, the research group of Williams showed that an enzyme and a transition-metal complex can be used in a one-pot reaction to facilitate the first example of a chemoenzymatic DKR. The reaction of cyclic allylic acetate **14** in the presence of catalyst system **1** afforded cyclic allylic alcohol **15** in good yield (81%) and excellent enantiomeric excess (96%) after 19 days.[36] The slow-reacting enantiomer is racemized in situ through a palladium-catalyzed rearrangement followed by an enantioselective, enzyme-catalyzed hydrolysis (Scheme 11). Later, Kim and co-workers successfully used this method for the preparation of acyclic 1,3-disubstituted allylic alcohols **17** in high yields and excellent enantiocontrol by using a combination of Pd/lipase **2** as the catalyst (Scheme 11).[40]

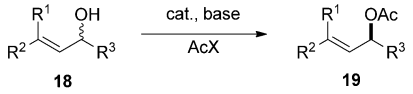
2.1.2. Ruthenium-Catalyzed Reactions

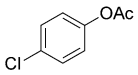
Bäckvall and co-workers[41] as well as others[42] used the Williams–Bäckvall method for the racemization of alcohols by hydrogen transfer. The resolution of allylic alcohols **18** into allylic acetates **19** was achieved by using various ruthenium catalysts and acylating agents (AcX; Table 1).



Scheme 11. Palladium-catalyzed DKR of allylic acetates.

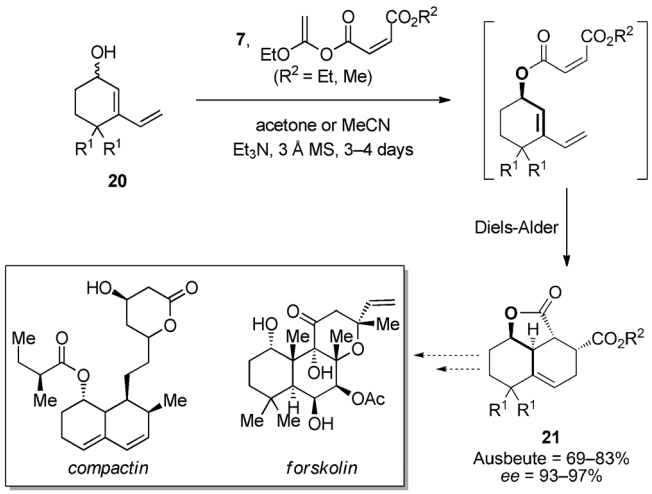
Table 1: Ruthenium-catalyzed DKR of allylic alcohols.



Ref.	Cat.	AcX	Base	Yield [%]	*ee* [%]
[41a]	**3**		*t*BuOK Na_2CO_3[a]	89	>99
[41b]	**3**		*t*BuOK Na_2CO_3[a]	71–>99	97–>99
[42a]	**4**		K_3PO_4	92	92
[42b]	**5**		*t*BuOK Na_2CO_3[a]	62–94	81–>99
[42c]	**6**		Et_3N	81–88	95–>99

[a] 5 mol% *t*BuOK, 1 equiv Na_2CO_3.

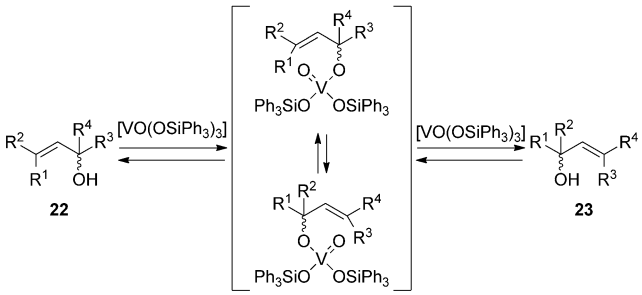
In 2004, Kita and co-workers reported a lipase-catalyzed domino DKR/Diels–Alder reaction starting from cyclic allylic alcohols (Scheme 12).[43] The process affords optically active polysubstituted decalins, which are useful intermediates in the synthesis of natural products such as compactin[44]—an HMG-CoA reductase inhibitor—and forskolin[45]—a protein kinase A activator (Scheme 12).



Scheme 12. Domino DKR/Diels–Alder reaction.

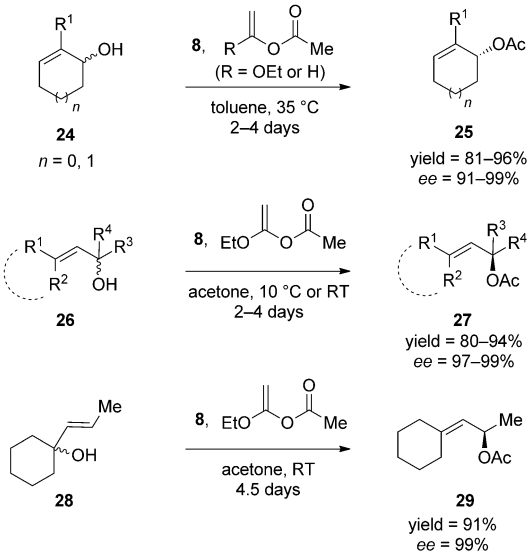
2.1.3. *Vanadium-Catalyzed Reactions*

Akai, Kita, and co-workers have successfully combined the ability of oxovanadium compounds to catalyze the interconversion between **22** and **23**[46] and the lipase-catalyzed kinetic resolution.[47] This isomerization reaction occurs by a 1,3-transposition of allyl vanadates (Scheme 13); therefore, this racemization process is similar to those involving π-allylmetal complexes as intermediates.



Scheme 13. Vanadium-catalyzed 1,3-transposition of allylic alcohols.

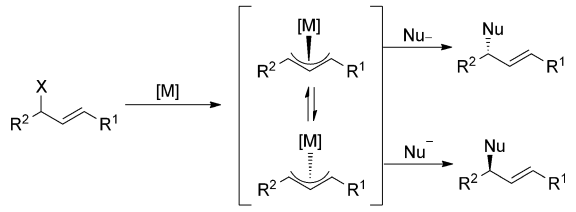
The overall transformation is a highly efficient DKR that is applicable to cyclic and acyclic allylic alcohols, including tertiary alcohols, which are converted into the corresponding allylic acetates in excellent yield and enantiomeric excess by using the combination of $[VO(OSiPh_3)_3]$/lipases **8** and vinyl acetate derivatives as acylating agents (Scheme 14). The utility of this method is exemplified by the transformation of tertiary allylic alcohol **28**, easily obtained from cyclohexanone, into enantiopure secondary allylic acetate **29** (Scheme 14).



Scheme 14. Vanadium-catalyzed DKR of allylic alcohols.

2.2. Chemical Dynamic Kinetic Resolution

Since the first example of non-enzymatic dynamic kinetic resolution (DKR) reported by Tai et al. in 1979,[48] this field of research has drawn considerable interest. A wide range of DKRs with chiral metal complexes or chiral auxiliaries have subsequently been reported.[49] The processes for accessing allylic alcohols and derivatives by DKR are frequently called dynamic kinetic asymmetric transformations (DYKATs). The majority of such transformations rely on the ability of transition metals to racemize allylic compounds through the formation of π-allylmetal intermediates. Selective access to the desired allylic products is only possible if there is a difference in the reactivity between the diastereomeric π-allylmetal complexes and the nucleophile, fast interconversion between the two complexes, a high level of stereoselectivity induced by the chiral ligand (for examples of ligands see Figure 2), and finally good regioselectivity between R^1 and R^2 (Scheme 15).

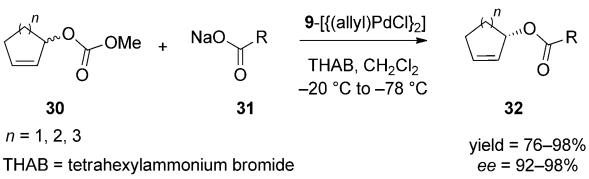


Scheme 15. DKR (or DYKAT) catalyzed by transition-metal complexes.

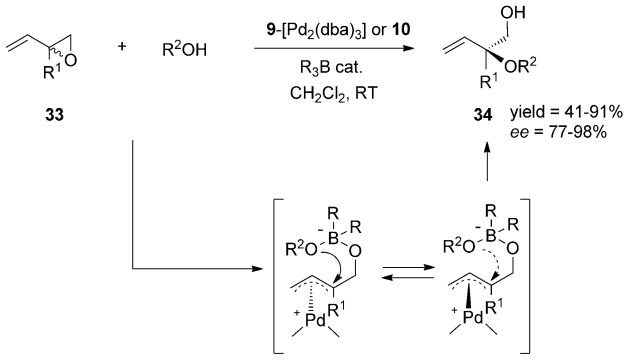
2.2.1. Palladium-Catalyzed Reactions

Processes involving the use of chiral palladium complexes[50] are probably the most efficient and well-studied systems (Figure 2); the Trost research group in particular have made many pioneering discoveries in the field.[39,51] In 1994, Trost and Organ reported the first deracemization of allylic esters using **9**-[{(allyl)PdCl}$_2$] as the chiral palladium complex.[52] This catalytic process proceeds under very mild conditions and is applicable to various cyclic allyl carbonates (5–7-membered rings) that can be converted into the corresponding cyclic allylic esters with various sodium carboxylates (generated in situ) used as nucleophiles (Scheme 16).

In 1998, Trost et al. demonstrated the efficiency of this process by transforming racemic vinyl epoxides into highly valuable nonracemic vinyl glycidols with **9**-[Pd$_2$(dba)$_3$] or **10** as the catalyst (Scheme 17).[53] Here, the addition of a trialkylborane (1 mol%) promotes the chemo-, regio-, and



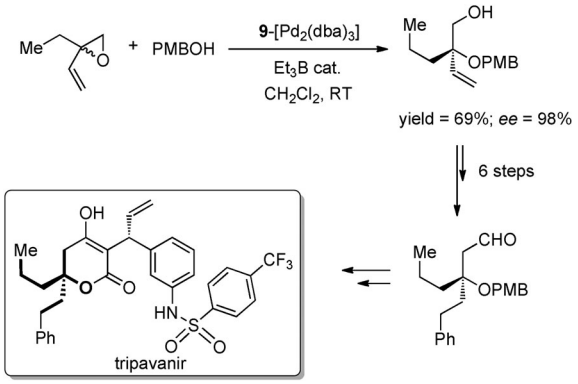
Scheme 16. Palladium-catalyzed deracemization of allylic carbonates.



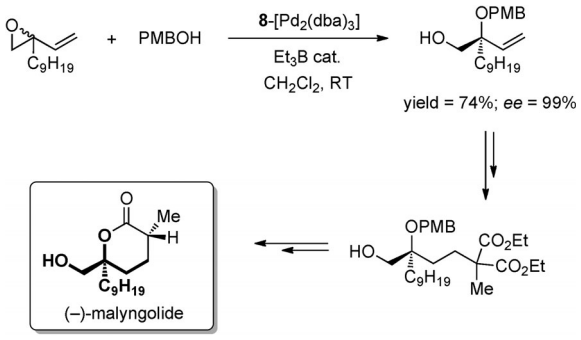
Scheme 17. Access to nonracemic vinyl glycidols by palladium-catalyzed DYKAT. dba = *trans*,*trans*-dibenzylideneacetone.

enantioselective addition of the alcohol to isoprene monoepoxide (R = Me) or butadiene monoepoxide (R = H) by forming in situ a dialkylalkoxyborane, which then generates an "ate" complex with the substrate (Scheme 17).

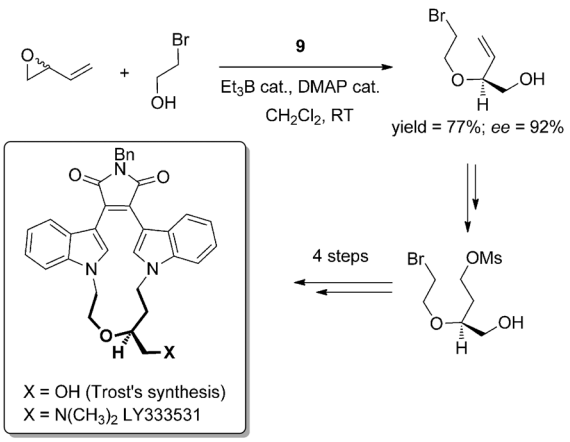
This method was applied successfully to the total synthesis of various complex natural products and potential therapeutic agents including tripavanir (Aptivus, Scheme 18)[54]—a nonpeptidic protease inhibitor used for the treatment of HIV/AIDS—the antibiotic (−)-malyngolide[55] (Scheme 19), and a precursor of LY333531 (ruboxistaurin)—a selective inhibitor of protein kinase C (PKC; Scheme 20).[56]



Scheme 18. Total synthesis of tripavanir by employing a DYKAT as a key step.

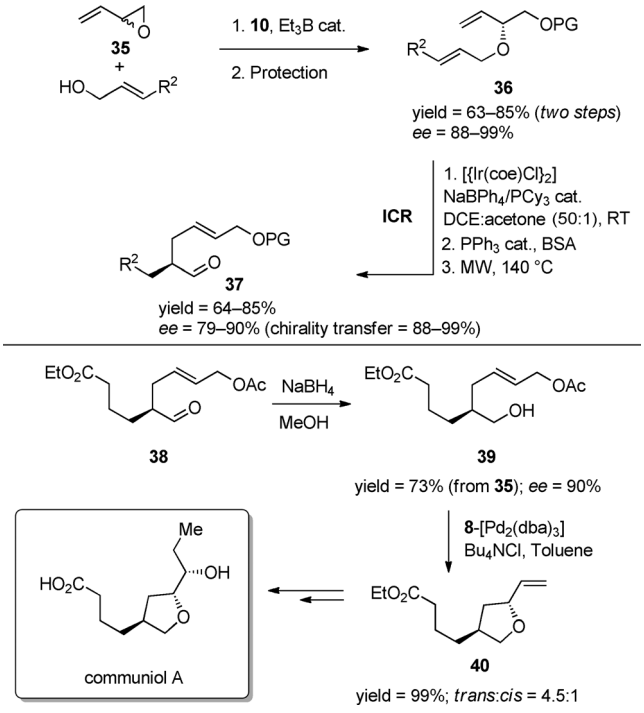


Scheme 19. Total synthesis of (−)-malyngolide by using a DYKAT as a key step. PMB = *para*-methoxybenzyl.



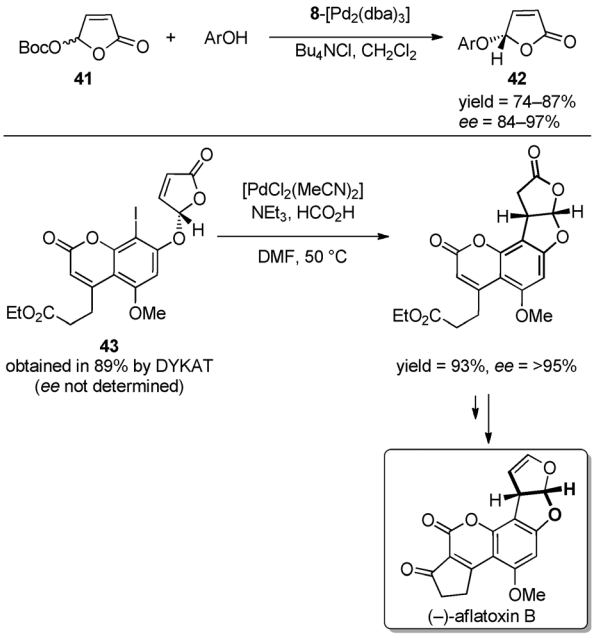
Scheme 20. Total synthesis of a precursor of LY333531. DMAP = 4-dimethylaminopyridine, Ms = mesyl, Bn = benzyl.

In 2006, Trost and Zhang combined this method with a highly efficient iridium-catalyzed isomerization–Claisen rearrangement (ICR),[57] which occurs with excellent chemo- and stereoselectivity (Scheme 21).[58] However, the free alcohol of the bisallyl ether **36** required protection prior to the ICR to obtain satisfactory yields of aldehydes **37**. The use of an acetyl protecting group allows the formation of an allylic ester **38**, which, after reduction to **39**, can undergo an intramolecular allylic substitution to generate tetrahydrofuran derivative **40**—an intermediate in the total synthesis of communiol A, a polyketide metabolite that exhibits interesting antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* (Scheme 21).



Scheme 21. Synthesis of communiol A by an isomerization–Claisen rearrangement (ICR). PG = protecting group, coe = cyclooctene, Cy = cyclohexyl, DCE = 1,2-dichloroethane, BSA = *O*,*N*-bistrimethylsilylacetamide, MW = microwaves.

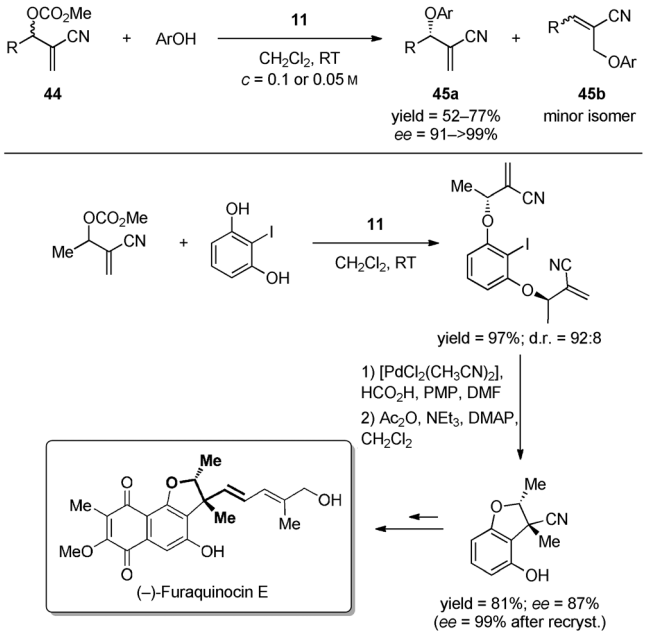
The palladium catalyst system developed by Trost et al. has also resulted in the development of an efficient method for the synthesis of nonracemic γ-alkoxybutenolides **42** from unsymmetrical racemic 5-acyloxy-2-(5*H*)-furanones **41** (Scheme 22).[59] These are important synthons for the asymmetric synthesis of natural products, as demonstrated by the total synthesis of (−)-aflatoxin B, a highly carcinogenic and toxic mold metabolite, by using coumarine derivative **43** (Scheme 22). The presence of a catalytic amount of Bu_4NCl (30 mol%) is required to increase the rate of racemization and, therefore, the enantiomeric excess obtained.



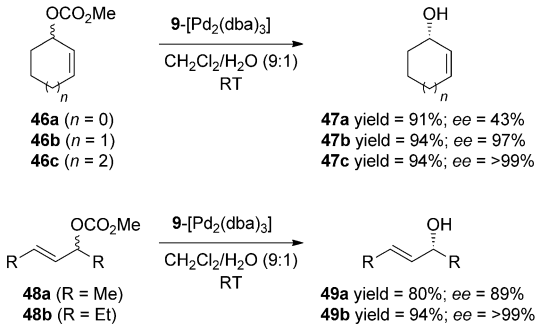
Scheme 22. Access to γ-alkoxybutenolides by DYKAT and application to the total synthesis of (−)-aflatoxin B.

This method has also proved to be a good alternative to the enantioselective Baylis–Hillman reaction, through the deracemization of carbonate derivatives of adducts **44** by using phenols as nucleophiles (Scheme 23).[60] For this method, the palladium catalyst **11** (Figure 2) bearing a more flexible ligand gave a better match of *ee* value and regioselectivity (between **45a** and **45b**) than catalysts **9** and **10** used previously. Again, this method has been applied to a total synthesis, the antibiotic furaquinocin E (Scheme 23), in which chiral cyano allylic alcohol was elaborated by an intramolecular reductive Heck cyclization, as in the synthesis of (−)-aflatoxin B (see above).[61]

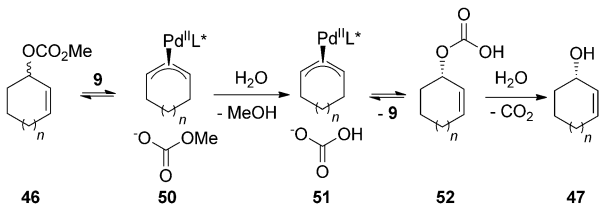
In 2003, Gais and co-workers elegantly used the Trost complex **9**-$[Pd_2(dba)_3]$ for the deracemization of symmetric cyclic and acyclic allylic carbonates in the presence of water, thereby affording enantioenriched allylic alcohols directly, in high yield and mostly excellent enantiomeric excess without an external nucleophile (Scheme 24).[62,63] The proposed mechanism (Scheme 25) commences with the formation of π-allylpalladium complex **50** bearing a methyl carbonate ion,



Scheme 23. Deracemization of Baylis–Hillman adducts by DYKAT and application to the total synthesis of (−)-furaquinocin E. PMP = 1,2,2,6,6-pentamethylpiperidine.

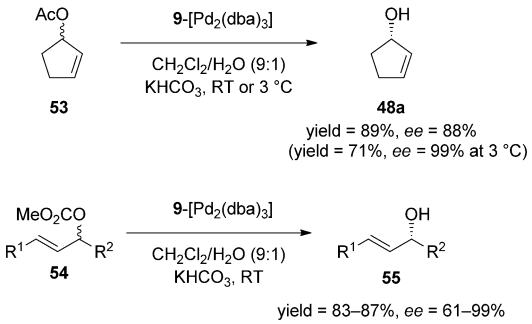


Scheme 24. Deracemization of symmetric allylic carbonates in the presence of water.



Scheme 25. Proposed mechanism for the deracemization of symmetric allylic carbonates in the presence of water.

and in the presence of water this forms bicarbonate **51**. Substitution and decarboxylation generates the allylic alcohol product. Surprisingly, the use of cyclopentenyl carbonate **46a** results in a very low *ee* value of the allylic alcohol being obtained (43% *ee*, Scheme 24). However, in the presence of a stoichiometric amount of $KHCO_3$ (1.4 equiv), cyclopentenyl acetate **53** reacts smoothly to afford **47a** in 89% yield and 88% *ee* (this can be improved to 99% *ee* at 3°C; Scheme 26).[63] These results have been ascribed by the authors to a strong memory effect of **46a** in the Pd-catalyzed allylic substitution.[64] The conditions developed for **53**, namely the presence of $KHCO_3$, were then applied to the

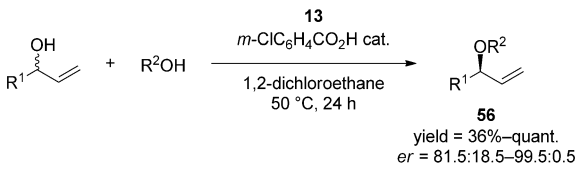


Scheme 26. Deracemization of cyclopentenyl acetate and nonsymmetric allylic carbonates in the presence of water and $KHCO_3$.

deracemization of nonsymmetric acyclic allylic carbonates to afford the corresponding allylic alcohols in moderate to excellent enantiomeric excess and perfect regioselectivity (the absence of $KHCO_3$ for the deracemization of **54** resulted in a significantly reduced *ee* value; Scheme 26).[63] In 2004, Faller and Wilt used **12** (Figure 2) for the resolution of nonsymmetric allylic carbonates by using sodium carboxylates as nucleophiles. Although, the branched allylic esters are obtained with high regioselectivities (up to 100:0), this system suffers from a very limited scope and/or moderate *ee* value (43–87%).[65]

2.2.2. *Iridium-Catalyzed Reactions*

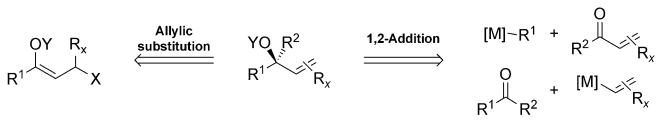
Although chiral iridium catalysts have been widely used in allylic substitutions of achiral starting materials[66] or in kinetic resolution reactions[67] to form allylic ethers and derivatives, only a single example of DKR that forms allylic ethers catalyzed by iridium has been reported. Roggen and Carreira recently described a highly efficient DKR of allylic alcohols (Scheme 27).[68] This report is notable as no "preactivation" of either the allylic alcohol (as the carbonate or ester) or the alcohol nucleophile (through alkoxide formation) is required. However, the latter has to be used in large excess (5 equiv). This new method is tolerant to various allylic alcohols (aromatic, heteroaromatic, aliphatic) and alcohols, including *p*-methoxybenzyl alcohol, and proceeds under relatively mild conditions (50°C). The corresponding allylic ethers **56** were isolated with very high selectivities.



