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SYNTHESES OF CHIRAL HETEROCYCLIC COMPOUNDS VIA ZIRCONIUM-CATALYZED ASYMMETRIC CARBOALUMINATION OF ALKENES (ZACA REACTION)

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Abstract – Shortly after the Zr-catalyzed carboalumination of alkynes was discovered in 1978, we sought expansion of the scope of this reaction so as to develop its alkene version for catalytic asymmetric C–C bond formation, namely the ZACA (**Z**r-catalyzed **a**symmetric **c**arboalumination of **a**lkenes). However, the discovery of such an asymmetric reaction proved to be quite challenging. The ZACA reaction was finally discovered in 1995 by suppressing three unwanted side reactions, i.e., (i) cyclic carbometalation, (ii) *β*-H transfer hydrometalation, and (iii) alkene polymerization, represented by the Ziegler-Natta polymerization. Three mutually complementary procedures for the enantioselective synthesis of methyl-substituted 1-alkanols have been developed, which allow highly flexible designs for the syntheses of chiral organic compounds. This review summarizes the syntheses of chiral heterocyclic compounds of biological and medicinal interest via ZACA reaction, which provides a widely applicable, efficient and selective method for catalytic asymmetric C–C bond formation.

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**This paper is dedicated to Professor Dr. Victor Snieckus on the occasion of his 77th birthday.*

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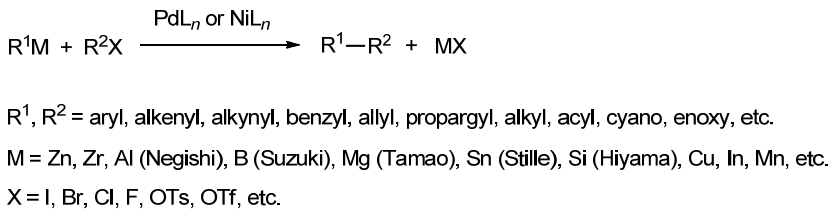
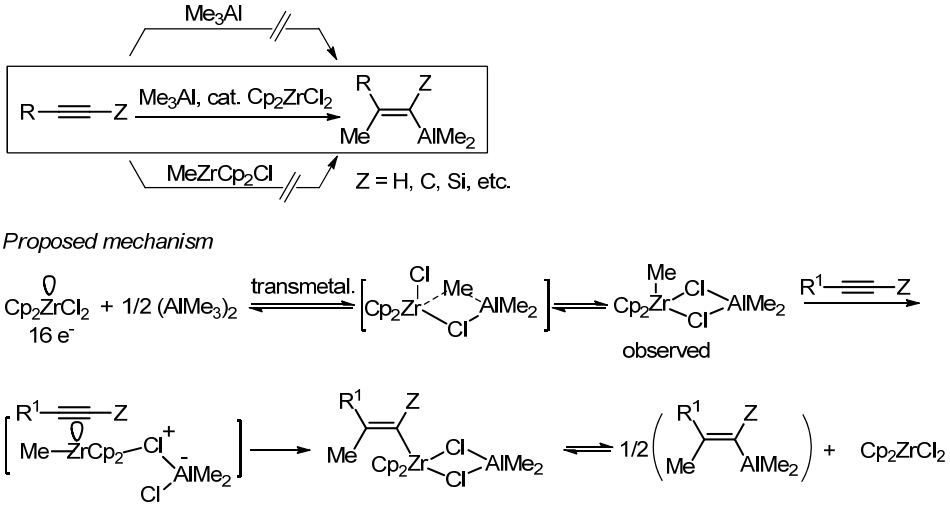
1. INTRODUCTION

Palladium-catalyzed cross-coupling, especially those involving Zn, Al, Zr (Negishi coupling),[1–3] and B (Suzuki coupling),[4,5] has become one of the most widely applicable, selective, and satisfactory methods for C–C bond formation. Two regio- and stereodefined carbon groups generated as R^1M (M = Zn, Al, B, Cu, Zr, etc.) and R^2X (X = I, Br, Cl, OTs, etc.) may now be cross-coupled to give R^1–R^2 with essentially full retention of all structural features. It does appear that the synthetic scope of the Pd-catalyzed cross-coupling is limited primarily by the availability of satisfactory routes to the requisite R^1M and R^2X. From an optimistic viewpoint, one can state and expect that the synthetic scope of the Pd-catalyzed cross-coupling will continue to expand with discoveries and developments of new selective and satisfactory routes to R^1M and R^2X in the future.