Scheme 27. Iridium-catalyzed DKR of unactivated allylic alcohols.

3. Access through Stereoselective C–C Bond Formation

Stereoselective C–C bond formation is one of the most powerful transformations in organic synthesis and has drawn considerable interest in various areas of research.[69] Among the diverse range of reactions developed, some of these have emerged as efficient stereoselective methods for the preparation of allylic alcohols. These methods fall into two classes: 1) nucleophilic 1,2-additions to aldehydes and ketones, and 2) allylic substitution reactions using C nucleophiles (Scheme 28).



Scheme 28. Access to allylic alcohols by C–C bond formation.

3.1. Stereoselective Nucleophilic 1,2-Additions to Aldehydes and Ketones

3.1.1. 1,2-Additions to α,β-Unsaturated Aldehydes and Ketones

3.1.1.1. Addition of Organozinc Reagents

Since the pioneering work of Oguni and Omi in 1984[70] in which catalytic amounts of (*S*)-leucinol **57** were used as chiral ligands for the enantioselective addition of organozinc reagents to aldehydes, a plethora of ligands have been developed[71] such as the well-known (−)-DAIB **58**[72a] and (−)-MIB **59**[72b] developed by Noyori and Nugent, respectively. Despite this, the first examples of asymmetric addition of organozinc reagents to ketones were only reported in 1998 by the research groups of Fu[73] and Yus,[74] who used **58** and **60** (Figure 3). Since only the addition to α,β-unsaturated carbonyl compounds affords allylic alcohols by this method, most of the reports contain only one or two examples of allylic alcohols, which are frequently derived from simple carbonyl compounds such as cinnamaldehyde and nonfunctionalized organozinc reagents. A large number of reviews[71,75] and books[76] have been published on this area, so only recent catalytic systems illustrating the different ligands employed are summarized in Table 2 and Figure 3 (**61**–**69**).

Several catalytic systems have been employed for the synthesis of a broad range of allylic alcohols. Knochel and coworkers have used chiral triflamide **70**[91] with an excess of $Ti(OiPr)_4$ or $Ti(OtBu)_4$ to catalyze the addition of functionalized alkylzinc reagents to α,β-unsaturated aldehydes (Scheme 29).[92,93] These organozinc reagents were prepared according to Knochel's reported iodine–zinc[92] or boron–zinc[93] exchange reactions. The efficiency of this method has been demonstrated by the additions to β-stannylated, β-silylated, and α-halogenated α,β-unsaturated aldehydes (Scheme 29).[94–96]

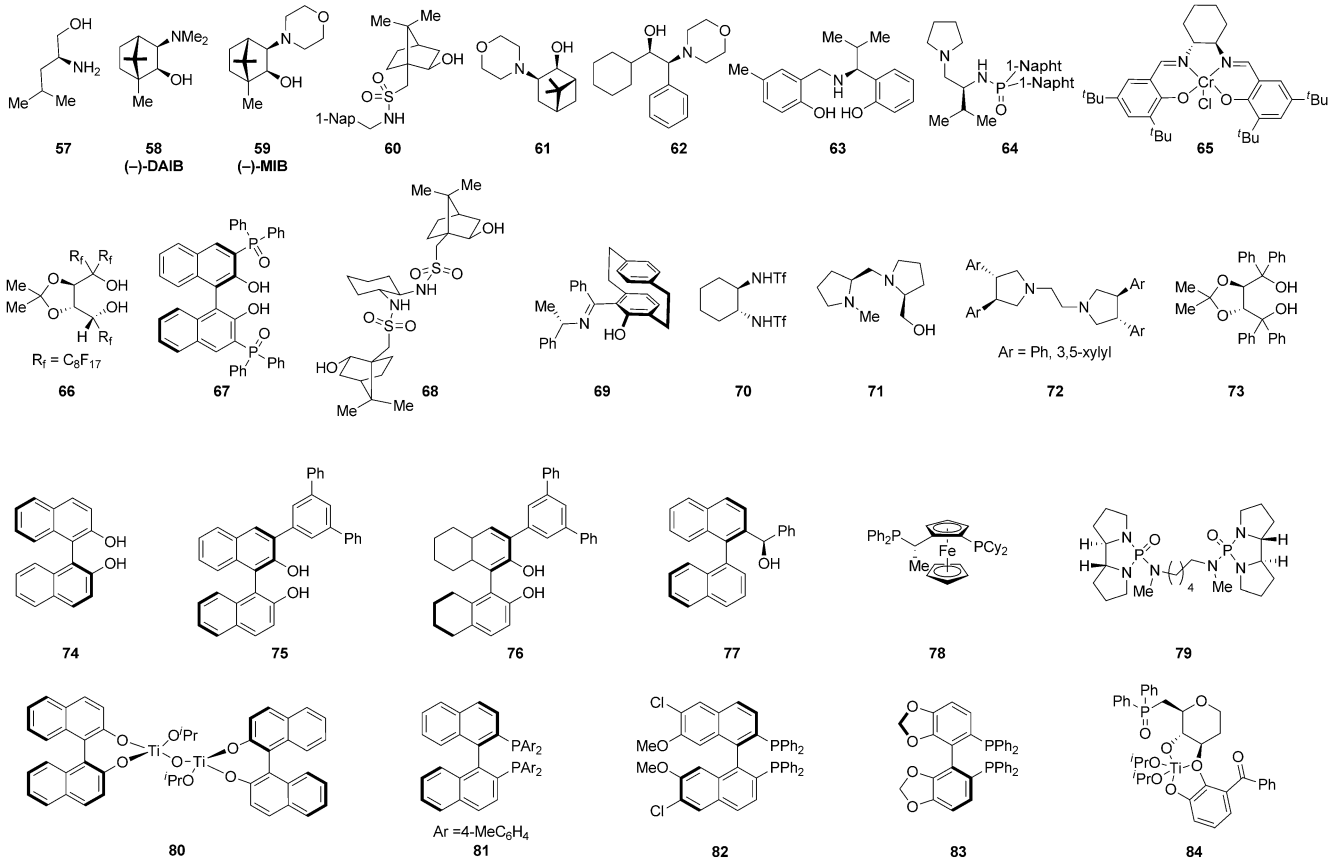
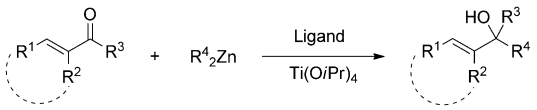


Figure 3. Chiral ligands for nucleophilic 1,2-additions to α,β-unsaturated carbonyl compounds. Nap = naphthyl.

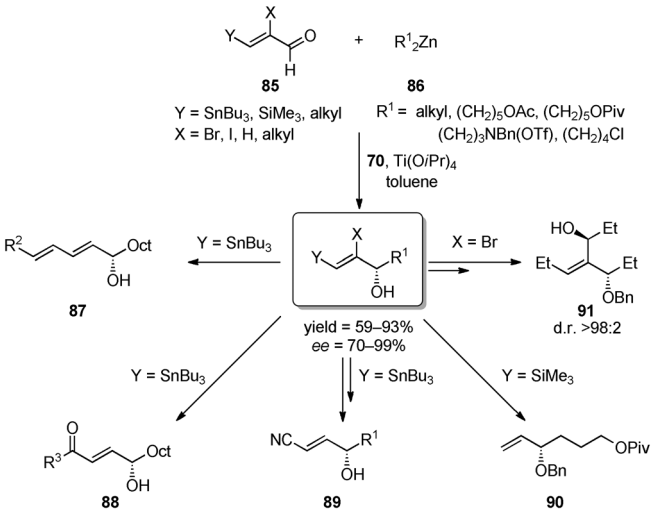
Table 2: Addition of organozinc reagents to aldehydes and ketones.



R^1 = H, Me, Ph, *c*-hex R^4 = alkyl, Ph
R^2 = H, Me, *c*-hex
R^3 = H, Me

Ref.	R^1,R^2,R^3	R^4	Ligand	Yield [%]	*ee* [%]
[77]	Ph,H,H	Et	**61**	99	95
[78]	H,Me,H	Et	**62**	95	94
[79]	Ph,H,H	Et	**63**	98	94
[80]	Ph,H,Me	Ph	**64**	81	98
[81]	*c*-hex,*c*-hex,H	*n*Pr	**64**	97	91
[82]	Me,Me,H	*i*Pr	**64**	97	97
[82]	Me,Me,H	*c*-hex	**64**	85	99
[83]	Ph,H,H	Me	**65**	81	89
[84]	Ph,H,H	Me	**66**[a]	93	92
[85]	Ph,H,H	Et	**67**	82	75
[85]	Me,Me,H	Et	**67**	63	81
[86, 87]	Ph,H,Me	Et	**68**[a]	90	>99
[88]	Ph,H,Me	Ph	**68**[a]	58	91
[88]	*c*-hex, *c*-hex, H	Ph	**68**[a]	94	93
[89]	*c*-hex, *c*-hex, H	Et	**68**[a]	56	96
[90]	Ph,Me,H	Et	**69**	100	86

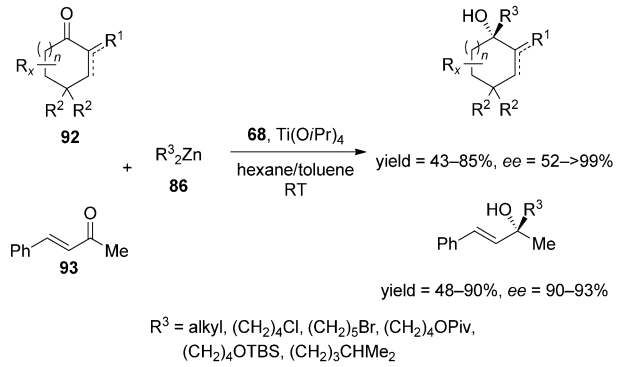
[a] Requires a (super)stoichiometric amount of $Ti(OiPr)_4$.



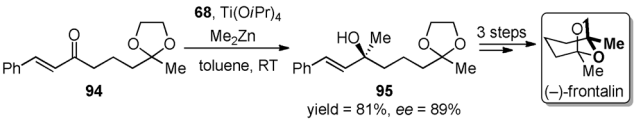
Scheme 29. Addition of functionalized dialkylzinc reagents to substituted α,β-unsaturated aldehydes. Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

The research group of Walsh has employed **68** in the presence of $Ti(OiPr)_4$ for the addition of various functionalized dialkylzinc reagents **86** to cyclic and acyclic enones **92**/**93**, thereby giving access to a broad range of tertiary allylic alcohols in moderate to excellent yields and *ee* values (Scheme 30).[89] The organozinc reagents were prepared as discussed previously.

Yus et al. used **68** to catalyze the enantioselective addition of dimethylzinc to functionalized enone **94**, which led to tertiary allylic alcohol **95** in good yield and enantiomeric excess (81%, 89% *ee*; Scheme 31).[97] Subsequent reductive



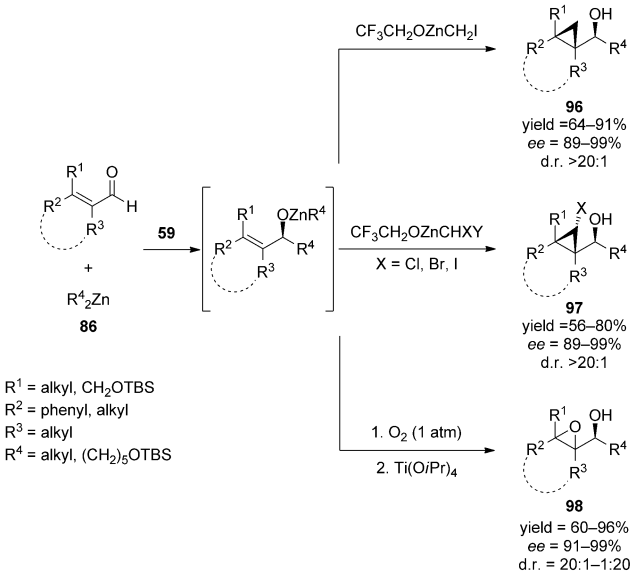
Scheme 30. Addition of functionalized dialkylzinc reagents to enones.



Scheme 31. Synthesis of (−)-frontalin.

ozonolysis and acidic hydrolysis furnished (−)-frontalin, an aggregation pheromone of the southern bark beetle *dendroctonus frontalis*.

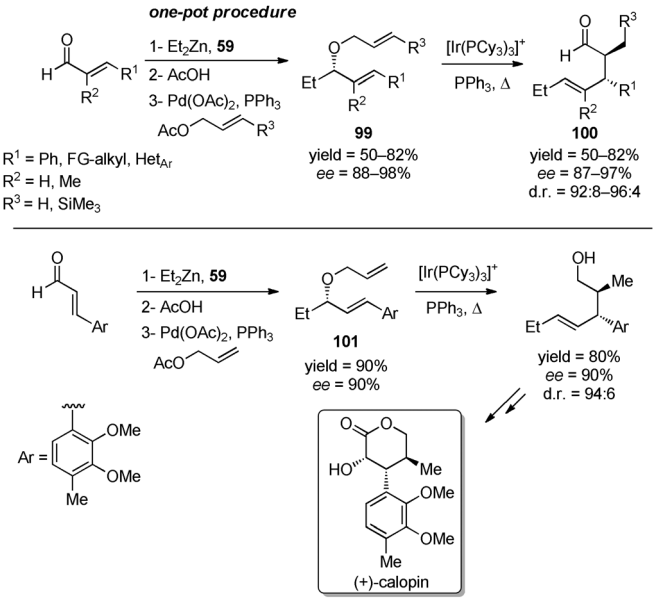
Walsh and co-workers developed asymmetric one-pot alkylation-cyclopropanation, alkylation–halocyclopropanation, and alkylation–epoxidation reactions of various functionalized α,β-unsaturated aldehydes by using (−)-MIB **59** (Scheme 32).[98a–c] After enantioselective alkylation with **86**, the allylic alkoxide intermediates were transformed in situ into cyclopropyl alcohols **96** or halocyclopropyl alcohols **97** with very high levels of selectivity by using carbenoids.[98a,b] Epoxy alcohols **98** could be produced in high diastereoregioselectivity by treating the allylic alkoxides with oxygen and a catalytic amount of $Ti(OiPr)_4$ (Scheme 32).[98c] The authors



Scheme 32. One-pot asymmetric alkylation–cyclopropanation/halocyclopropanation/epoxidation. TBS = *tert*-butyldimethylsilyl.

suggest that the oxidant is formed upon insertion of oxygen into a Zn–C bond, thereby generating the peroxy species R^4-Zn-OOR^4. Subsequent transmetalation of this species to the allylic titanium alkoxide is followed by directed epoxidation. Depending on the nature of the aldehyde (R^1 = H or Ph/Me), the *erythro* or *threo* products were generated selectivity. Related one-pot alkylation-epoxidation reactions of enones have also been reported by Walsh and co-workers.[98d,e]

Nelson and Wang have used (−)-MIB **59** to prepare enantioenriched di(allyl) ethers **99** rapidly and efficiently by a one-pot enantioselective alkykation–O-allylation reaction (Scheme 33).[57d] A subsequent isomerization–Claisen rearrangement (ICR)[57c] afforded enantioenriched Claisen adduct **100** with excellent diastereoselectivity and reliable transfer of chirality. This expedient two-step protocol was tolerant to various functional groups. The usefulness of this method was exemplified by the enantioselective synthesis of (+)-calopin by using **101** as the precursor (Scheme 33).



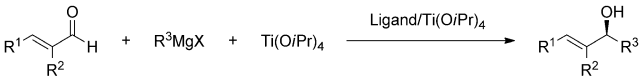
Scheme 33. Enantioselective access to di(allyl)ethers/ICR reaction.

3.1.1.2. *Addition of Grignard Reagents*

In this section, methods involving the transmetalation of Grignard reagents to other metals are also discussed.

Pioneering work in this field was conducted by the research groups of Mukaiyama,[99] Tomioka,[100] and Seebach,[101–104] who used **71**, **72**, and **73** to promote the asymmetric additions to aldehydes[99–103] and ketones.[104] These methods usually require a stoichiometric amount of chiral modifier[99–102,104] and/or strict exclusion of the magnesium salts generated by the transmetalation of the Grignard reagents (RMgX) with $ZnCl_2$[101,102] or $ClTi(OiPr)_3$ to achieve high enantiomeric excess.[103] In these cases, R_2Zn and $RTi(OiPr)_3$ are the nucleophilic species. More recently, the research groups of Da,[105,106] Harada,[107,108] and Marciá and Yus[109] reported practical and efficient "catalytic" systems for the asymmetric addition of Grignard reagents to aldehydes by using a catalytic amount of BINOL derivatives **74–77** (Figure 3) with 0.89 to 15 equivalents of $Ti(OiPr)_4$ and without any salt-exclusion step. These methods were applied to the synthesis of allylic alcohols; however, as for the addition of organozinc reagents, a limited number of examples are described in which only simple α,β-unsaturated aldehydes and Grignard reagents were used (Table 3).

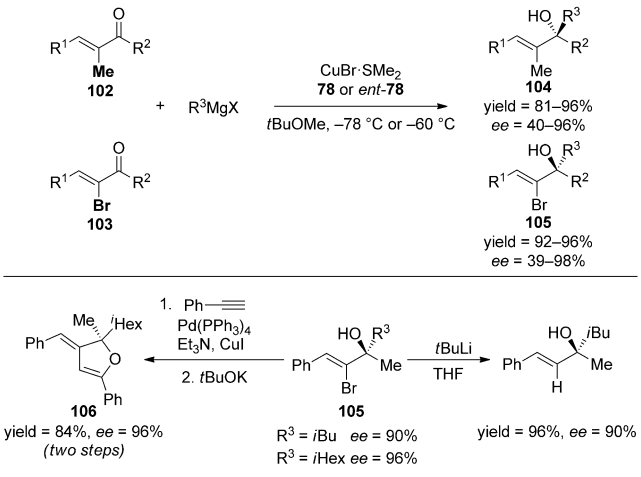
Table 3: Addition of Grignard reagents in the presence of $Ti(OiPr)_4$.



Ref.	R^1,R^2	R^3	[Ti] equiv	Ligand	Yield [%]	*ee* [%]
[105]	Ph,H	*i*Bu	0.89[a]	**74**	70	90
[106]	Ph,H	$Ph(CH_2)_2$	1.35[a]	**74**	70	79
[107]	Ph,H	*n*Bu	5.8	**75**	60	91
[107]	H,Me	*n*Bu	5.8	**75**	49	84
[108]	H,Me	Ph	3.0	**76**	87	97
[108]	Me,H	Ph	3.0	**76**	78	86
[109]	Ph,H	Me	15.0	**77**	90	68

[a] 2.0–2.4 equiv of bis[2-(*N*,*N*′-dimethylamino)ethyl] ether (BDMAEE) were used.

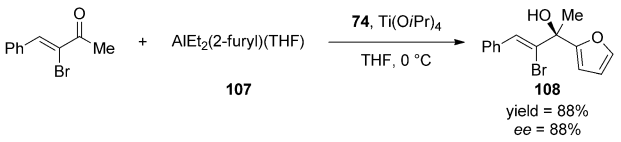
Recently, Madduri, Minnaard, and Harutyunyan have reported the first truly catalytic enantioselective 1,2-addition of Grignard reagents to ketones.[110] Various alkyl and functionalized alkyl Grignard reagents have been added to α-methyl-[110a] and α-bromo-substituted[110b] α,β-unsaturated ketones **102/103** by using $CuBr{\cdot}SMe_2$ and Josiphos ligand **78** as the catalyst system (Scheme 34). Highly valuable chiral tertiary allylic alcohols were obtained in good yields and with moderate to excellent enantioselectivity. Furthermore, α-bromo-substituted tertiary alcohols **105** can be debrominated with retention of configuration to furan derivatives **106** by Sonogashira coupling in the presence of *t*BuLi followed by cyclization (Scheme 34).



Scheme 34. Cu^I-catalyzed direct addition of Grignard reagents to ketones.

3.1.1.3. Addition of Organoaluminum Reagents

Gau and co-workers have reported the addition of (2-furyl)aluminum reagent **107** to an α-bromo-substituted α,β-unsaturated ketone by employing (*S*)-BINOL **74** (Figure 3) and a stoichiometric amount of Ti(O*i*Pr)$_4$ (Scheme 35).[111]

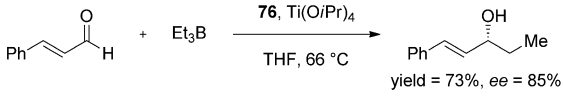


Scheme 35. Enantioselective addition of an organoaluminum compound to an α,β-unsaturated ketone.

108, which was obtained in good yield and enantiomeric excess, is a useful intermediate for the synthesis of bioactive compounds because of the diverse reactivity of the furan moiety.[112]

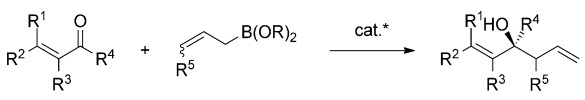
3.1.1.4. Addition of Boron Reagents

Aryl and alkyl boron reagents have been used in numerous asymmetric 1,2-addition reactions to carbonyl compounds as a result of their availability and stability (for indirect addition of boron reagents to α,β-unsaturated carbonyl compounds by boron/zinc exchange, see Sections 3.1.1.1 and 3.1.2.1).[113] Direct additions of arylboron reagents in the presence of rhodium[114] or palladium[115] complexes bearing chiral ligands have also been reported. However, there are very few direct addition methods that result in the formation of allylic alcohols.[114d] In 2008, Muramatsu and Harada reported the first direct addition of trialkylboranes to aldehydes catalyzed by **76** (used previously for Grignard additions)[108] with an excess of Ti(O*i*Pr)$_4$ (3 equiv; Scheme 36).[116]



Scheme 36. Direct addition of trialkylboron derivatives to α,β-unsaturated aldehydes.