Scheme 1. General reaction scheme of cross-coupling reactions

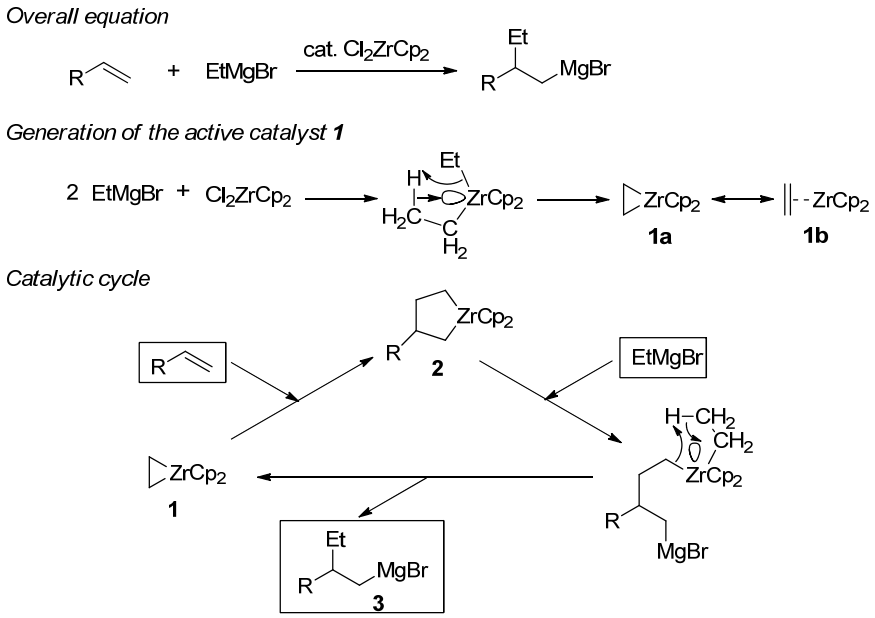
The alkyne elementometalation–Pd-catalyzed cross-coupling tandem process has provided a very attractive, efficient, and selective route to various conceivable types of alkenes.[6] In view of a large number of naturally occurring organic compounds of important biological activities containing trisubstituted alkenes, especially those with branching Me groups, it became highly desirable to have the corresponding carbometalation, especially methylmetalation, of alkynes. In 1978, we discovered the Zr-catalyzed carboalumination of alkynes.[7] The Zr-catalyzed methylalumination of alkynes (ZMA reaction) was shown to involve one-step *syn*-addition of a Me–Zr bond to 1-alkynes in an *anti*-Markovnikov manner followed by Zr-to-Al transmetalation on the resultant carbon group.[8,9] This reaction involves acyclic carbometalation of a "super-acidic"[10,11] Zr-Al bimetallic system (Scheme 2).