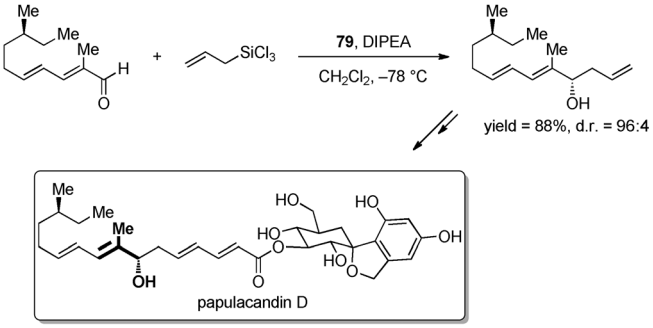
Allylborane reagents have also been used for "direct addition" to α,β-unsaturated ketones to form tertiary allylic and homoallylic alcohols (Scheme 37). Since comprehensive reviews on catalytic enantioselective allylation reactions have been published in this field by Denmark and Fu,[117] Hall,[118] and recently by Yus et al.,[119] the allylboration of ketones and aldehydes will not be discussed in this Review.



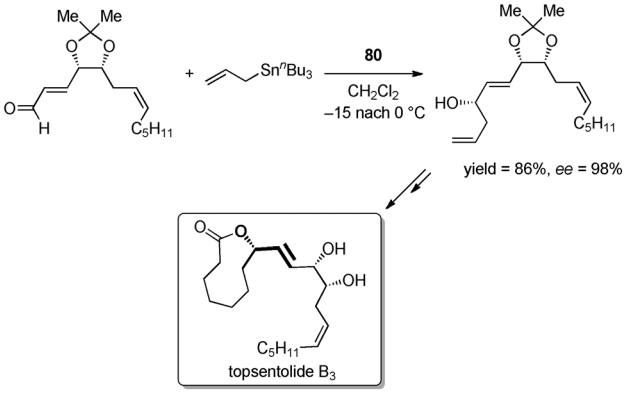
Scheme 37. Allylboration of α,β-unsaturated carbonyl compounds.

3.1.1.5. Addition of Organostannanes, Organosilanes, and Allylic Derivatives

As in the case of organoboron reagents, organostannanes and organosilanes have mostly been used in asymmetric allylation reactions, and this topic is well covered by reviews.[117,119] However, the allylation of α,β-unsaturated carbonyl compounds has been elegantly employed in various total syntheses, including the synthesis of papulacandin D (Scheme 38),[120,121] topsentolide B$_3$[122] (Scheme 39), and the C4–C24 fragment of macrolactin A (Scheme 40).[123] These illustrate once again the importance of chiral allylic alcohols as structural motifs in natural products and their utility as building blocks for further transformations.



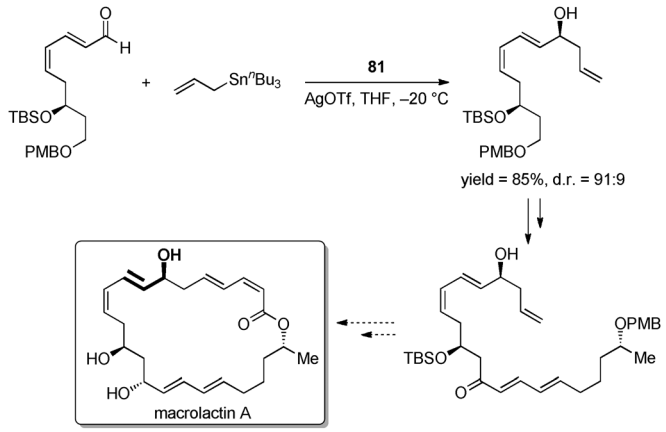
Scheme 38. Total synthesis of papulacandin D. DIPEA = *N*,*N*-diisopropylethylamine.



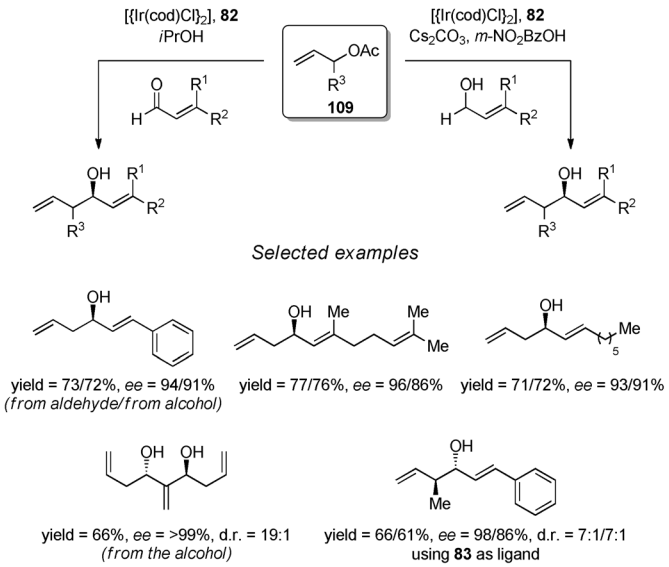
Scheme 39. Total synthesis of topsentolide B$_3$.

3.1.1.6. Addition of Allylic Derivatives

Krische and co-workers have used allylic acetates **109** as surrogate allyl metals, thereby avoiding the use of stoichiometric amounts of organometallic reagents, in a novel iridium-catalyzed transfer-hydrogenative allylation. This stereoselective carbonyl allylation can be performed from the oxidation level of the aldehyde (using isopropanol as the stoichiometric reductant) or alcohol, whereby the substrate alcohol serves both as a hydrogen source and as the aldehyde precursor (Scheme 41). Various α,β-unsaturated aldehydes and alcohols were compatible with this protocol and the allylic alcohols were obtained with good yields and very high selectivities (Scheme 41).[124]



Scheme 40. Synthesis of the C4–C24 fragment of macrolactin A.

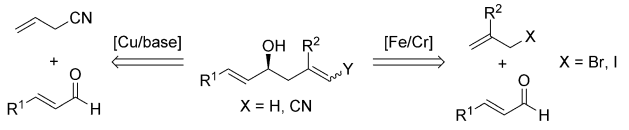


Scheme 41. Iridium-catalyzed transfer-hydrogenative allylation. cod = cycloocta-1,5-diene.

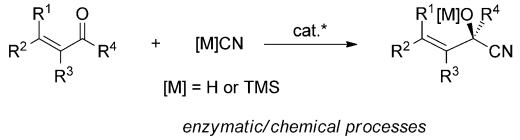
Allylic halides (with Cr)[125] and allylic cyanides (with Cu)[126] have also proved to be good "nucleophiles" for the allylation of α,β-unsaturated aldehydes such as cinnamaldehyde (Scheme 42). These asymmetric methods have been previously summarized in the literature[119] and will not be discussed in detail in this Review.

3.1.1.7. ***Addition of Cyanide***

The 1,2-addition of cyanide to carbonyl compounds leads to the formation of cyanohydrins, which are versatile building blocks that undergo a variety of further transformations. Some of the various methods are highly efficient for the synthesis of allylic cyanohydrins in enantiopure form from α,β-unsaturated carbonyl compounds. Various cyanide sources including HCN, TMSCN, and EtOCOCN have been used for this transformation (Scheme 43). Both enzymatic and chemically catalyzed approaches have been studied and are summarized in many reviews.[127]



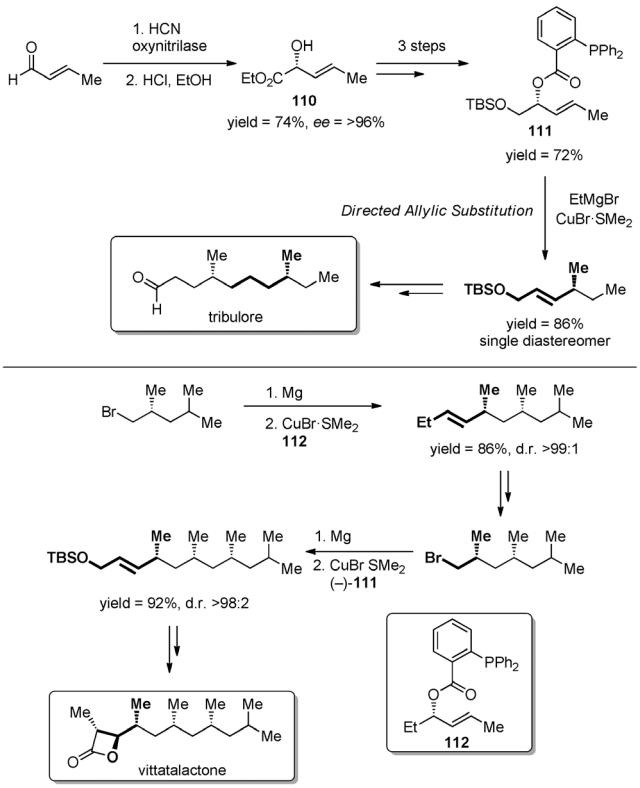
Scheme 42. Addition of allylic halides and cyanides to α,β-unsaturated carbonyl compounds.



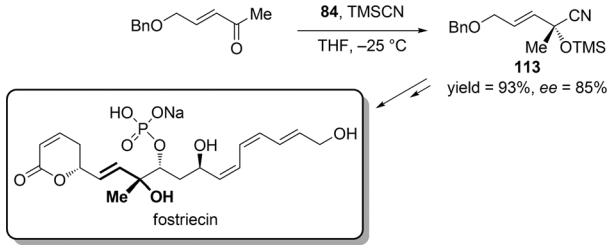
Scheme 43. 1,2-Addition of [M]CN to α,β-unsaturated carbonyl compounds. TMS = trimethylsilyl.

The Breit research group synthesized allylic alcohol **110** by a highly enantioselective addition of HCN to crotonaldehyde catalyzed by oxynitrilase, followed by transformation of the nitrile into an ethyl ester (Scheme 44).[128] Allylic ester **111** was obtained in good yield (72%) after reduction, protection of the primary alcohol, and Steglich esterification with *ortho*-diphenylphosphanylbenzoic acid. This ester has been used as a key building block for the stereospecific construction of the major structural motifs of polyketides, such as tribulore and vittatalactone, by employing an *o*-DPPB-directed allylic substitution with Grignard-derived organocopper reagents (Scheme 44).[128,129]

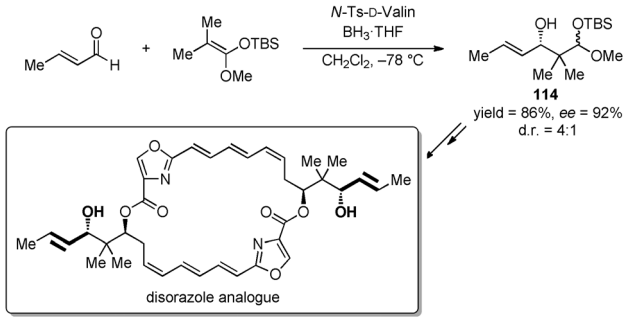
Shibasaki and co-workers have reported a formal total synthesis of fostriecin by a titanium-catalyzed cyanosilylation of ketones (Scheme 45).[130] Tertiary α-cyanoallylic alcohol



Scheme 44. Enzyme-catalyzed addition of HCN to crotonaldehyde.



Scheme 45. Total synthesis of fostriecin by the titanium-catalyzed addition of TMSCN. Bn = benzyl.



Scheme 46. Total synthesis of a disorazole analogue. Ts = toluene-4-sulfonyl.

113 was obtained in acceptable yield and enantiomeric excess in the presence of the titanium complex of D-glucose-derived ligand **84**. The main advantage of this catalytic system is that the reaction can be performed on a 50 g scale, and **84** can be recovered by column chromatography on silica gel and used several times without any loss of activity.

3.1.1.8. Aldol Reactions

Asymmetric aldol reactions can also be considered as nucleophilic 1,2-additions to carbonyl compounds. Many reviews have been published on this topic[131] and, therefore, these reactions will not be discussed in detail. As an example, Kalesse and co-workers have recently used a Kiyooka aldol reaction to form secondary allylic alcohol **114**, an intermediate in the total synthesis of disorazole analogues, a class of polyketides displaying anticancer activity against a variety of transformed cell lines (Scheme 46).[132]

3.1.2. 1,2-Additions of Vinylmetal Reagents to Aldehydes and Ketones

3.1.2.1. 1,2-Additions of Vinylzinc Reagents

The asymmetric addition of vinylmetal reagents to carbonyl compounds represents a general method for the synthesis of chiral allylic alcohols (Figure 4). Indeed, irre-

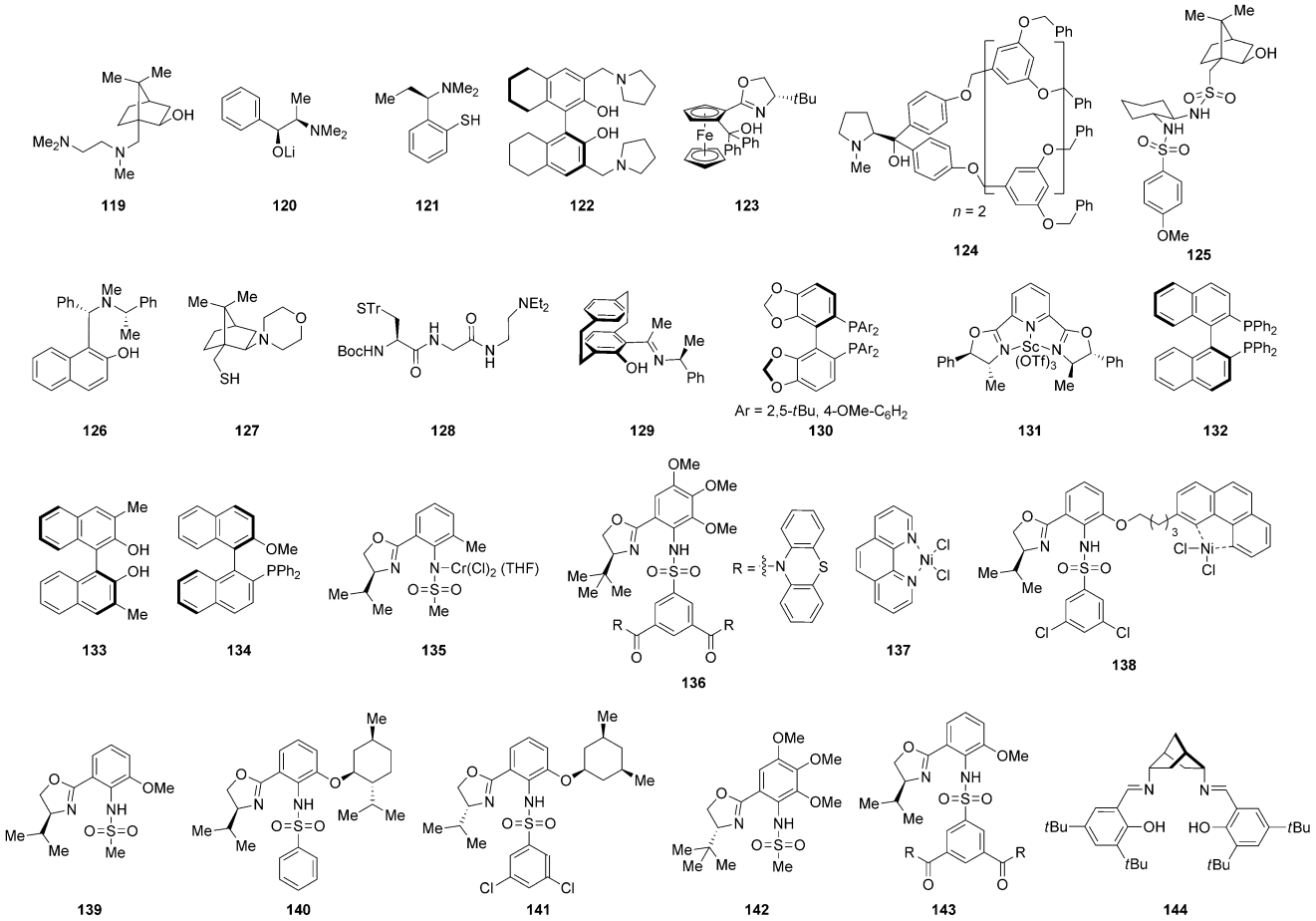
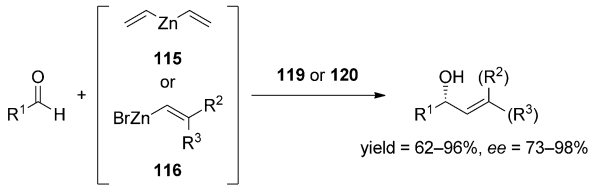


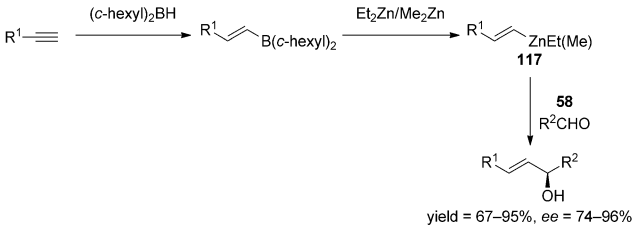
Figure 4. Chiral ligands and metal complexes for the addition of vinylmetal species to carbonyl compounds.

spective of the aldehyde or ketone used, such reactions lead to secondary or tertiary allylic alcohols. Oppolzer and Radinov published the first results in this area, by reporting the addition of vinylzinc species **115** or **116** to aliphatic and aromatic aldehydes catalyzed by chiral amino alcohol derivatives **119** or **120** (Figure 4; Scheme 47).[133,134]



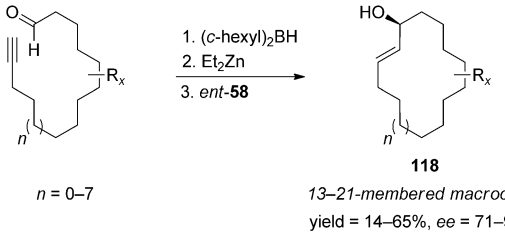
Scheme 47. Oppolzer's asymmetric addition of vinylzinc derivatives to aldehydes.

In 1992, Oppolzer and Radinov described the asymmetric addition of mixed (alkenyl)(alkyl)zinc reagents **117** to aldehydes with exclusive transfer of the alkenyl group.[135] Such zinc reagents are prepared by an efficient protocol consisting of alkyne hydroboration with dicyclohexylborane, followed by transmetalation of the resulting (*E*)-1-alkenylboranes with Et_2Zn or Me_2Zn (Scheme 48). High yield and enantiomeric excess could be obtained for the addition of these zinc reagents to various aldehydes in the presence of Noyori's ligand (−)-DAIB **58** (Figure 3).

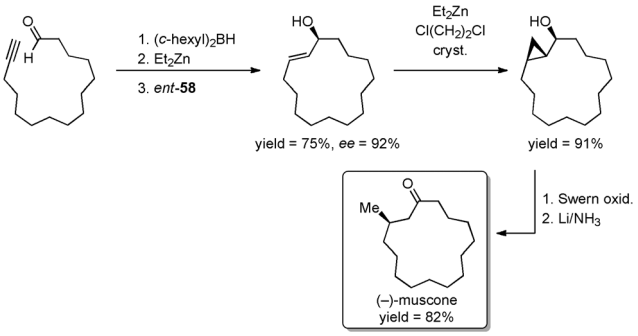


Scheme 48. Oppolzer's vinylation of aldehydes.

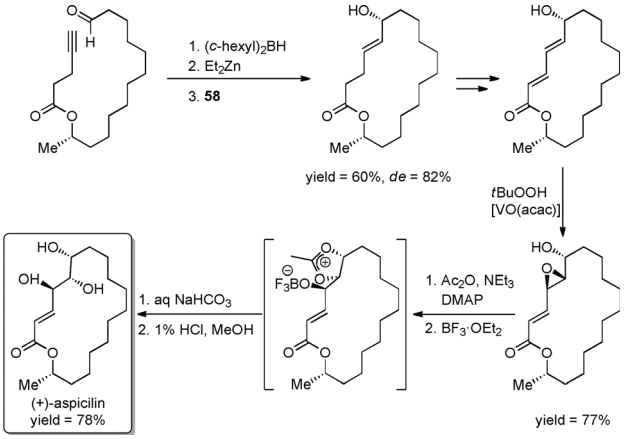
Later, Oppolzer et al. applied this method to the synthesis of macrocyclic allylic alcohols **118** from ω-alkynals (Scheme 49).[136] Although the yields for the 13- to 21-membered macrocycles were sometimes low, except for 13-membered rings, very high enantiomeric excess was obtained (≥90%) by using (+)-DAIB (*ent*-**58**, Figure 3). The utility of this asymmetric intramolecular 1,2-adition has been proved by the synthesis of (−)-muscone[137] (Scheme 50) and (+)-aspicilin[138] (Scheme 51), in which the allylic alcohols



Scheme 49. Macrocyclization using Oppolzer's vinylation of aldehydes.



Scheme 50. Total synthesis of (−)-muscone.

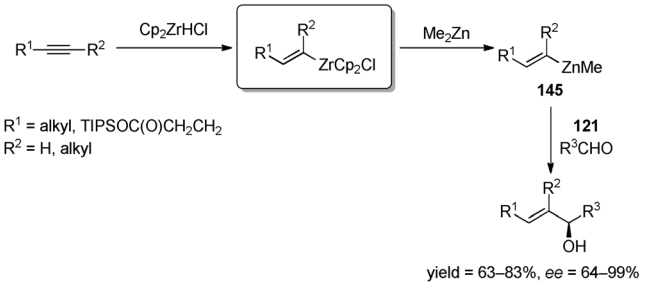


Scheme 51. Total synthesis of (+)-aspicilin.

formed were transformed using diastereoselective cyclopropanation or epoxidation to obtain the desired natural products.

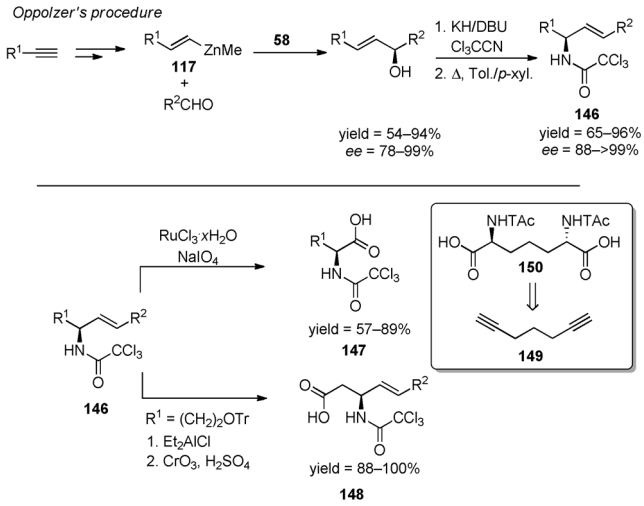
In 1998, Wipf et al., described a new procedure for the preparation of (alkenyl)(alkyl)zinc reagents **145** involving hydrozirconation instead of hydroboration (Scheme 52).[139,140] The catalytic asymmetric addition of these reagents to aldehydes using van Koten's amine **121**[141] (Figure 4) afforded allylic alcohols derived from terminal and internal alkynes (Scheme 52).