Scheme 2. Bimetallic acyclic carboalumination mechanism

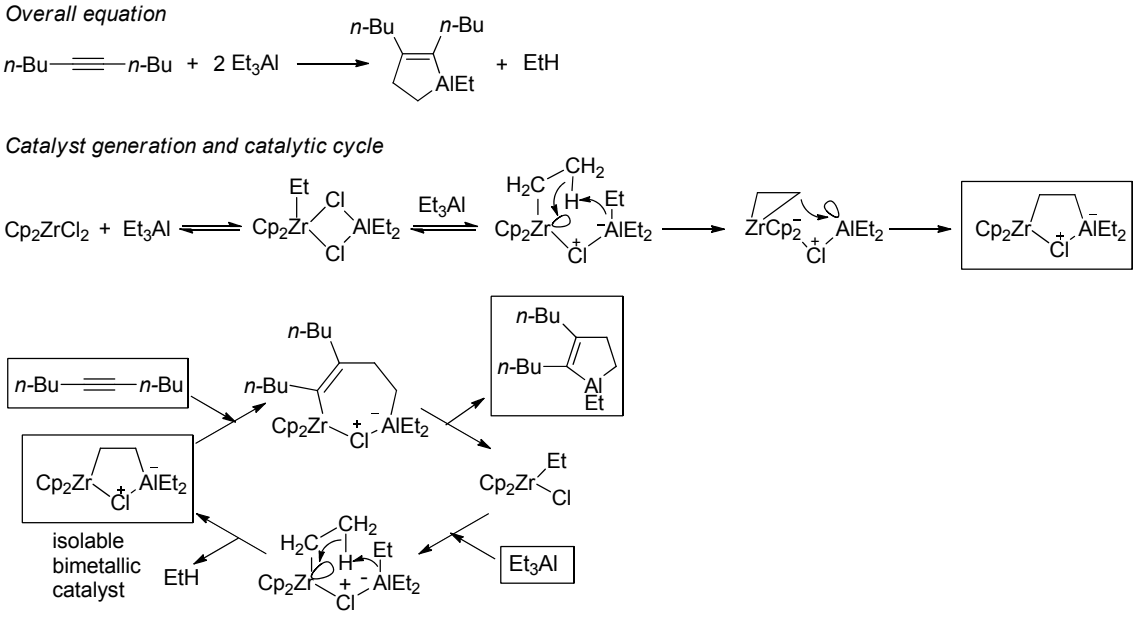
Several years later, Dzhemilev reported a seemingly analogous reaction of Zr-catalyzed carbomagnesiation of alkenes with EtMgBr (Scheme 3).[12] There did not appear any forcing reasons to suspect that the mechanisms of these two closely analogous reactions should be radically different. Through our systematic investigations of the "$ZrCp_2$" chemistry,[13] however, we accidentally clarified that the Dzhemilev ethylmagnesiation of alkenes actually proceeded through a highly intricate series of transformations involving (i) formation of Et_2ZrCp_2, (ii) β-agostic interaction-induced intramolecular "acid-base" interaction producing a zirconacyclopropane (**1a**) which may also be viewed as a zirconocene-ethylene π-complex (**1b**), (iii) carbozirconation of an alkene with **1** to give, typically a cyclic 3-substituted zirconacyclopentane **2**, (iv) subsequent reaction of **2** with another molecule of EtMgBr leading to β-agostic interaction-induced "acid-base" interaction producing a 2-ethyl-1-alkylmagnesium bromide **3** with regeneration of the ethylene-$ZrCp_2$ π-complex **1**. All of the steps proposed above have been independently and amply supported (Scheme 3).[13,14] We believe that both the discovery of the Dzhemilev ethylmagnesiation and our mechanistic clarification[14] have not only clearly established the existence of both acyclic and cyclic carbozirconation processes but also alerted us to sharply and carefully distinguish some seemingly analogous carbometallation reactions of zirconocene derivatives.

We were later further surprised by the existence of bimetallic (involving both Zr and Al) cyclic carbozirconation of alkynes and alkenes that may be viewed as a hybrid of acyclic and cyclic carbozirconation (Scheme 4).[15] We also noted that our bimetallic (Zr-Al) cyclic carbozirconation process closely resembled the corresponding carbotitanation of alkenes with titanium-carbene species that can be viewed as a two-membered titanacycle (Tebbe reagent) generated from a Ti-Al bimetallic system.[16] Without going into detailed mechanistic discussions, the following brief summary may be presented: (i) Formation of metallacycles including metal-carbene complexes (two-membered metallacycles) is a widely



Scheme 3. Mechanism for the Dzhemilev ethylmagnesiation via a cyclic transition structure

observable phenomenon with coordinatively unsaturated organotransition-metal complexes, especially in those cases where coordinatively unsaturated dialkylated organotransition-metal species, that are readily prone to β- or even α-agostic interaction-induced cyclization are generated.[17] (ii) The propensity for generating the requisite "coordinatively unsaturated dialkyltransition-metal species" rests on a delicate balance between the alkylating power of the respective alkylmetal reagents, e.g., RLi > RMgX > $RAlX_2$, and their ability to avoid formation of coordinatively saturated "ate" complexes. Thus, for example, trialkylalanes, e.g., Et_3Al, do not dialkylate $ZrCp_2Cl_2$ to give Et_2ZrCp_2. On the other hand, Grignard

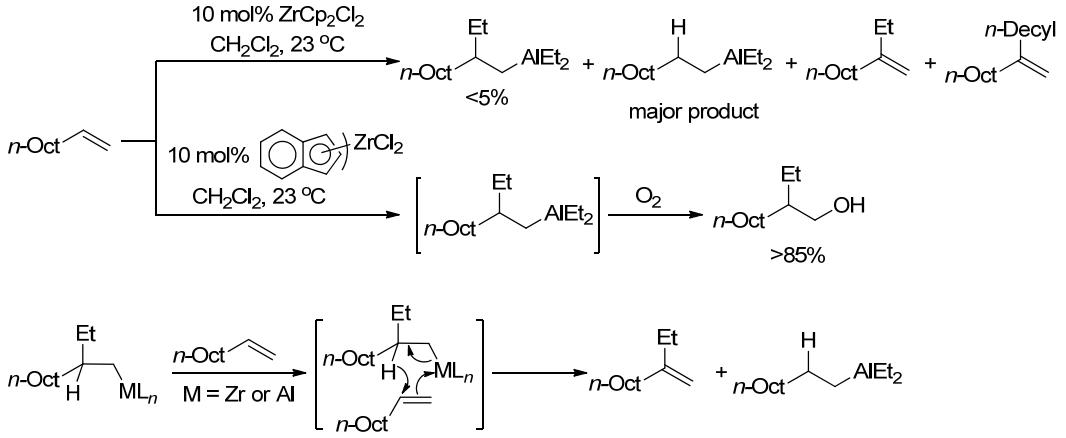


Scheme 4. Bimetallic carboalumination mechanism via a cyclic transition structure