Walsh and co-workers used Nugent's ligand (−)-MIB **58** (Figure 3) to catalyze the addition of a broad range of mixed (alkenyl)(alkyl)zinc reagents **117** to aldehydes.[142,143] The allylic alcohols could be transformed into allylic amines **146** by an Overman rearrangement. Such allylic amines could be



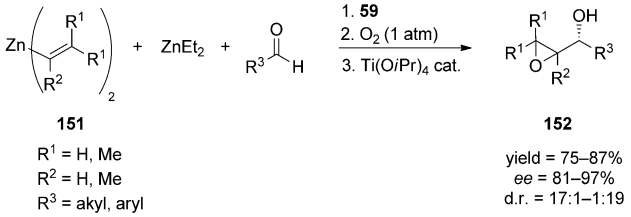
Scheme 52. Addition of vinylzinc reagents prepared by Wipf's procedure. Cp = C_5H_5, TIPS = triisopropylsilyl.

further elaborated to α-amino acids **147**[142] and γ-unsaturated β-amino acids **148**[143] (Scheme 53). The use of bisalkyne **149** affords α,α-diamino diacid **150**; certain related molecules play a crucial role in the bacterial biosynthesis of α-amino acids (Scheme 53).[142]



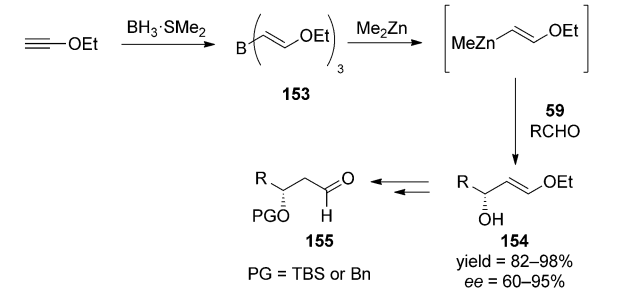
Scheme 53. Vinylation of aldehydes and application to the synthesis of α-amino acids and γ-unsaturated β-amino acids. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TAc = trichloroacetyl, Tr = triphenylmethyl.

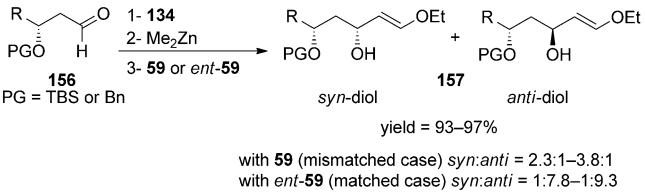
As discussed earlier (Scheme 32), Walsh and co-workers have developed one-pot processes for the cyclopropanation,[98a] iodocyclopropanation,[98b] and epoxidation[144a] of allylic alkoxides formed by the addition of organozinc to aldehydes (Scheme 54). Whilst very high selectivities could be obtained from the (iodo)cyclopropanation reactions, only moderate diastereoselectivity could be obtained from the epoxidation reactions. However, the use of divinylzinc reagents **151** as nucleophiles allowed the formation of epoxy alcohols **152** with excellent diastereoselectivity (Scheme 55).[98c] Related highly stereoselective one-pot processes toward *syn*-vinylcyclopropyl alcohols and *anti*-cylcopropyl alcohols have also been developed by Walsh and co-workers.[144b]



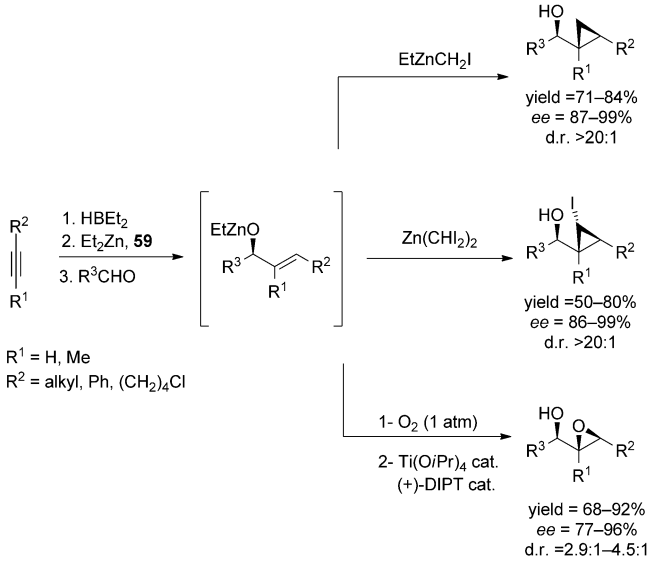
Scheme 55. One-pot addition/epoxidation reaction.

Walsh and co-workers have also reported the formation of enantioenriched β-hydroxy aldehydes by the addition of ethoxyvinylzinc reagents to aldehydes—an alternative to the asymmetric aldol reaction.[145] β-hydroxy enol ethers **154** were obtained with moderate to excellent enantiomeric excess and very high yield by using only 0.4 equiv of **153** to generate the vinylzinc species and **59** (Scheme 56). The corresponding β-hydroxy aldehydes **155** can be obtained from a two-step procedure involving alcohol protection and enol ether hydrolysis with $Hg(OAc)_2$ and KI. This method was applied to the diastereoselective synthesis of 1,3-diols, important building blocks in the total syntheses of many natural products (Scheme 56). By using **59** (the mismatched catalyst), *syn*-diols **157** were obtained with moderate selectivities, albeit in very high yields. However, the matched combination with *ent*-**59** resulted in a high diatereoregioselectivity of the *anti*-





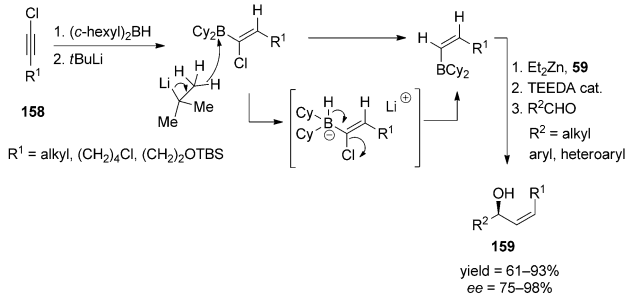
Scheme 56. Synthesis of β-hydroxy aldehydes and β,δ-dihydroxy enol ethers.



Scheme 54. One-pot asymmetric vinylation–cyclopropanation/halocyclopropanation/epoxidation. DIPT = diisopropyl tartrate.

diol **157**. These β,δ-dihydroxy enol ethers could, in principle, be utilized for the construction of 1,3-polyols.

Starting from 1-chloro-1-alkynes **158**, Walsh and co-workers have developed the first general approach to the production of enantioenriched (*Z*)-allylic alcohols.[146] Hydroboration of **158** followed by reaction with *t*BuLi and transmetalation with diethylzinc generates (*Z*)-disubstituted vinylzinc intermediates, which upon reaction with aldehydes form enantioenriched (*Z*)-allylic alcohols **159**. TEEDA (tetraethylethylenediamine) is used to chelate LiCl, which otherwise promotes rapid 1,2-addition, thereby forming racemic products (Scheme 57).



Scheme 57. Access to enantioenriched (*Z*)-allylic alcohols.

This method was combined with an epoxidation process, as discussed previously, thereby producing epoxy alcohols **160**–**163** (Figure 5) in moderate yields and excellent selectivities in one pot.[146]

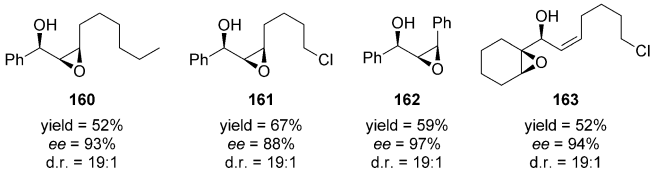
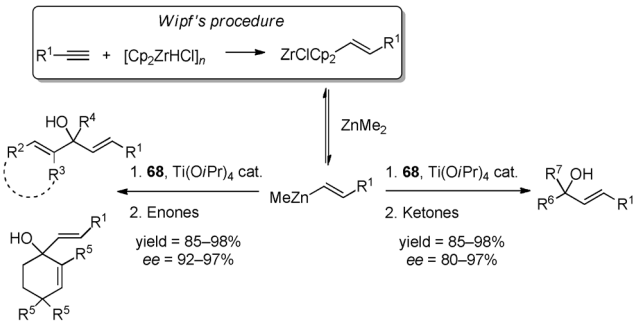


Figure 5. Epoxy alcohols obtained by the epoxidation of (*Z*)-allylic alkoxides.

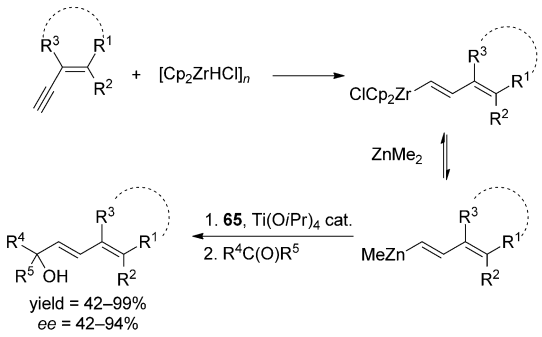
The research group of Walsh has intensively studied the vinylation of ketones to give tertiary allylic alcohols. By using **68** (Figure 3) and a catalytic amount of $Ti(OiPr)_4$, vinylzinc derivatives prepared by the method developed by Wipf et al. (see Scheme 52) could be added to various ketones (aromatic, aliphatic) as well as cyclic and acyclic enones, thereby affording valuable enantioenriched tertiary allylic alcohols in excellent yield and enantiomeric excess (Scheme 58).[147,148]

This catalytic system was shown to be efficient for the dienylation of ketones when 1-ene-3-ynes were used as starting materials (Scheme 59).[148]

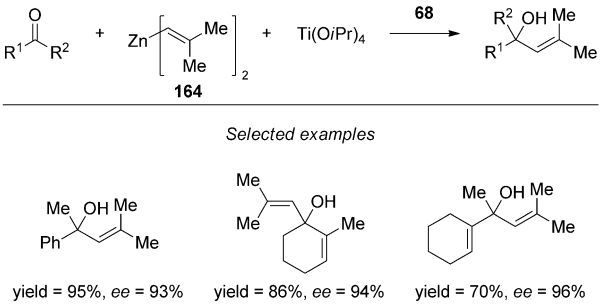
Li and Walsh used divinylzinc reagent **164** to access enantioenriched trisubstituted tertiary allylic alcohols, which is not possible by the hydrozirconation of alkynes (Scheme 60).[148]



Scheme 58. Addition of vinylzinc reagents to ketones and enones.



Scheme 59. Dienylation of ketones.

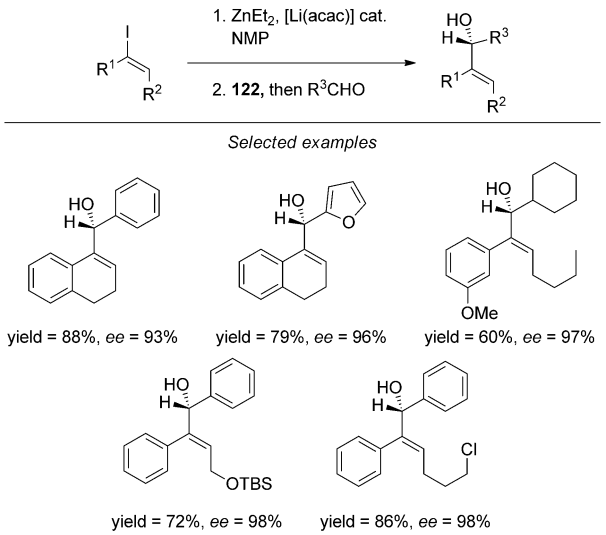


Scheme 60. Addition of divinylzinc to ketones and enones.

Recently, Pu and co-workers reported the in situ preparation of vinylzinc reagents through the reaction of vinyl iodides with diethylzinc (Scheme 61). These reagents could be added to aldehydes in the presence of **122** (Figure 4) as a promoter to yield a very broad range of secondary allylic alcohols in good yields and excellent selectivities.[149] This method gives access to allylic alcohols that are often not accessible by using the previous methods, involving hydroboration (Oppolzer's method) or hydrozirconation (Wipf's method).

Bolm and co-workers[150] as well as Zhao and co-workers[151] have used alkenylboronic acids and alkenyl boronates in 1,2-additions. Various secondary allylic alcohols were obtained in moderate yield but high enantiomeric excess in the presence of diethylzinc and **123** and **124**, respectively, as promoters.

The research groups of Yus,[87] Chan,[152] Uang,[153] Seto,[154] and Bräse[155] have also contributed to the development of the



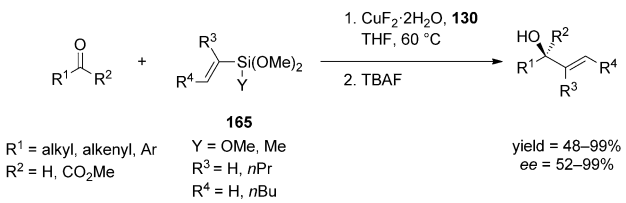
Scheme 61. Vinylation of aldehydes using vinyl iodides. NMP = *N*-methylpyrrolidine.

addition of vinylzinc reagents to aldehydes through the use of **125**, **126**, **127**, **128**, and **129**. In all cases, the vinylzinc reagents were prepared following Oppolzer's procedure.

3.1.2.2. 1,2-Additions of Vinylsilane Reagents

In this section, methods involving in situ transmetalation of the starting vinylsilane reagents are also discussed.

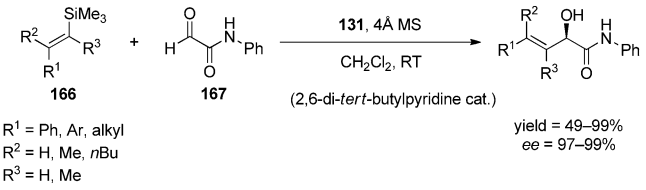
Shibasaki, Kanai, and co-workers have developed an efficient catalytic system for the enantioselective intermolecular addition of vinylsilane reagents **165** to carbonyl compounds (Scheme 62).[156] In the presence of $CuF_2{\cdot}2H_2O$ and



Scheme 62. Copper-catalyzed addition of vinylsilane reagents to carbonyl compounds. TBAF = tetrabutylammonium fluoride.

chiral SEGPHOS derivative **130** (Figure 4), various aldehydes, including challenging enolizable aliphatic aldehydes, were transformed into the corresponding secondary allylic alcohols in high yields and excellent enantioselectivities. This reaction also proceeds with internal alkenylsilanes ($R^3 = n$Pr), albeit in a poor yield and enantioselectivity (48% yield, 52% *ee*), but chemoselectively with activated aromatic ketones (R^1 = Ph, $R^2 = CO_2Me$).

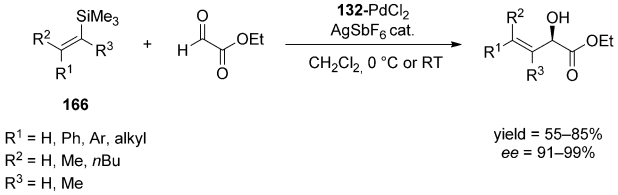
Evans and Aye used Sc^{III}-pybox complex **131** to catalyze the direct addition of substituted vinylsilanes **166** to glyoxamide **167** (Scheme 63).[157] Various 2-substituted and 2,2-disubstituted vinylsilanes were successfully added with excellent enantiomeric excess. A catalytic amount of base



Scheme 63. Scandium-catalyzed addition of vinylsilane reagents to glyoxamide. MS = molecular sieves.

(3.5 mol%) was required with 2,2-dialkyl-substituted vinylsilanes to avoid product isomerization to the corresponding homoallylic alcohol. Internal vinylsilane (R^1, R^2, R^3 = Me) also proved to be a satisfactory coupling partner and a (*Z*)-allylic alcohol was obtained from (*Z*)-2-*n*-butylvinylsilane (R^1, R^3 = H, $R^2 = n$Bu). Interestingly, (*Z*)-phenylvinylsilane (R^1, R^3 = H, R^2 = Ph) was found to afford only the (*E*)-allylic alcohol.

In 2009, Mikami and co-workers reported a palladium-catalyzed enantioselective alkenylation of ethyl glyoxylate with vinylsilanes **166** by using a cationic palladium and BINAP catalyst (Figure 4; Scheme 64).[158] In contrast to the

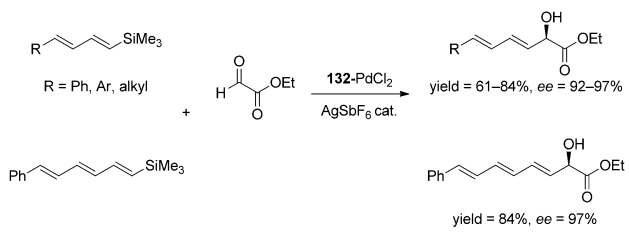


Scheme 64. Palladium-catalyzed addition of vinylsilane reagents to ethyl glyoxylate.

system developed by Evans and Aye (Scheme 63), (*Z*)-phenylvinylsilane afforded the corresponding allylic alcohol with a very good *Z*/*E* ratio (96:4). This method was also effective for the dienylation and trienylation of ethyl glyoxylate. The corresponding allylic alcohol derivatives were in all cases obtained in high yields and excellent enantioselectivities (Scheme 65).

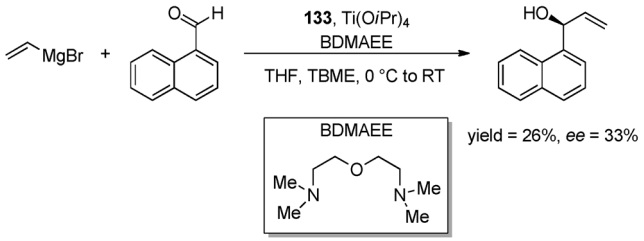
3.1.2.3. 1,2-Additions of Vinyl Grignard Reagents

There is only a single report of the enantioselective addition of vinyl Grignard reagents to carbonyl compounds. Da et al. reported the addition of vinylmagnesium bromide to 1-naphthaldehyde in the presence of **133** (Figure 4), a stoi-



Scheme 65. Palladium-catalyzed dienylation and trienylation of ethyl glyoxylate.

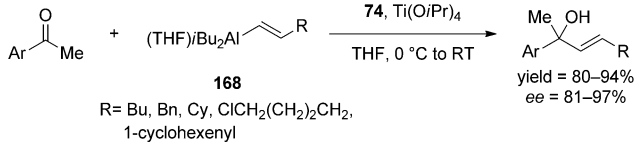
chiometric amount of $Ti(OiPr)_4$, and bis[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAEE) to deactivate the Grignard reagent (Scheme 66).[105] However, the allylic alcohol was isolated in very low yield and enantiomeric excess.



Scheme 66. Enantioselective addition of a vinyl Grignard reagent to 1-naphthaldehyde. TBME = *tert*-butyl methyl ether.

3.1.2.4. 1,2-Additions of Vinylaluminum Reagents

Biradar and Gau used the efficient catalytic system of (*S*)-BINOL/$Ti(OiPr)_4$, used previously for the addition of arylaluminum reagents to α,β-unsaturated aldehydes (Scheme 35), to catalyze efficiently the addition of various vinylaluminum reagents to acetophenone derivatives, thereby producing tertiary allylic alcohols in high yield and high enantiomeric excess (Scheme 67).[159]



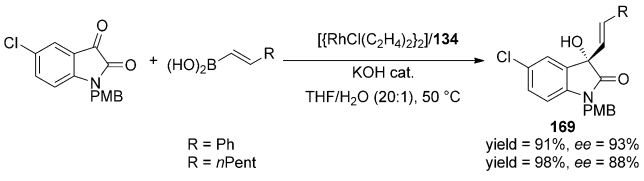
Scheme 67. Addition of vinylaluminum reagents to ketones.

3.1.2.5. 1,2-Additions of Vinylboron Reagents

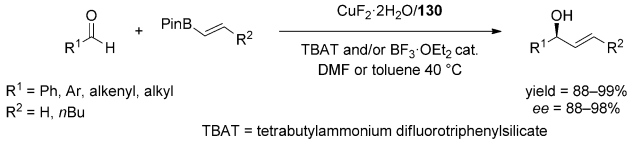
In 2006, Hayashi and co-workers described a rhodium-catalyzed direct addition of alkenylboronic acids to isatins by using chiral phosphine ligand **134** (Figure 4).[160] Structurally interesting 3-alkenyl-3-hydroxy-2-oxindoles **169** were produced in high yields and selectivities (Scheme 68).

The same year, Tomita, Kanai, and Shibasaki reported a highly efficient copper-catalyzed direct addition of alkenyl boronates to a broad range of aldehydes by using chiral phosphine **130** (Figure 4; Scheme 69).[161]

Recently, Shono and Harada used BINOL derivative **75** (Figure 3) in the presence of $Ti(OiPr)_4$ to catalyze the

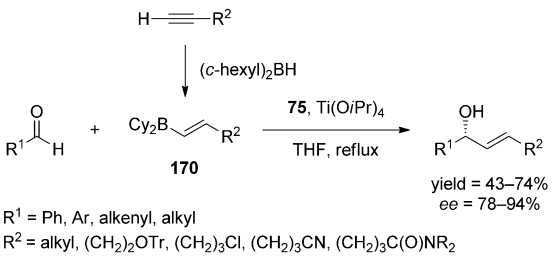


Scheme 68. Rhodium-catalyzed direct asymmetric addition of alkenylboronic acids to isatins.



Scheme 69. Copper-catalyzed asymmetric additions of alkenyl boronates to aldehydes. Pin = pinacolato.

addition of 1-alkenylboron reagents **170**, prepared in situ, to aldehydes (Scheme 70).[162] Various functional groups were tolerated, including nitriles and amides. The corresponding secondary allylic alcohols were obtained with high *ee* values.

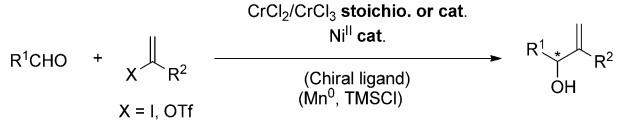


Scheme 70. Asymmetric direct addition of alkenylboron reagents to aldehydes.

3.1.2.6. 1,2-Additions of Vinylchromium Reagents (Nozaki–Hiyama–Kishi Reaction)

Only catalytic, asymmetric Nozaki–Hiyama–Kishi reactions will be discussed in this section.

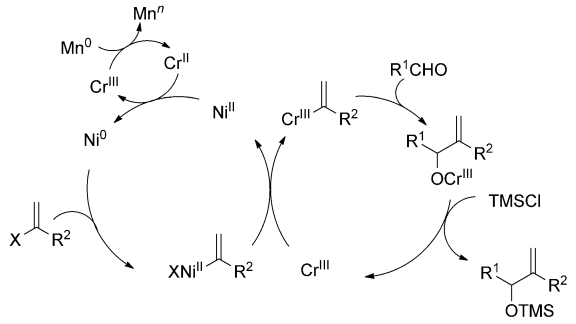
The Nozaki–Hiyama–Kishi (NHK) reaction is the 1,2-addition of organochromium reagents, derived from aryl, allyl, vinyl, alkyl, propargyl, and alkynyl halides or sulfonates to aldehydes.[163] Additions of vinylchromium reagents therefore generate allylic alcohols. Takai, Hiyama, Nozaki et al. first described the addition of alkenyl halides mediated by $CrCl_2$.[164] It was later shown by Kishi and co-workers[165] and by Takai, Nozaki et al.[166] that this reaction was in fact promoted by a catalytic amount of $NiCl_2$ (Scheme 71). It was



Scheme 71. Cr/Ni-catalyzed Nozaki–Hiyama–Kishi vinylation of aldehydes.

assumed that alkenyl iodides and triflates were activated by Ni^0, thereby forming alkenylnickel(II) intermediates that undergo transmetalation with chromium prior to 1,2-addition to the aldehyde. The major drawback of the reaction is that it requires superstoichiometric amounts of chromium, which considerably limits its synthetic utility. In 1996, Fürstner et al. overcame this limitation with the development of a catalytic variant of the NHK reaction.[167] Chromium loadings can be

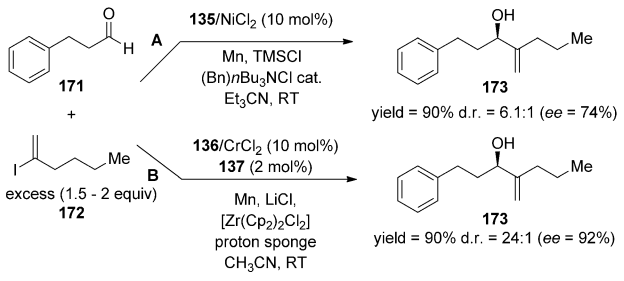
reduced to 15 mol% by using Mn^0 as a chromium reducing agent and TMSCl to dissociate the chromium alkoxide intermediate (Schemes 71 and 72). Recently, Klein, Berkessel, and co-workers used UV/Vis spectroscopy as well as electrochemical and spectroelectrochemical methods to study in detail the catalytic roles of nickel and chromium in the vinylation reaction (Scheme 72).[168] Since the seminal report



Scheme 72. Proposed mechanism of the Cr/Ni-catalyzed Nozaki–Hiyama–Kishi vinylation of aldehydes.

of Fürstner et al., enantioselective Cr/Ni-mediated vinylation processes have been developed by the research groups of Kishi and Berkessel, who used chiral sulfonamide and salen-type ligands, respectively (Figure 4).[163b] The main advantage of this Cr/Ni-mediated reaction compared to the methods discussed previously in this section is the high chemoselectivity of the organochromium reagents for aldehydes; however, the enantioselectivity of the process is often lower (see below).

In 2002, Kishi and co-workers described an enantioselective vinylation of dihydrocinnamaldehyde with vinyl iodide **172** catalyzed by chiral chromium(III) sulfonamide complex **135** (Figure 4) and $NiCl_2$.[169] Allylic alcohol **173** was obtained in nearly quantitative yield, although only with moderate enantioselectivity (Scheme 73, **A**). Later, Kishi and co-workers demonstrated that the nature of the Ni catalyst played a central role in this vinylation reaction, and tested many different Ni^{II} sources in combination with the chiral chromium complex derived from **136** for the coupling between **171** and **172**. The best results in terms of conversion and enantiomeric excess were obtained using nickel(II) complex **137** (Figure 4), which yielded the allylic alcohol with very high enantiomeric excess.[170] Here, $[Zr(Cp)_2Cl_2]$ was used instead



Scheme 73. Enantioselective Cr/Ni-catalyzed reaction of alkenyl halides.

of TMSCl to dissociate the chromium alkoxide (Scheme 73, **B**). The use of ligand **138**, which contains binding sites for both metals and thus places them in proximity, allowed significant reductions in both the amount of chromium used (1–2 mol%) and the molar ratio of the coupling partners (**171**/**172** 1:1 to 1:1.1).[171]

Over the last decade, effective, structurally diverse chiral sulfonamide ligands have been developed (**139**–**143**, Figure 4) for the selective synthesis of chiral allylic alcohols by Cr/Ni-mediated addition of alkenyl iodides to aldehydes.[172] The great efficiency of these new ligands has been demonstrated in the total synthesis of various challenging natural products and intermediates,[173] including building blocks of E7389 and halichondrin B/C[174] (Figure 6 and Schemes 74 and 75) as well as aplyrorine A-mycalolide B hybrid compound[175] (Figure 6,

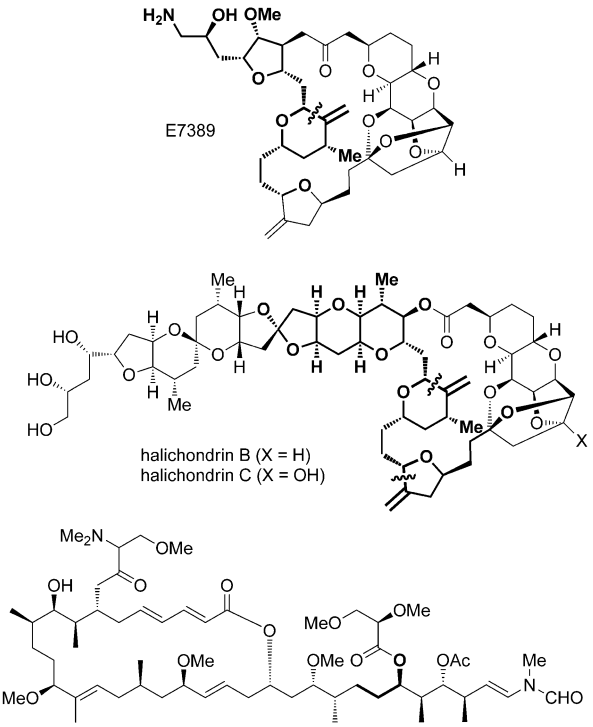
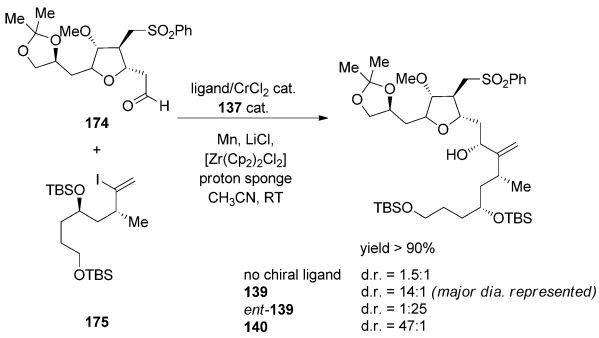
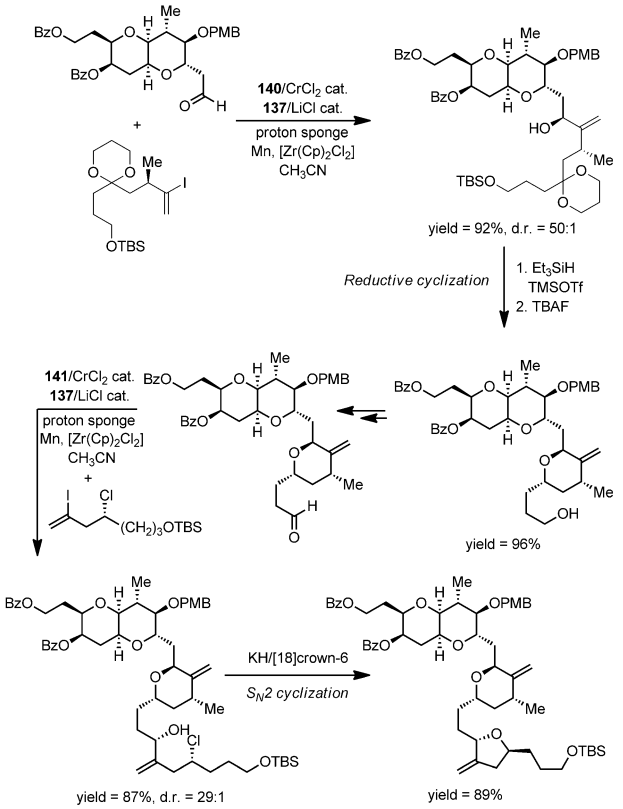


Figure 6. Structure of halichondrin B/C and the aplyronine A-mycalolide B hybrid compound.

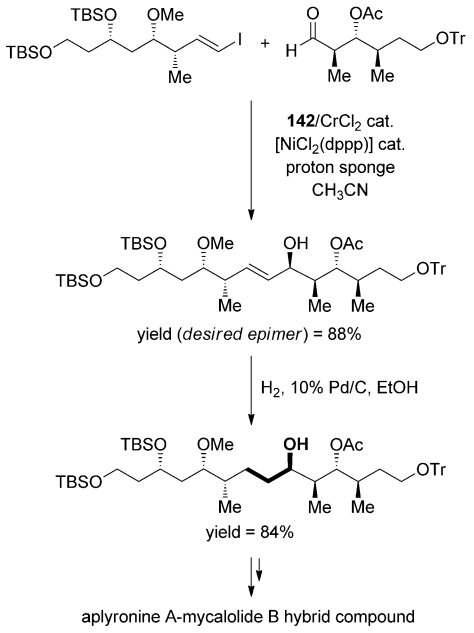


Scheme 74. Synthesis of the E7389 C20–C35 building block.



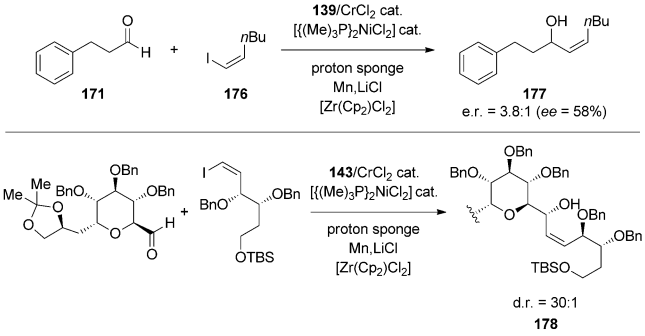
Scheme 75. Synthesis of the halichondrin C14–C38 building block.

Scheme 76). The coupling between **174** and **175** depicted in Scheme 74 shows that the chiral chromium catalysts **139** and **140** (Figure 4) can significantly improve the selectivity or override the natural selectivity of the substrates.



Scheme 76. Total synthesis of aplyronine A–mycalolide hybrid compound. dppp = propane-1,3-diylbis(diphenylphosphane).

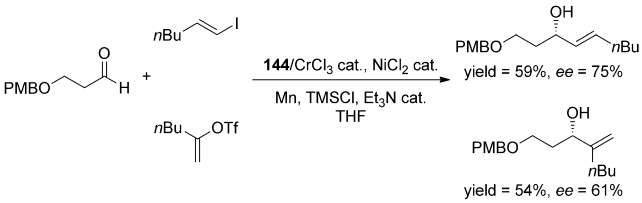
Recently, Kishi and co-workers studied the influence of the Ni^{II} source on the addition of (*Z*)-disubstituted alkenyl iodide **176** to **171** (Scheme 77).[176] They found that the coupling required less than two hours when $[\{(Me)_3P\}_2NiCl_2]$



Scheme 77. Synthesis of the palytoxin C8–C24 building block by Cr/Ni-catalyzed addition of a (*Z*)-alkenyl iodide to an aldehyde.

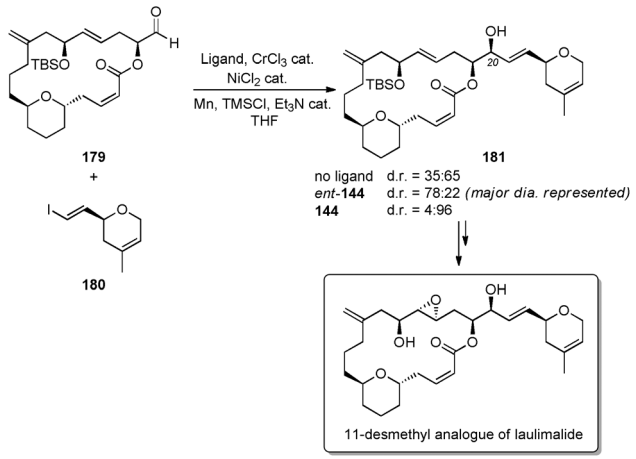
in combination with the chiral chromium complex derived from **139** was used (Figure 4), and afforded (*Z*)-allylic alcohol **177** with complete retention of the double-bond configuration, but with moderate enantioselectivity (Scheme 77). However, the matched combination between the substrate and chiral chromium complex derived from **143** (Figure 4) gave allylic alcohol **178**, a palytoxin building block,[177] with very high selectivity (Scheme 77).

In parallel with the work of Kishi and co-workers, Berkessel et al. used the chromium (II) complex preformed in situ from chiral salen-type ligand **144** (Figure 4).[178] However, the enantiomeric excess obtained was relatively moderate (Scheme 78). This catalytic system was then used in the



Scheme 78. Enantioselective Cr/Ni-mediated reaction with an alkenyl halide and triflate.

synthesis of desmethyl analogues of laulimalide, which exhibits nanomolar activity against cancer cell lines and is, therefore, an interesting structure for the development of anticancer agents (Scheme 79).[179] The natural selectivity of the reaction between **179** and **180** could be overridden by using *ent*-**144**, thereby producing the desired epimer of allylic alcohol **181** with satisfactory diastereoselectivity (d.r. = 78:22). Note that the matched case using **144** gave 20-*epi*-**181** with excellent diastereoselectivity (d.r. = 4:96).



Scheme 79. Total synthesis of the 11-desmethyl analogue of laulimalide.

3.1.3. 1,2-Additions of Allenyl- and Propargyl-Metal Reagents to Aldehydes

Yamamoto and co-workers have developed an efficient and general direct method to produce valuable enantioenriched (1,3-butadien-2-yl)carbinols **185** through an unprecedented, regioselective 1,2-addition of homoallenylbromide **184** to aldehydes catalyzed by **182** (Figure 7, Scheme 80).[180–182]

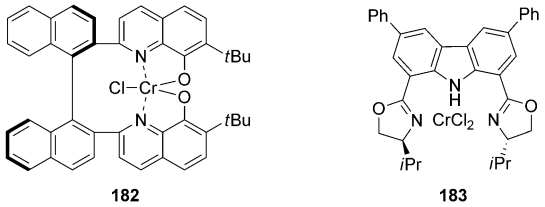
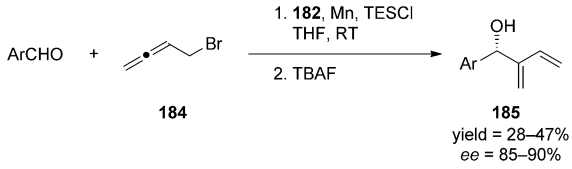


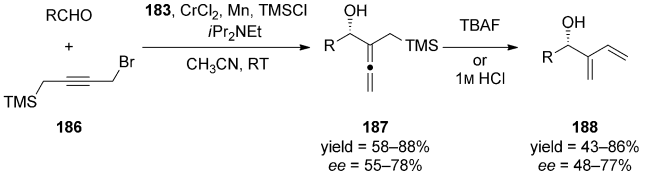
Figure 7. Chiral catalysts for the stereoselective access to (1,3-butadien-2-yl)carbinols.



Scheme 80. 1,2-Addition of homoallenyl bromide to aldehydes. TES = triethylsilyl.

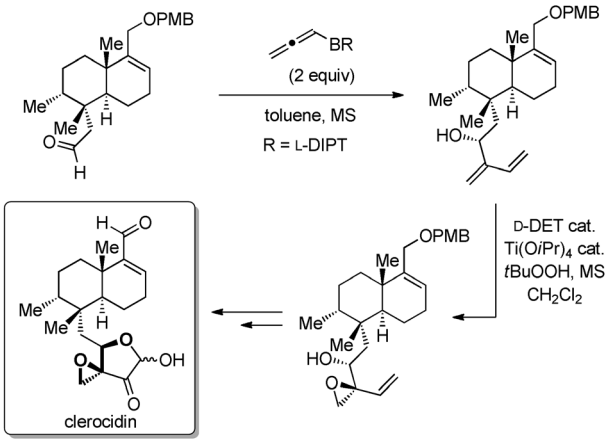
Durán-Galván and Connell have reported a method to access enantioenriched (1,3-butadien-2-yl)carbinols **188** by desilylation and isomerization of allenyl alcohols **187**, obtained by an enantioselective Nozaki–Hiyama allenylation[183] of aldehydes with 4-bromobut-2-ynyltrimethylsilane **186** (Figure 7, Scheme 81). However, both the yields and enantioselectivities were moderate.[184]

Brown's homoallenylboration[185] can be used as an alternative to Cr-mediated reactions, as exemplified by the



Scheme 81. 1,2-Addition of **186** to aldehydes.

total synthesis of clerocidin, an antiobiotic that exhibits antitumor activities (Scheme 82).[186] However, a superstoichiometric amount of the chiral boron reagent is required.



Scheme 82. Total synthesis of clerocidin. DET = diethyltartrate.

3.1.4. Alkylative and Reductive Coupling Reactions

Access to enantiomerically enriched allylic alcohols by alkylative or reductive coupling is an attractive alternative to vinylation reactions involving the preparation of the vinylmetal compound by hydrometalation and/or transmetalation, because of the improved atom economy and the minimization of metallic waste products. Pioneered by Ojima et al.,[187] reductive coupling has drawn considerable interest, mostly using nickel- and rhodium-based catalysts.[188] However, only a limited number of enantioselective processes, with a structurally diverse range of chiral ligands (Figure 3, Figure 8), have been developed.

In 2003, Jamison and co-workers used phosphine **189** (Figure 8) as a chiral ligand for the asymmetric, regioselective nickel-catalyzed reductive coupling of alkynes and aldehydes. This protocol allows access to trisubstituted secondary allylic alcohols **194** with moderate to excellent enantiomeric excess and excellent regioselectivity (Scheme 83).[189] However, a drawback of this method is that two equivalents of triethylborane are required as a terminal reductant.

In 2006, Sa-ei and Montgomery reported a highly diastereoselective reductive coupling between α-siloxy aldehydes and alkynylsilanes catalyzed by a nickel–N-heterocyclic carbene complex. The valuable *anti*-1,2-diols were isolated with excellent diastereoisomeric excess (> 98:2) by using various aldehydes and alkynes.[190]

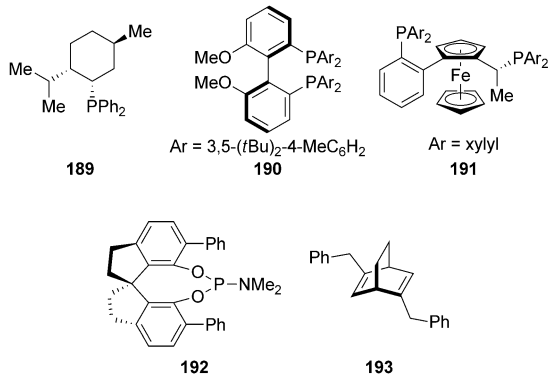
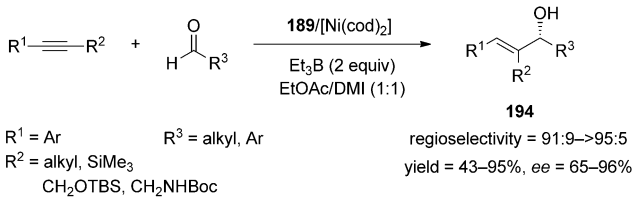


Figure 8. Chiral ligands for reductive and alkylative coupling.



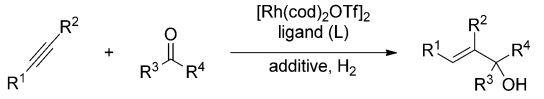
Scheme 83. Nickel-catalyzed reductive coupling of alkynes and aldehydes. DMI = *N*,*N*′ = dimethyl-2-imidazolidinone, Boc = *tert*-butoxycarbonyl.

More atom economic processes have been developed by Krische and co-workers by performing the reductive coupling under hydrogenation conditions, thereby avoiding the use of metal-based reducing agents and minimizing the formation of waste products.[191] Atom-economic rhodium-catalyzed asymmetric reductive coupling reactions of 1,3-diynes,[192,193] 1,3-enynes,[194–196] and acetylene[197] with various carbonyl compounds (aldehydes, glyoxal, ethyl glyoxylate, α-ketoesters) have been successfully developed, thereby affording structurally diverse allylic alcohols, which can be further elaborated, for example, by epoxidation, hydrogenation, and cross-metathesis (Table 4, Figure 8). Intramolecular reductive coupling of acetylenic aldehydes has also been developed under hydrogenation conditions to give cyclic allylic alcohols in excellent enantiomeric excess.[198]

This hydrogenative C–C coupling strategy has recently been employed by Krische and co-workers in an elegant total synthesis of bryostatin 7.[199] The rhodium-catalyzed reductive coupling of aldehyde **195** and enyne **196**, which yielded **197** in good yield and regioselectivity, was used as a key coupling step in the synthesis of fragment **198** (Scheme 84).

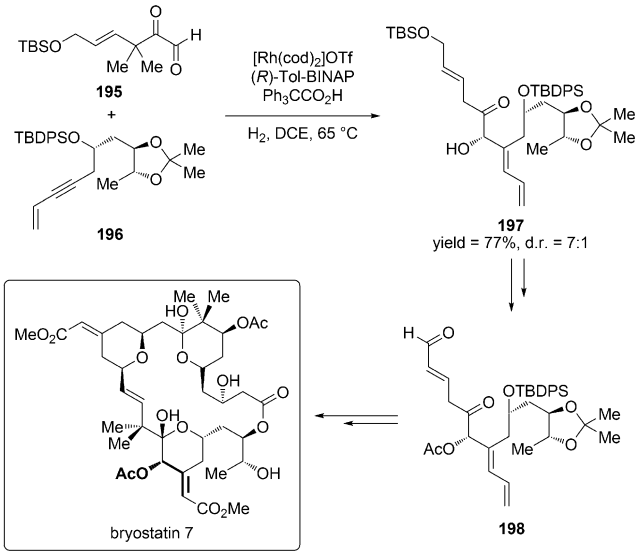
In contrast to reductive coupling reactions, alkylative coupling reactions involve the transfer of an alkyl group instead of a hydrogen atom. The advantage of alkylative coupling reactions is that tetrasubstituted allylic alcohols can be obtained directly. Zhou and co-workers have used dimethylzinc as an alkylating agent for intermolecular, asymmetric Ni-catalyzed alkylative coupling of alkynes and aldehydes (Scheme 85).[200] Allylic alcohols **199** were obtained with moderate to excellent regioselectivity; however, high enantiomeric excess was achieved in all cases. Hayashi and co-workers have developed an intramolecular arylative coupling process using a chiral rhodium catalyst derived from chiral diene **193** (Figure 8) in combination with arylboronic acids

Table 4: Reductive coupling under catalytic hydrogenation conditions.

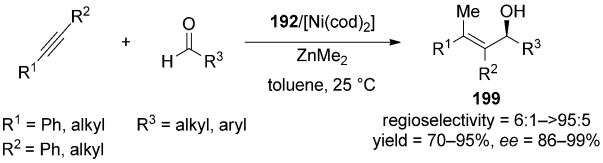


Ref.	R^1	R^3	R^4	L	Yield [%]	*ee* [%]
[192]		H		**82**	55–96[a]	89–99
[193]		H		**190**	71–84[b,c]	89–94
[194]		H		**190**	70–82[b,d]	86–97
[195]		Ar alkyl		**191**	73–98[b,d]	90–93
[196]		H	Ar_{Het}	**81**/**191**	71–96[b,d]	90–>99
[197]	H = R^2	H	FG-alkyl	**190**	77,85[d–f]	89,88

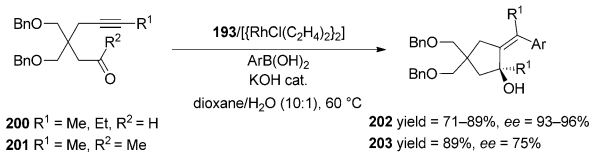
[a] Regioselectivity = 4:1 to >99:1. [b] Regioselectivity = >99:1; [c] R^2 = TMS. [d] In the presence of a catalytic amount of Ph_3CCO_2H. [e] In the presence of 2 equiv of Na_2SO_4. [f] Disubstituted (*Z*)-allylic alcohols were obtained.



Scheme 84. Reductive coupling in the total synthesis of bryostatin 7. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 85. Intermolecular nickel-catalyzed alkylative coupling.

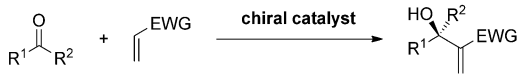


Scheme 86. Rhodium-catalyzed arylative cyclization.

(Scheme 86).[201] Various ynals **200** and an ynone **201** were cyclized to the corresponding tetrasubstituted cyclic allylic alcohols **202** and **203** in high yield and excellent enantiomeric excess.

3.1.5. Morita–Baylis–Hillman Reaction

The Morita–Baylis–Hillman (MBH) reaction is a powerful, atom-economic C–C bond-forming reaction and has drawn considerable interest since the seminal reports of Morita et al. as well as Baylis and Hillman.[202] This reaction consists of the coupling of an acceptor-activated alkene with a carbonyl electrophile catalyzed mostly by tertiary amines or phosphines. Aldehydes and ketones have been widely used as electrophiles, thus allowing the formation of secondary and tertiary allylic alcohols, respectively. Since all MBH reactions of carbonyl compounds generate allyllic alcohols, it can be considered as a general method for their synthesis. A range of chiral catalysts, including cinchona alkaloid derivatives,[203] chiral DMAP analogues,[204] BINOL-derived Brønsted acids,[205] and binaphthyl-based amine-thioureas,[206] have been employed to afford enantioenriched adducts (Scheme 87). However, as a large number of comprehensive

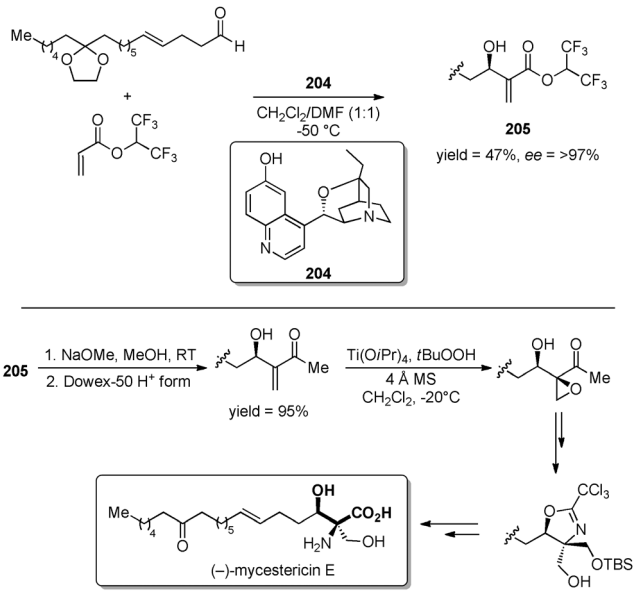


Scheme 87. Enantioselective Morita–Baylis–Hillman reaction. EWG = electron-withdrawing group.

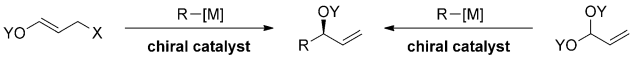
reviews have been published on the development of the asymmetric MBH reaction, the plethora of ligands developed, and the applications in organic synthesis, this reaction will not be discussed in detail in this Review.[207] An illustrative example is the total synthesis of (−)-mycestericin E by Hatakeyama and co-workers which utilized an enantioselective, cinchona alkaloid catalyzed MBH reaction as a key step (Scheme 88).[208]

3.2. Allylic Substitution Reactions Using C Nucleophiles

Allylic substitution has emerged as a general and powerful method for accessing allylic alcohols (Scheme 89; for allylic substitution in dynamic kinetic resolutions see Section 2.2). However, despite the broad range of catalytic systems reported for the formation of C–C bonds by allylic substitution,[209] few of them permit the formation of enantioenriched allylic alcohols (Scheme 89).



Scheme 88. Total synthesis of (−)-mycestericin E.

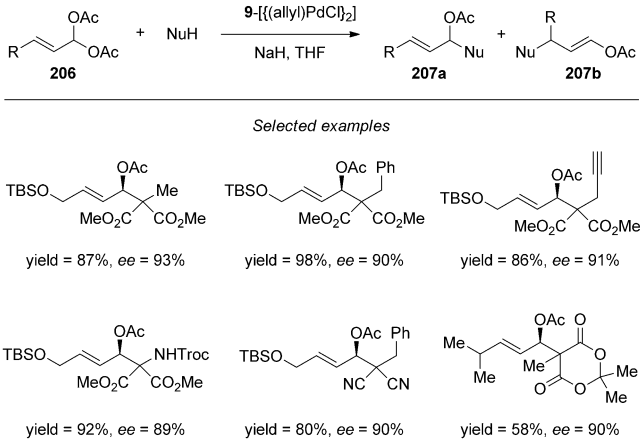


Scheme 89. Allylic substitution using C nucleophiles.

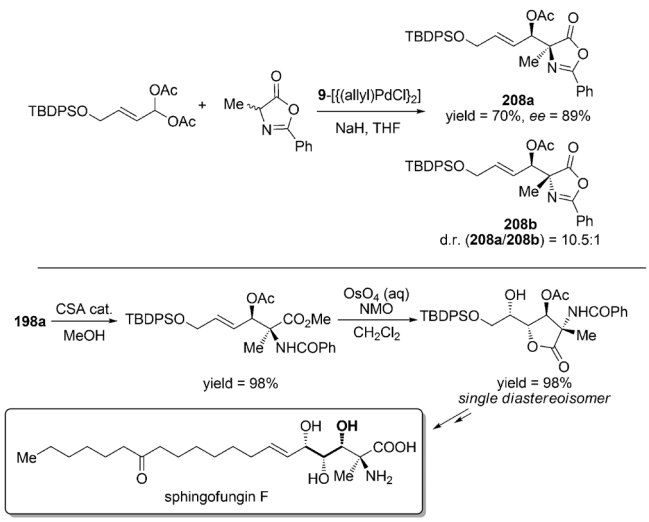
3.2.1. Palladium-Catalyzed Reactions

Trost et al. have used chiral palladium catalyst **9**-[{allylPdCl}$_2$] (Figure 2) for the enantioselective alkylation of geminal dicarboxylates **206** with various C nucleophiles (Scheme 90). Allylic acetates **207a** were isolated with excellent enantiomeric excess and perfect regioselectivity.[210]

This method was successfully applied to the synthesis of sphingofungins E and F, as depicted in Scheme 91.[211]



Scheme 90. Enantioselective palladium-catalyzed alkylation of geminal dicarboxylates. Troc = trichloroethoxycarbonyl.



Scheme 91. Total synthesis of sphingofungin F.

3.2.2. *Copper-Catalyzed Reactions*

Feringa and co-workers have used chiral copper complexes derived from Taniaphos ligand **209** and phosphoramidite ligand **210**[212] (Figure 9) to catalyze the enantioselective

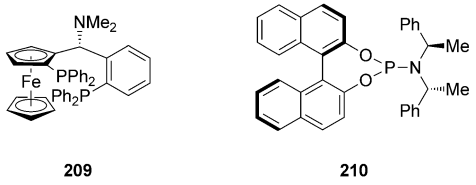
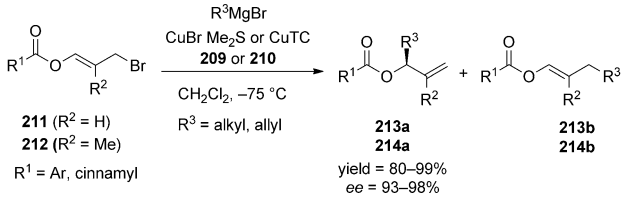


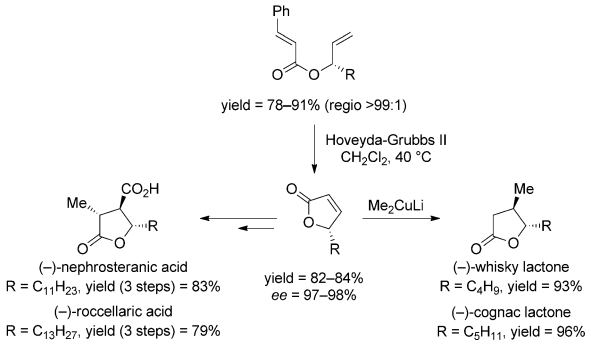
Figure 9. Chiral phosphine ligands for the copper-catalyzed alkylation of 3-bromopropenyl esters.

allylic alkylation[213] (S_N2'-type substitution) of 3-bromopropenyl esters **211** and **212** by using alkyl and functionalized-alkyl Grignard reagents[214] as nucleophiles (Scheme 92).[215] This powerful method yields enantioenriched disubstituted allylic esters **213a**, with perfect regioselectivity for the branched product ($R^2 = H$, **213a**/**213b** > 99:1) and excellent enantiomeric excess. However, the alkylation of trisubstituted ester **212** ($R^2 = Me$) gave allylic esters **214a** with only moderate regioselectivity (2:1–2.5:1), although with excellent enantiomeric excess.



Scheme 92. Enantioselective copper-catalyzed alkylation of 3-bromopropenyl esters. TC = 2-thiophenecarboxylate.

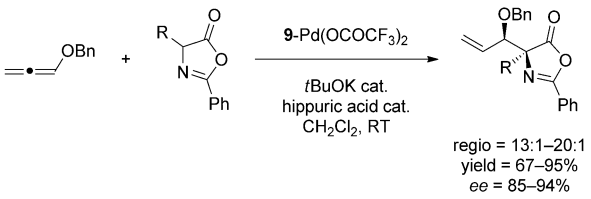
The synthetic utility of this allylic alkylation has been demonstrated by the synthesis of a series of natural butenolides, including (−)-whisky lactone, (−)-cognac lactone, (−)-nephrosteranic acid, and (−)-roccellaric acid (Scheme 93).[216]



Scheme 93. Synthesis of natural butenolides.

3.3. *Addition of Pronucleophiles to Alkoxyallenes*

In 2003, Trost et al. reported a highly regio- and stereoselective addition of azalactones to alkoxyallenes that affords useful allylic alcohol precursors of quaternary amino acids (Scheme 94).[217]



Scheme 94. Palladium-catalyzed addition of azalactones to alkoxyallenes.

4. *Access by Stereoselective C–O Bond Formation*

4.1. *Allylic Substitution Reactions Using O Nucleophiles*

In contrast to allylic substitution with C nucleophiles, allylic substitution reactions with O nucleophiles yield derivatives of allylic alcohols. A broad range of catalyst systems have been developed by using palladium, ruthenium, iridium, copper, and rhodium complexes derived from chiral ligands for this transformation (Figure 10).[209] As the reactions of racemic allylic substrates have been discussed previously (Section 2.2), this section will only deal with allylic substitution reactions of prochiral allylic substrates.

4.1.1. *Palladium-Catalyzed Reactions*

Similar to the palladium-catalyzed dynamic kinetic transformations (DYKAT) discussed previously (Section 2.2.1), Trost et al. used chiral palladium complexes **9** and **11** (Figure 2) to catalyze asymmetric allylic substitution reactions of unsymmetrical linear allylic carbonates **223** with

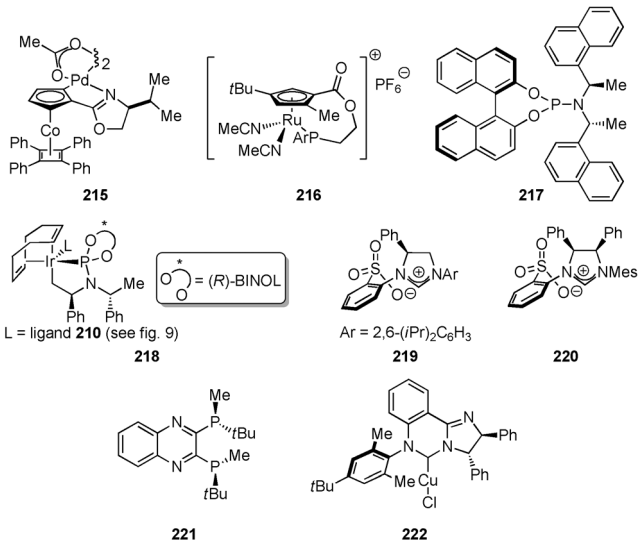
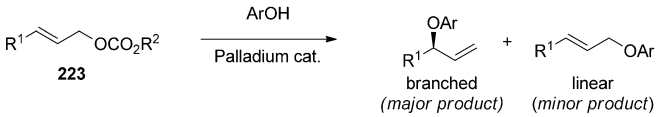
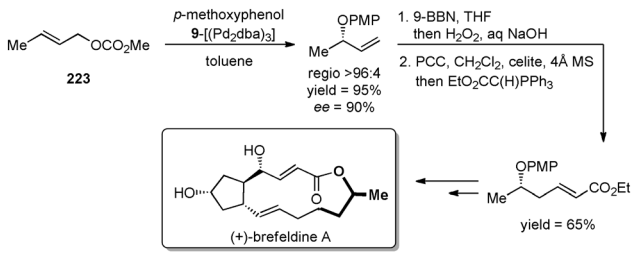


Figure 10. Chiral ligands/catalysts for allylic substitution involving O nucleophiles.

phenol nucleophiles (Scheme 95).[39,218] Good regioselectivities for the branched allylic ether and high enantiomeric excess were usually obtained, as demonstrated by the total syntheses of (+)-brefeldine A,[219] callipeltoside A, and deschlorocallipeltoside A[220] depicted in Schemes 96 and 97.

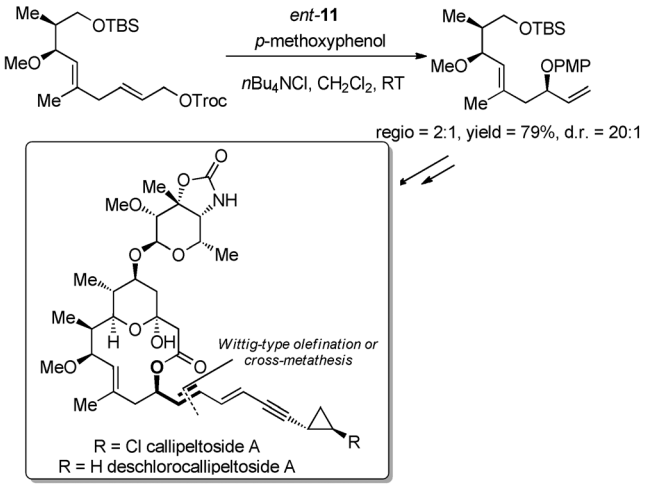


Scheme 95. Enantioselective palladium-catalyzed allylic substitution of linear allylic carbonates.

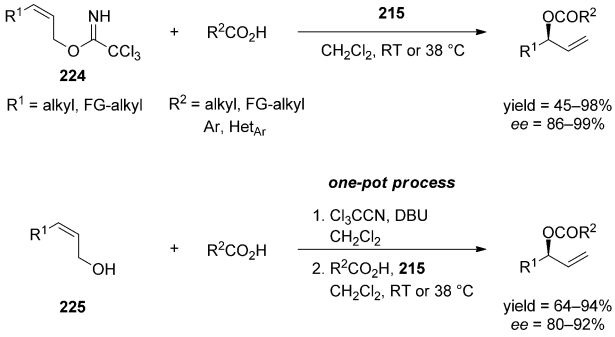


Scheme 96. Total synthesis of (+)-brefeldine A. 9-BBN = 9-borabicyclo-[3.3.1]nonane, PMP = *p*-methoxyphenyl, PCC = pyridinium chlorochromate.

Overman and co-workers have synthesized chiral allylic esters from trichloroacetimidate derivatives of prochiral (*Z*)-allylic alcohols **224** (Scheme 98).[221,222] Various allylic esters were isolated with excellent enantiomeric excess and impressive regioselectivity (up to 800:1) in favor of the branched adducts by using chiral palladium complex **215** (Figure 10). This transformation can be carried out in a one-pot process from (*Z*)-2-alken-1-ols **225**, thereby affording allylic esters with slightly lower enantiomeric excess.



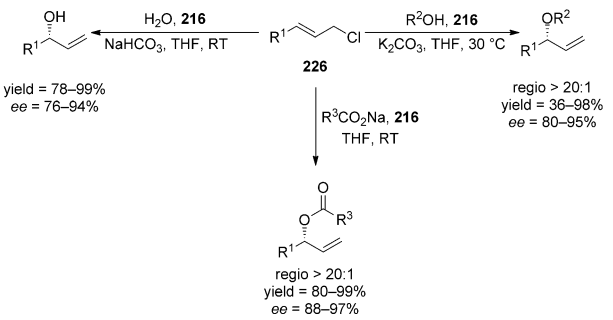
Scheme 97. Total synthesis of callipeltoside A and deschlorocallipeltoside A.



Scheme 98. Palladium-catalyzed allylic substitution of trichloroacetimidates. FG = functional group.

4.1.2. ***Ruthenium-Catalyzed Reactions***

Onitsuka et al. have used planar-chiral ruthenium complex **216** (Figure 10) to catalyze enantioselective allylic substitution reactions of allylic chlorides **226**.[223–225] Alcohols,[223] sodium carboxylates,[224] and water[225] proved to be compatible nucleophiles, and afforded branched allylic ethers, esters, and alcohols, respectively (Scheme 99), with excellent enantiomeric excess and regioselectivity.

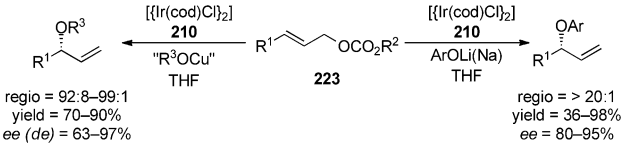


Scheme 99. Ruthenium-catalyzed allylic substitution reactions.

Related syntheses of enantioenriched allylic ethers and alcohols by ruthenium-catalyzed allylic substitution of allylic chlorides **226** have been reported by Bruneau, Renaud, and co-workers by using chiral bisoxazoline ligands.[226] However, these methods suffer from limited scope and/or low enantiomeric excess.

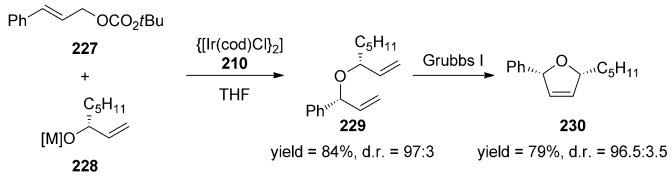
4.1.3. *Iridium-Catalyzed Reactions*

Iridium complexes have also proved to be efficient catalysts for the synthesis of branched allylic alcohols and their derivatives.[66,227] Hartwig and co-workers used phosphoramidite ligand **210** (Figure 9) in combination with [{Ir(cod)Cl}$_2$] for the allylic substitution of prochiral allylic carbonates **223** with lithium (or sodium) phenoxides[228] and copper alkoxides[229] (Scheme 100). This reaction could be



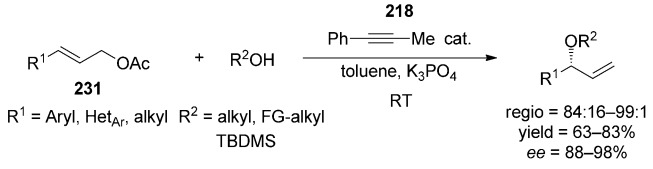
Scheme 100. Iridium-catalyzed allylic substitution with alkoxides.

employed for the diastereoselective synthesis of *cis*-disubstituted dihydrofuran **230**, through the reaction of **227** and copper alkoxide **228**, derived from (*R*)-1-octen-3-ol (Scheme 101).[229]



Scheme 101. Diastereoselective access to disubstituted dihydrofurans.

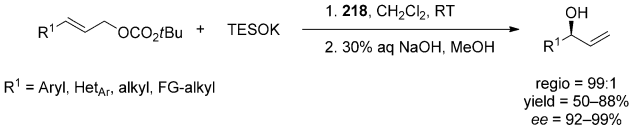
Later, Hartwig and co-workers reported a method involving cyclometalated iridium complex **218** (Figure 10)[230] for the enantioselective synthesis of allylic ethers from allylic acetates **231** and alcohols (Scheme 102).[231] This enantioselective etherification was compatible with a broad range of allylic acetates and alcohols, including silanols, which are particularly useful nucleophiles, as the products can be easily deprotected. A catalytic amount of alkyne was used to suppress the formation of vinyl ether side products. The



Scheme 102. Direct enantioselective iridium-catalyzed etherification. TBDMS = *tert*-butyldimethylsilyl.

authors suggest that it poisons an isomerization catalyst present in small quantities.

Carreira and co-workers have also used **218** (Figure 10) for the enantioselective allylation of potassium triethylsiloxide (Scheme 103).[232] The product allylic siloxides could be deprotected under mild conditions to afford allylic alcohols in high yield and excellent enantiomeric excess.

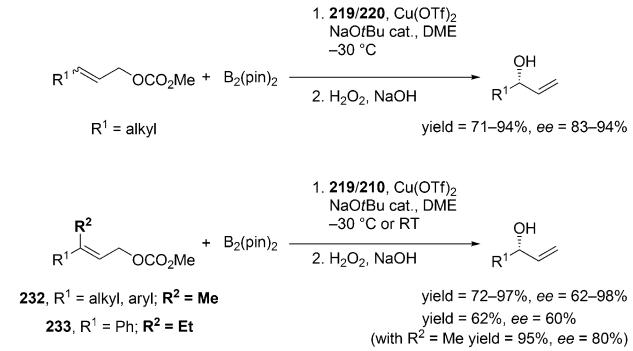


Scheme 103. Enantioselective iridium-catalyzed access to allylic alcohols using TESOK.

Recently, You and co-workers have reported a new route to enantiopure chromene and 2,5-dihydrobenzo[*b*]oxepine derivatives based on an enantioselective iridium-catalyzed allylic etherification/ring-closing metathesis sequence.[233]

4.1.4. *Copper-Catalyzed Reactions*

Guzman-Martinez and Hoveyda reported the use of the copper complexes of chiral bidendate NHCs **219** and **220** (Figure 10) to catalyze the allylic substitution of allylic carbonates with bis(pinacolato)diboron (Scheme 104).[234]



Scheme 104. Copper-catalyzed allylic substitution with B_2Pin_2. DME = 1,2-dimethoxyethane.

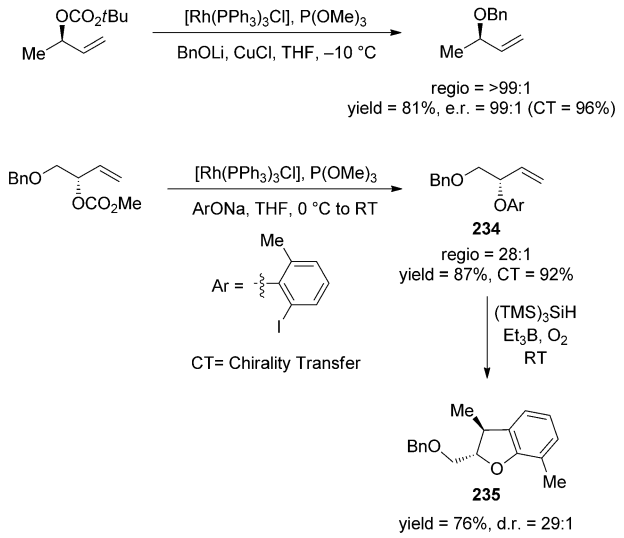
The allylic boronates were obtained with excellent enantioselectivities, whilst subsequent oxidation with hydrogen peroxide afforded allylic alcohols in high yields. Both *Z*- and *E*-disubstituted allylic carbonates were good reaction partners, and the efficiency of this new method was demonstrated with the synthesis of various tertiary allylic alcohols from trisubstituted allylic carbonates **232**. Whilst perfect regioselectivity for the branched adduct was observed in most cases, the use of ethyl-substituted allylic carbonate **233** led to 20% of the corresponding linear allylic alcohol, along with a reduced enantiomeric excess of the branched product.

Highly efficient asymmetric copper-catalyzed allylic substitution reactions involving bis(pinacolato)diboron as the nucleophile have also been reported by Ita, Sawamura, and

co-workers[235] as well as McQuade and co-workers,[236] who used **221** or **222** as the chiral ligand or catalyst (Figure 10).

4.1.5. Rhodium-Catalyzed Reactions

Evans et al. have reported the enantiospecific rhodium-catalyzed allylic etherification of branched allylic carbonates with sodium phenolates or copper alkoxides (Scheme 105).[237,238] As this method requires enantiopure

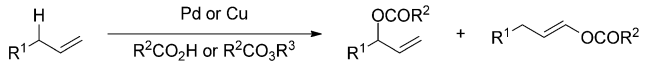


Scheme 105. Enantiospecific rhodium-catalyzed etherification.

starting materials, its utility is limited; however, the transformation of **234** into dihydrobenzo[*b*]furan derivative **235** with very high diastereoselectivity demonstrates the usefulness of the allylic ethers formed (Scheme 105).[237]

4.2. Allylic C–H Oxidation Reactions

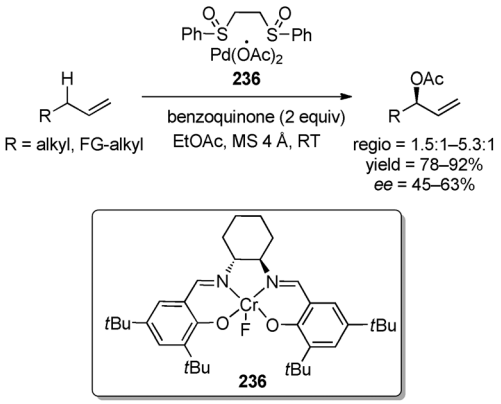
A particularly attractive approach for accessing allylic alcohol derivatives is allylic C–H oxidation, as simple alkenes can be transformed in one step into valuable allylic building blocks. In contrast to allylic substitution, no preactivation of the substrate is required, thereby reducing the amount of waste. To date, most of the studies in this field have focused on the use of palladium and copper catalysts (Scheme 106).[239]



Scheme 106. Allylic C–H oxidation of alkenes.

4.2.1. Palladium-Catalyzed Reactions.

Although several palladium-catalyzed C–H esterification methods have been developed,[240,241] only that described by White and co-workers yields the branched isomer selectively.[242] Enantioenriched allylic acetates can be obtained from terminal alkenes and acetic acid when the bissulfoxide-Pd^{II} complex is combined with a chiral Lewis acid and an excess (2 equiv) of benzoquinone as the terminal oxidant (Scheme 107).[243] This unique enantioselective palladium-



Scheme 107. Enantioselective palladium-catalyzed C–H oxidation.

catalyzed C–H oxidation process is tolerant to various functional groups (ester, amide, protected alcohol); however, only moderate regioselectivity and enantiomeric excess were obtained.

4.2.2. Copper-Catalyzed Reactions (Kharasch–Sosnovsky Reaction)

Since the seminal report of Kharasch and Sosnovsky,[244] the copper-catalyzed allylic C–H oxidation of alkenes with peresters has drawn considerable attention. Important contributions to the development of efficient enantioselective processes were made by the research groups of Pfaltz,[245] Andrus,[246] Singh,[247] Katsuki,[248] and Kim[249] by using bisoxazolines **237**–**239**,[245,246] pybox **240**,[247] trisoxazolines **241**,[248] and iminophosphoranylferrocenes **242**[249] as ligands (Figure 11). However, satisfactory enantiomeric excess was only obtained with symmetric cyclic alkenes (Scheme 108). As this method suffers from a very limited scope, and

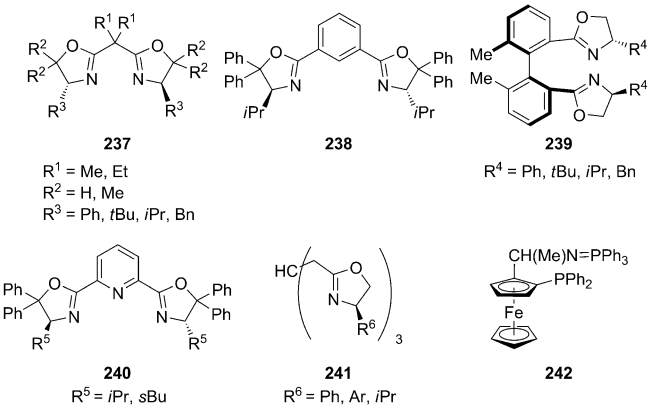
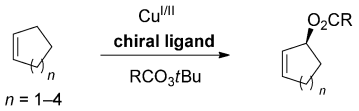


Figure 11. Chiral ligands in the copper-catalyzed allylic C–H oxidation of alkenes.



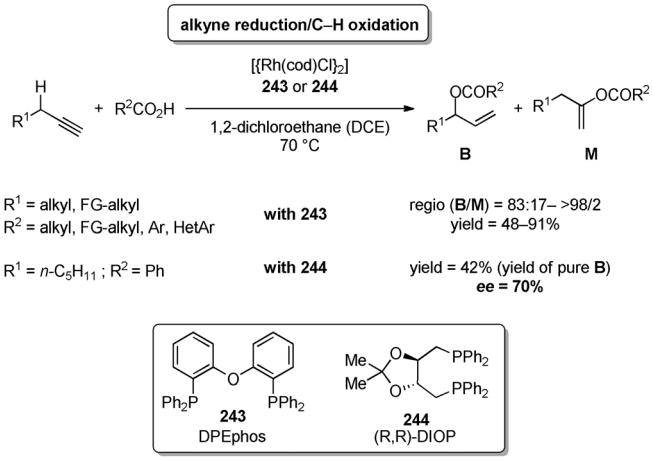
Scheme 108. Copper-catalyzed allylic C–H oxidation of symmetric cyclic alkenes.

excellent reviews have already been published in this field, this topic will not be discussed in detail.[250]

4.3. Addition of O Nucleophiles to π Systems

4.3.1. Redox-Neutral Coupling of Alkynes

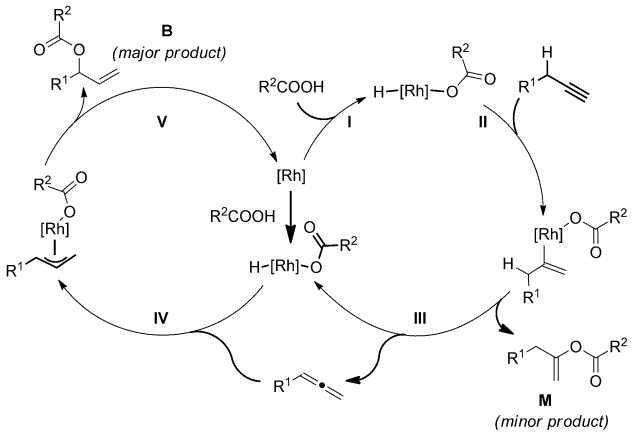
Recently, Breit and co-workers reported a general, atom-economic route to branched allylic esters by an unusual rhodium-catalyzed coupling of terminal alkynes with carboxylic acids (Scheme 109).[251] This transformation is a redox-



Scheme 109. Redox-neutral atom-economic rhodium-catalyzed coupling of terminal alkynes with carboxylic acids.

neutral, formal propargylic C–H oxidation with a concomitant hydride shift.[252–255] The alkyne serves as an internal oxidant that is reduced in situ to an alkene, thereby avoiding the need for a (super)stoichiometric amount of external oxidant, in contrast to the allylic C–H oxidation reactions discussed earlier. The use of a catalyst system of $[\{Rh(cod)Cl\}_2]$/**243** led to racemic branched allylic esters in high yields and excellent selectivity for the branched product **B** over the *gem*-enol ester **M** (Markovnikov product). This simple atom-economic procedure is compatible with many functional groups and tolerates structural variation on both the alkyne and the carboxylic acid reaction partner. An enantioenriched allylic ester derived from benzoic acid and 1-octyne could be obtained in moderate yield but with promising enantioselectivity by using chiral phosphine DIOP **244**, which has a similar bite angle and flexibility range as **243**.

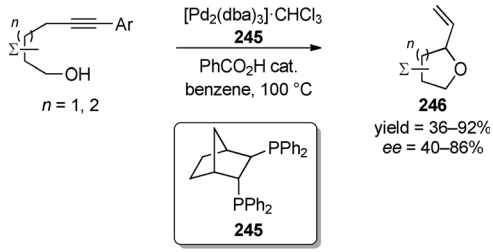
The proposed mechanism of this coupling is depicted in Scheme 110. After oxidative addition of the carboxylic acid to the Rh^I center (step I), Markovnikov-selective hydrometalation generates a σ-vinylrhodium(III) species (step II). This



Scheme 110. Proposed mechanism for the rhodium-catalyzed coupling of terminal alkynes with carboxylic acids.

undergoes either reductive elimination to form *gem*-enol ester by-product **M** or β-hydride elimination to produce an allene (step III). Hydrometalation of this allene forms a π-allylrhodium species (step IV), which after reductive elimination yields branched allylic ester **B** (step V).

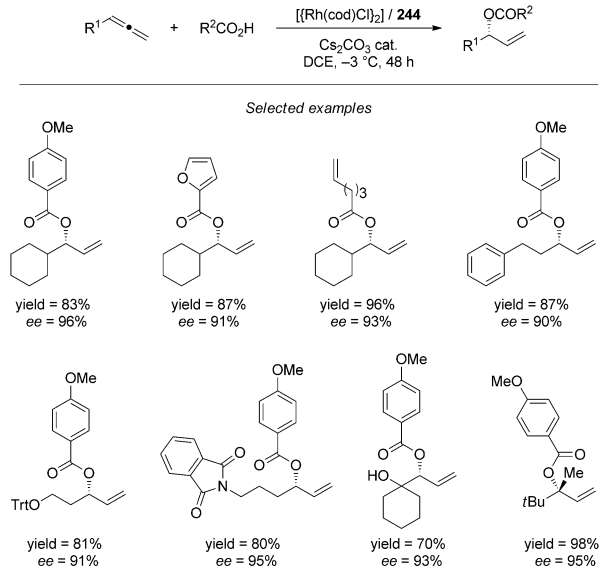
Yamamoto and co-workers reported an intramolecular enantioselective palladium-catalyzed hydroalkoxylation of alkynes, which is believed to proceed by a similar mechanism (Scheme 111). Disubstituted allylic furans and pyrans **246** were obtained in moderate to good yields and enantioselectivities.[256]



Scheme 111. Intramolecular enantioselective palladium-catalyzed hydroalkoxylation of alkynes.

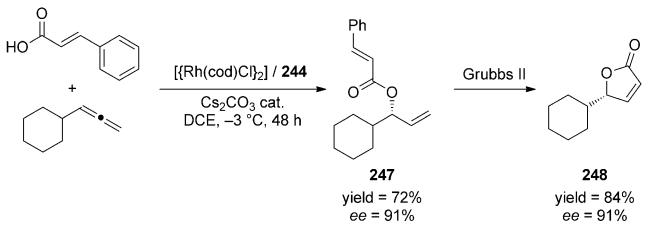
4.3.2. Enantioselective Coupling Reactions with Allenes

Since allenes are a readily accessible and remarkably stable substrate class,[257] Breit and co-workers investigated whether allenes undergo coupling with carboxylic acids, and were able to develop a highly enantioselective and atom-economic rhodium-catalyzed protocol for the synthesis of allylic esters.[258] Various allenes reacted with carboxylic acids under mild conditions in the presence of Rh^I/**244** to afford allylic esters in excellent enantiomeric excess and perfect regioselectivity (Scheme 112).[259] The method allows the synthesis of tertiary allylic alcohols with excellent enantioselectivity from 1,1-unsymmetrically disubstituted allenes (Scheme 112).



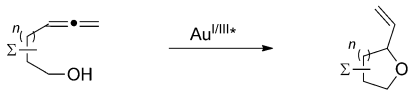
Scheme 112. Enantioselective rhodium-catalyzed coupling of allenes with carboxylic acids.

The allylic ester derived from cinnamic acid **247** could be cyclized to the corresponding γ-butyrolactone **248**, in very good yield without loss of chirality (Scheme 113).



Scheme 113. Access to enantioenriched γ-butyrolactone.

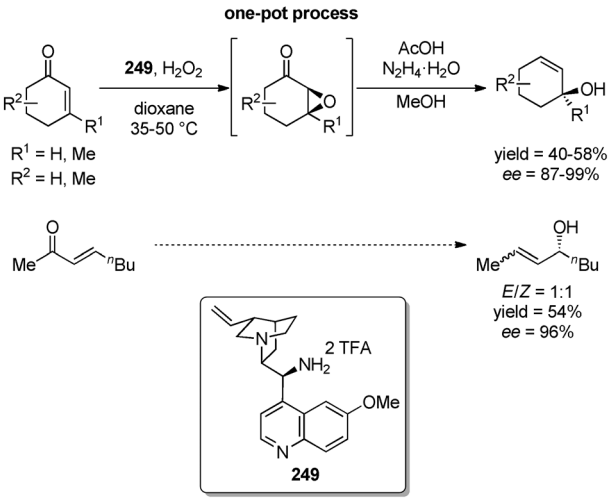
Numerous highly enantioselective gold-catalyzed cyclization reactions of hydroxyalkylallenes have been developed (Scheme 114). However, as many reviews have been published on this subject,[260] these reactions will not be discussed in this Review.



Scheme 114. Enantioselective gold-catalyzed cyclization of alkoxyallenes.

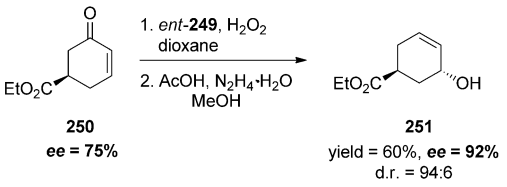
4.4. Other Reactions

Jørgensen and co-workers recently reported a method to access enantioenriched, cyclic allylic alcohols from simple enones by a one-pot organocatalytic epoxidation/Wharton reaction sequence (Scheme 115).[261] Various substituted six- and seven-membered cyclic enones were suitable substrates, which afforded secondary and tertiary allylic alcohols with



Scheme 115. One-pot organocatalytic epoxidation/Wharton reaction sequence.

impressive levels of enantioselectivity, although moderate yields. However, a mixture of geometric isomers (*E*/*Z* ratio = 1:1) was obtained when acyclic enones are used. The use of enantioenriched cyclohexenone **250** led to enantioenrichment, and allylic alcohol **251** was obtained with excellent levels of enantio- and diastereoselectivity in favor of the *trans* adduct (Scheme 116).

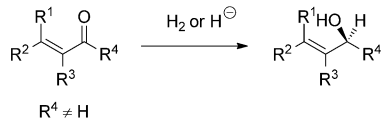


Scheme 116. Synthesis of disubstituted cyclohexenol **251**.

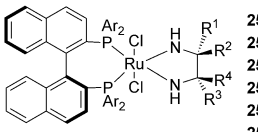
5. Access from Stereoselective C–H bond Formation

An alternative approach to the synthesis of allylic alcohols is the 1,2-reduction of α,β-unsaturated ketones (Scheme 117). The two main methods to achieve this are reduction by hydrogenation or by metal hydride sources.

Noyori and co-workers have developed a highly efficient catalytic system for the hydrogenation of various α,β-unsaturated ketones by using Ru^{II}-phosphine-1,2-diamine catalyst systems **252a–e** (Figure 12).[262–266] The efficiency of these complexes was exemplified by the hydrogenation of β-ionone,[263,265] (*R*)-carvone,[264] (*R*)-pulegone,[264] and 2,4,4-trimethyl-2-cyclohexenone.[264,266] These produce allylic alco-



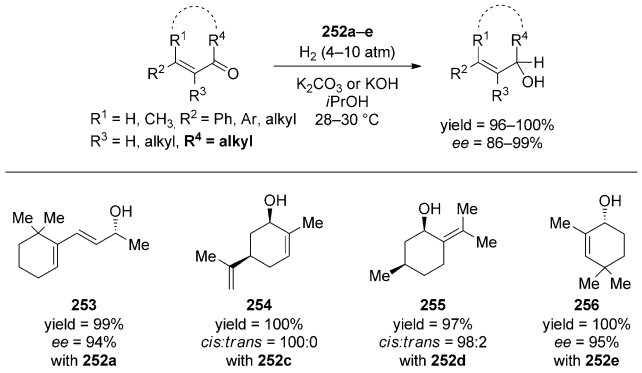
Scheme 117. Access to enantioenriched allylic alcohols by 1,2-reduction of α,β-unsaturated ketones.



252a Ar = 3,5-Me-Ph, $R^1 = R^2$ = 4-MeOPh, R^3 = *i*Pr
252b Ar = 3,5-Me-Ph, R^1 = H, R^2 = Ph, R^3 = Ph, R^4 = H
252c Ar = Ph, R^1 = Ph, R^2 = H, R^3 = H, R^4 = Ph
252d Ar = Ph, R^1 = H, R^2 = Ph, R^3 = Ph, R^4 = H
252e Ar = 4-Me-Ph, R^1 = Ph, R^2 = H, R^3 = H, R^4 = Ph
252f Ar = 4-Me-Ph, $R^1 = R^2 = R^3$ = H, R^4 = Ph

Figure 12. Chiral catalysts for the 1,2-reduction of α,β-unsaturated ketones.

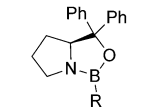
hols **253**, **254**, **255**, and **256**, respectively, which are important intermediates in the flavor and fragrance industry (Scheme 118).



Scheme 118. Asymmetric hydrogenation of α,β-unsaturated ketones using Noyori's catalyst system.

In 2008, Ohkuma and co-workers reported the first highly enantioselective hydrogenation of aryl vinyl ketones by using a derivative of ruthenium complex **252 f** (Figure 12).[267] The corresponding allylic alcohols were isolated in very high yield and excellent enantiomeric excess.

The Corey–Bakshi–Shibata (CBS) reduction of enones using chiral oxazaborolidines **257** as catalysts and boranes as the reducing agents has also proved to be an effective method to access enantioenriched allylic alcohols (Figure 13).[268,269]

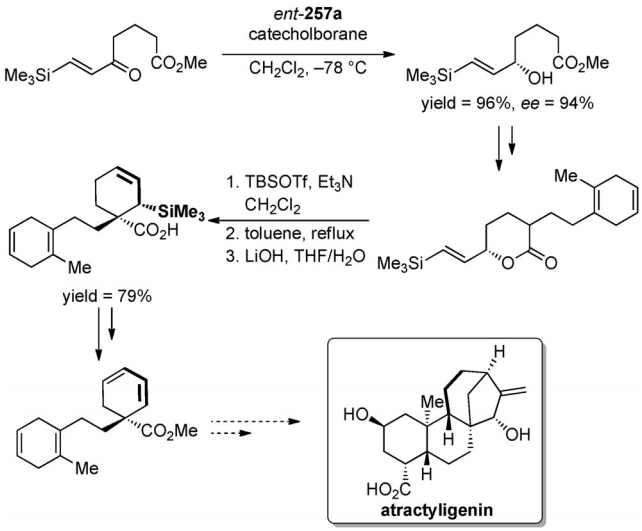


257a R = CH_2SiMe_3
257b R = Me

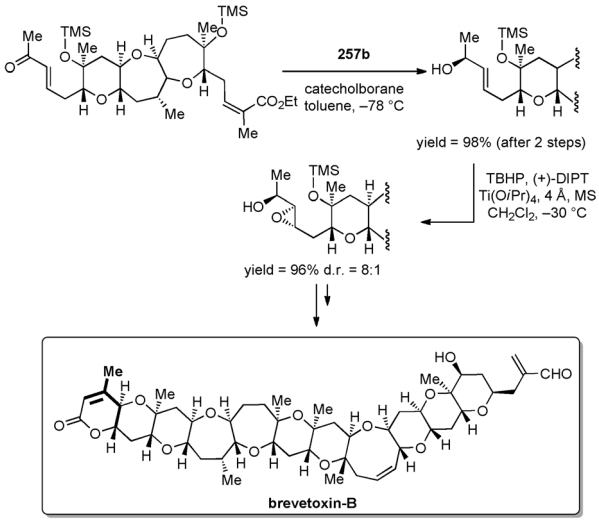
Figure 13. Chiral oxazaborolidines for the CBS reduction.

The utility of this method has been demonstrated by numerous applications in the total synthesis of natural products,[270] such as atractyligenin,[270j] brevetoxin-B,[270k] and (−)-frondosin-B,[270l] as depicted in Schemes 119–121. These syntheses provide further examples of the versatility of the allylic alcohol motif.

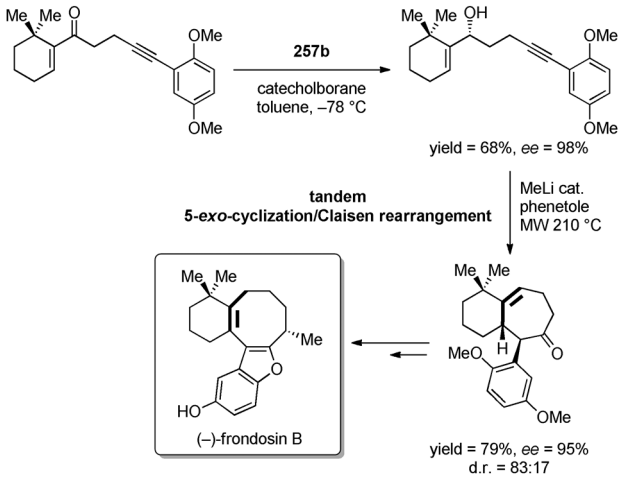
Recently, Aue and Lipshutz have reported regio- and enantioselective copper-catalyzed reductions of β,β-disubstituted enones by using SEGPHOS-derivative **130** (Figure 4) as



Scheme 119. Enantioselective route to atractyligenin.

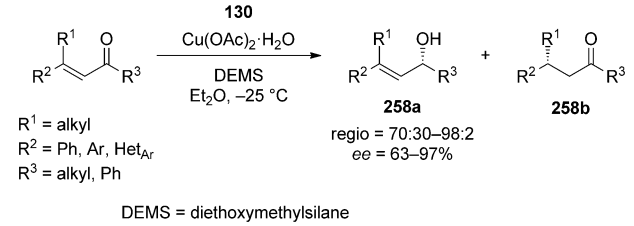


Scheme 120. Total synthesis of brevetoxin B. TBHP = *tert*-butyl hydroperoxide.



Scheme 121. Total synthesis of (−)-frondosin B.

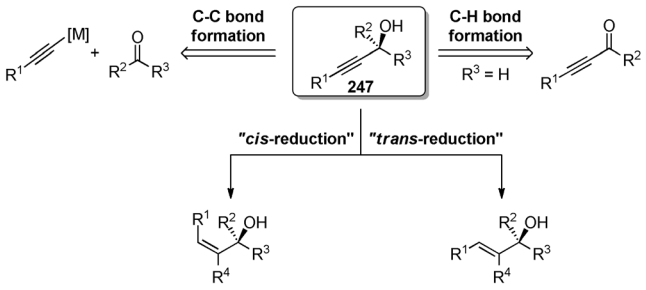
the ligand and diethoxymethylsilane as the reductant (Scheme 122).[271] Allylic alcohols were isolated with moderate to excellent enantiomeric excess and good 1,2-regioselectivity (ratio **258a**/**258b**).



Scheme 122. Copper-catalyzed 1,2-reduction of β,β-disubstituted enones.

6. Access from Enantioenriched Propargylic Alcohols

The transformation of enantioenriched propargylic alcohols by *cis* or *trans* reduction of the alkyne is an attractive indirect approach to secondary and tertiary allylic alcohols, and considerable advances in the development of efficient asymmetric methods for their synthesis have been made recently (Scheme 123). Propargylic alcohols can be efficiently



Scheme 123. Access to allylic alcohols from enantioenriched propargylic alcohols.

prepared through C–C bond formation by asymmetric alkynylation of carbonyl compounds (aldehydes/ketones) or by C–H bond formation by the asymmetric reduction of propargylic ketones (Scheme 123).

6.1. Access to Enantioenriched Propargyl Alcohols

As these methods only permit the synthesis of allylic alcohol precursors, and reviews on this topic have already been published,[272] this section will cover only selected examples and their application in total syntheses (see Section 6.2).

6.1.1. Access by C–C Bond Formation

A broad range of catalyst systems for the enantioselective alkynylation of carbonyl compounds have been developed (Scheme 124),[272] mostly involving the addition of alkynylzinc

Scheme 124. Access to enantioenriched propargyl alcohols by catalytic enantioselective alkynylation of carbonyl compounds.

reagents, formed in situ in the presence of chiral promoters[273,274] (e.g. **259**–**262**,[273a–g] **129**,[273h] **263**,[273i] **264**,[273j] **74a**,[273k] **265**–**268**,[273l–p] Figure 14), and catalytic[273a,d] or stoichiometric amounts[273b,c,e–u] of zinc reagents. Other metals such as copper[275] (with **269**), indium[276] (**74b**), ruthenium[277] (**270**), lithium[278] (**271**), and titanium[279] (**74a**) have also been used. Catalytic asymmetric additions of trimethoxysilylalkynes to ketones[280] and of iodoalkynes to aldehydes[281] catalyzed by lithium binaphtholate **272** and chiral chromium complex **182** (NHK-type reaction), respectively, have also been studied (Figure 14).

6.1.2. Access by C–H Bond Formation

The ruthenium-catalyzed asymmetric transfer hydrogenation developed by Noyori and co-workers[262,282] using complexes **273** and **274** (Figure 15) and the CBS reduction involving chiral oxazaborolidines **257a**/**b**[268,283] (Figure 13) have proved to be the most efficient and widely used catalytic systems for the synthesis of enantioenriched propargyl alcohols by the 1,2-reduction of propargyl ketones (Scheme 125).

6.2. Transformation into Allylic Alcohols

6.2.1. Access to (Z)-Allylic Alcohols

Hydrogenation using Lindlar's catalyst is the most efficient and convenient method for the synthesis of (*Z*)-allylic alcohols from propargylic alcohols. It has been used in various total syntheses, such as the synthesis of erythronolide A by Carreira and co-workers (Scheme 126).[284] Enantioenriched propargylic alcohol **275**, prepared by Noyori transfer hydrogenation (Scheme 125), was reduced to (*Z*)-allylic alcohol **276** in high yield; this was further elaborated by a diastereoselective cycloaddition with oxime **277** (Scheme 126).

Recently, Yang and co-workers described a highly diastereoselective reductive coupling between aldehydes or ketones and propargylic alcohols derived from (trimethylsilyl)acetylene (Scheme 127).[285] A broad range of 1,3-*syn* allylic alcohols **278** were obtained in high yields and moderate to excellent stereoselectivities by using $Ti(OiPr)_4$ and *i*PrMgCl as the reducing agent.

Gao and O'Doherty transformed propargylic alcohol **279** into (*Z*)-allylic alcohol **280** by a rhodium-catalyzed *trans*-hydroboration under Miyaura conditions.[286] The vinyl boronate was later coupled to vinyl iodide **281** to afford **282**, a precursor of fostriecin (Scheme 128).

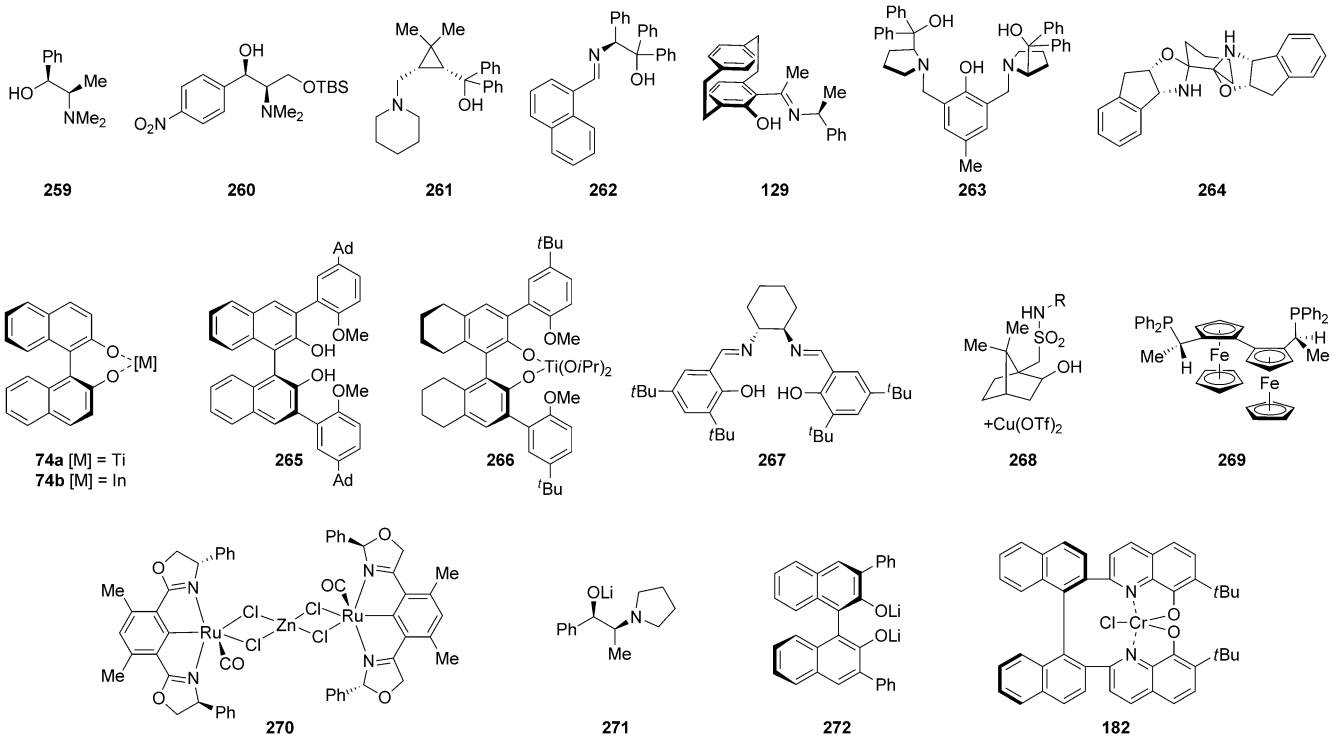


Figure 14. Chiral ligands/complexes for the asymmetric alkynylation of aldehydes and ketones.

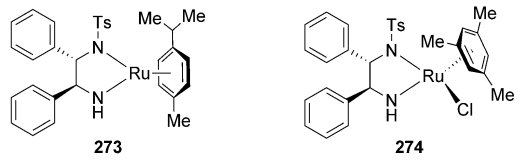
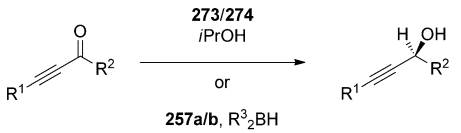
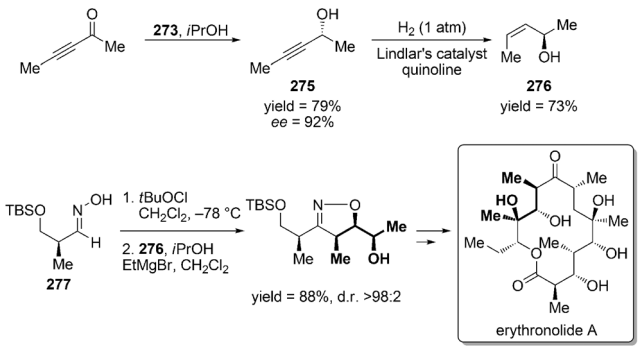


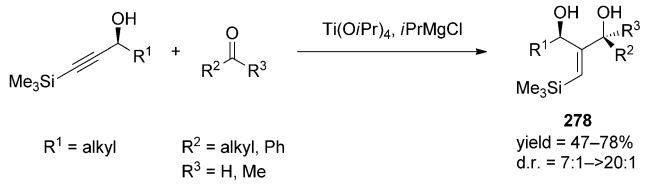
Figure 15. Chiral ruthenium catalysts for the asymmetric 1,2-reduction of propargyl ketones.



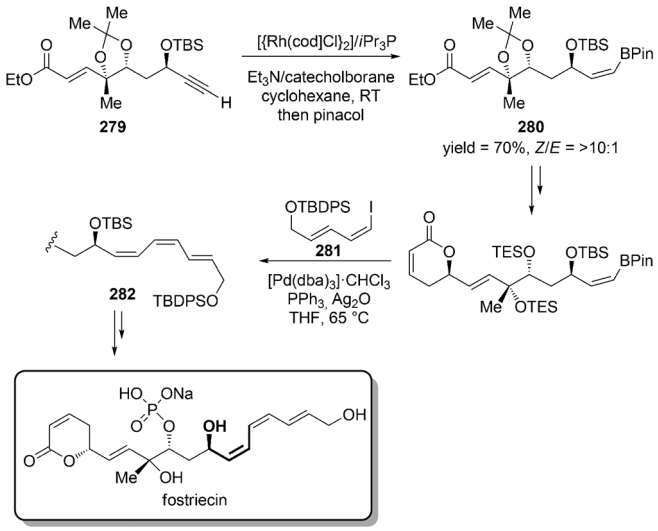
Scheme 125. Access to enantioenriched propargyl alcohols by asymmetric 1,2-reduction of propargyl ketones.



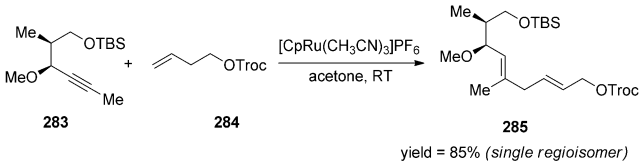
Scheme 126. Total synthesis of erythronolide A.



Scheme 127. Reductive coupling between propargylic alcohols and aldehydes or ketones.



Scheme 128. Total synthesis of fostriecin.

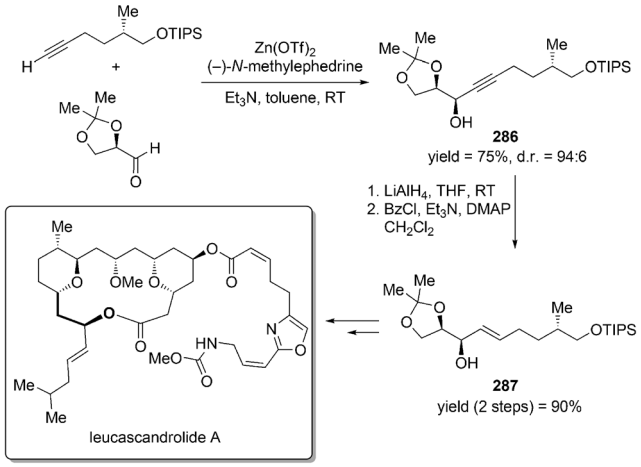


Scheme 129. Regioselective ruthenium-catalyzed Alder-ene reaction.

Trost and co-workers used a highly regioselective ruthenium-catalyzed Alder-ene reaction between propargyl ether **283** and homoallylic carbonate **284** to synthesize trisubstituted (*Z*)-allylic alcohol **285** (Scheme 129). This was further elaborated by an asymmetric palladium-catalyzed allylic etherification in the total synthesis of callipeltoside A (see Scheme 97).

6.2.2. *Access to (E)-Allylic Alcohols*

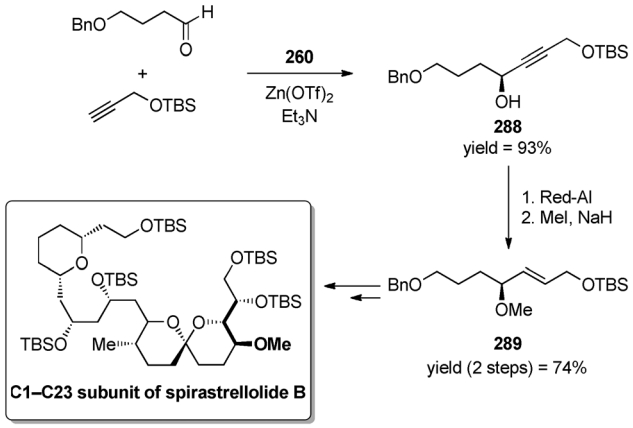
The triple bond of enantioenriched propargyl alcohols can be easily reduced with $LiAlH_4$ to access (*E*)-allylic alcohols, as demonstrated by the synthesis of allylic alcohol **287**, an intermediate in the total synthesis of leucascandrolide A (Scheme 130).[287] Propargylic alcohol **286** was obtained by the Zn/(−)-*N*-methylephedrine-mediated addition reaction developed by Carreira and co-workers.[288]



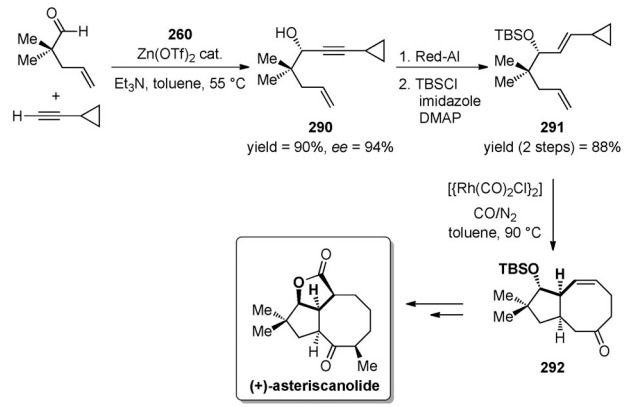
Scheme 130. Total synthesis of leucascandrolide A.

Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) has been used as an alternative reducing agent. Keaton and Phillips obtained propargylic alcohol **288**, following a procedure developed by Jiang et al.,[273e] by using **260** (Figure 13) as a chiral promoter (Scheme 131).[289] Subsequent reduction with Red-Al afforded (*E*)-allylic alcohol **289**, which was elaborated to a subunit of spirastrellolide B (Scheme 131).

The catalytic asymmetric alkynylation of aldehydes developed by Jiang et al.[273d] (using **260**, Figure 13) has been successfully used by Yu and co-workers in the total synthesis of (+)-asteriscanolide (Scheme 132).[290] Reduction of enantioenriched propargylic alcohol **290** with Red-Al, followed by protection with TBS afforded the protected allylic alcohol



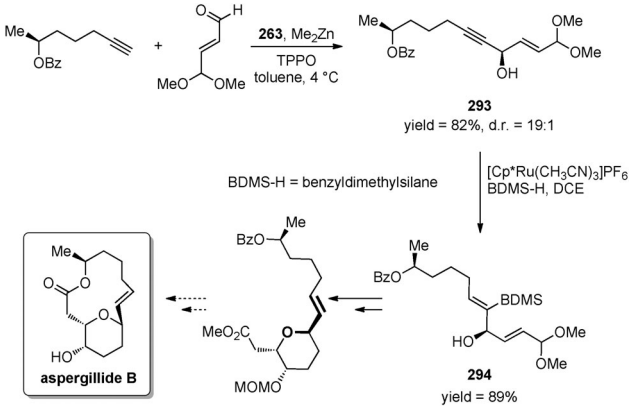
Scheme 131. Synthesis of the C1–C23 subunit of spirastrellolide B.



Scheme 132. Total synthesis of (+)-asteriscanolide.

291, which was further elaborated by a highly diastereoselective [(5 + 2) + 1] cycloaddition reaction to yield key bicyclic cyclooctenone **292** (Scheme 132).

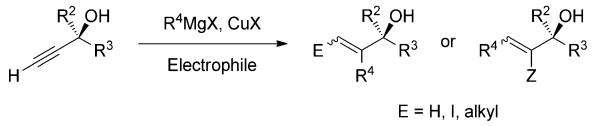
Recently, Trost and Bartlett combined their ProPhenol-catalyzed asymmetric alkynylation of aldehydes (using **263**, Figure 14) with ruthenium-catalyzed *trans*-hydrosilylation of alkynes to rapidly and efficiently obtain functionalized, enantioenriched (*E*)-allylic alcohols (e.g. **293** and **294**, Scheme 133), which are key intermediates in a formal synthesis of aspergillide B (Scheme 133).[291]



Scheme 133. Formal synthesis of aspergillide B. TPPO = triphenylphosphine oxide, Cp* = C_5Me_5.

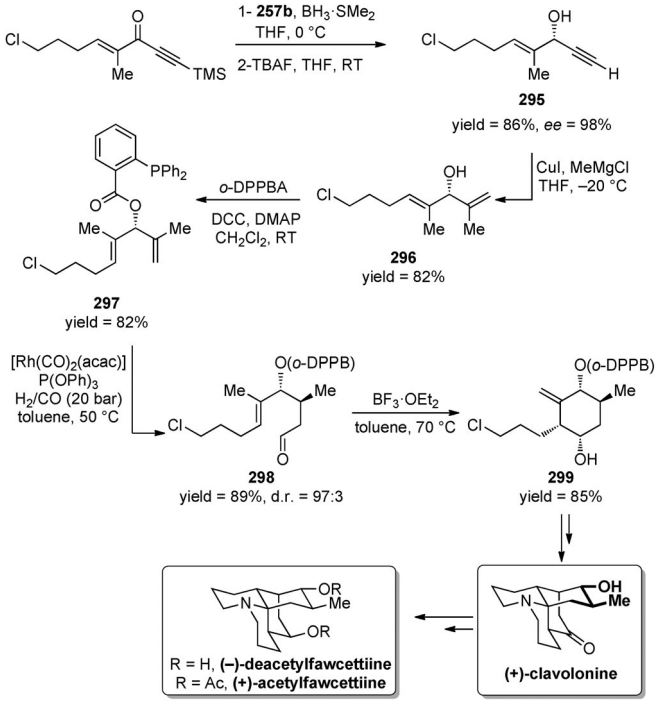
Access to complex enantioenriched (*E*)-allylic alcohols from propargylic alcohols by ruthenium-catalyzed *trans*-hydrosilylation has also been used by Kleinbeck and Carreira in the total synthesis of bafilomycin A_1.[292]

Carbometalation of propargylic alcohols is a powerful method for the regioselective generation of various di- and trisubstituted (*E*)-allylic alcohols (Scheme 134).[293,294]



Scheme 134. Carbometalation of propargyl alcohols.

Laemmerhold and Breit used this approach in the preparation of allylic alcohol **296** from enantioenriched propargylic alcohol **295** with high chemo- and regioselectivity (Scheme 135).[295] Alcohol **295** was obtained by CBS reduction of the corresponding ketone (see Section 6.1.2 and Scheme 125). After transformation of **296** into *o*-DPPB ester **297**, directed hydroformylation gave aldehyde **298** with excellent chemo-, regio-, and diastereoselectivity. A subsequent Lewis acid mediated carbonyl-ene cyclization gave cyclohexanol **299**, which is a key intermediate in the total synthesis of (+)-clavolonine, (−)-deacetylfawcettiine, and (+)-acetylfawcettiine (Scheme 135).



Scheme 135. Total synthesis of (+)-clavolonine, (−)-deacetylfawcettiine, and (+)-acetylfawcettiine. DPPBA = diphenylphosphinobenzoic acid, DCC = *N*,*N*′-dicyclhexylcarbodiimide.

7. Summary and Outlook

Many highly efficient catalytic asymmetric methods for the synthesis of enantioenriched allylic alcohols have been developed over the past three decades. These protocols permit the synthesis of structurally diverse, functionalized allylic alcohols that can be elaborated by a broad range of reactions, thus allowing the synthesis of many complex natural products and therapeutic agents.

To date, the most general methods for the synthesis of these versatile chiral building blocks are the dynamic kinetic resolution (DKR) of allylic alcohols and esters, enantioselective vinylation of carbonyl groups, and the asymmetric allylic substitution reaction. Whilst powerful, these approaches have limitations in terms of reaction time (DKR) as well as step and/or atom ecomony, as the latter two classes require stoichiometric amounts of organometallic reagents or activated allyl electrophiles, respectively. Recently, growing attention has been given to C–H oxidation reactions and related processes that permit the formation of allylic alcohols directly from bulk chemicals such as alkenes and alkynes. Although these approaches present significant challenges with respect to reactivity as well as regio- and stereoselectivity, initial reports in this field have demonstrated its potential utility, and future advances seem likely.

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