reagents, e.g., EtMgBr, readily dialkylate to give a 16 electron Et_2ZrCp_2. Triethylation does proceed, but it is readily reversible. All these make alkylmagnesium derivatives some of the optimal reagents for converting $ZrCp_2Cl_2$ into zirconacycles. (iii) Even with alkylalanes, however, zirconacycles may still be formed by "bimetallic intramolecular acid-base interaction" discussed above.

At the time we discovered the Zr-catalyzed carboalumination of alkynes in 1978,[7] a dreamy thought of expanding the scope of this reaction so as to embrace its alkene version for asymmetric C–C bond formation, which would amount to the single-step version of the Ziegler-Natta alkene polymerization captured senior author's mind. However, this seemingly easy task proved to be quite challenging, and several intermittent attempts over seventeen years supported heavily by our ongoing systematic investigations of zirconocene chemistry were needed to finally discover in 1995 the ZACA reaction,[18,19] as detailed below.

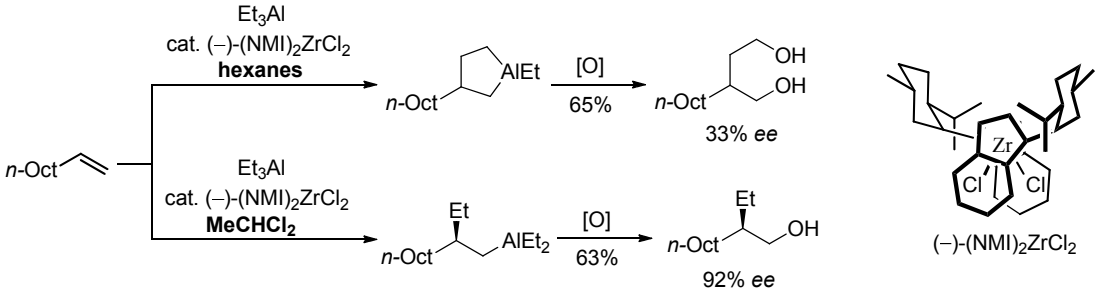
Our initial investigations leading to negative results were conducted with the parent $ZrCp_2Cl_2$. It was finally decided to conduct the following two studies: (i) detailed fact-finding investigation of the reaction of 1-decene with 10 mol% of $ZrCp_2Cl_2$ in CH_2Cl_2 and (ii) search for satisfactory procedures based on (i). These studies immediately led to some most useful results shown in Scheme 5. With $(Me_5C_5)_2ZrCl_2$, no reaction was observed under the same conditions.[18,19] Clearly, zirconocene derivatives with sufficiently, but not excessively, bulky ligands to suppress unwanted side reactions, most notably β-H transfer hydrometallation, while promoting the desired carbometallation, were needed to realize the desired alkene carbometallation.



Scheme 5. Reaction of 1-decene with Et_3Al in the presence of various zirconocene derivatives

Yet another ambush was the initially unexpected Al-Zr bimetallic cyclic carbometallation of alkenes. Before 1995, we believed that dialkylation of zirconocene derivatives would be mandatory for observing the formation of zirconacyclopropanes by β-agostic interaction-induced cyclization. It was, however,

found that the reaction of 1-decene with Et_3Al in the presence of Erker's $(NMI)_2ZrCl_2$[20] in hexanes would proceed by cyclic carbometallation (Scheme 6),[19] even though there were ample indications that trialkylalanes do not lead to dialkylation of zirconocene derivatives. It was indeed this surprising finding that led to the clarification and establishment of the bimetallic cyclic mechanism for carbozirconation of alkynes mentioned earlier (Scheme 4).[15] Fortunately, it was soon learned that the use of more polar solvents including CH_2Cl_2, $MeCHCl_2$, and $(CH_2Cl)_2$ almost totally suppressed the undesired cyclic carbometallation process thereby promoting formation of the desired products (Scheme 6).[19]

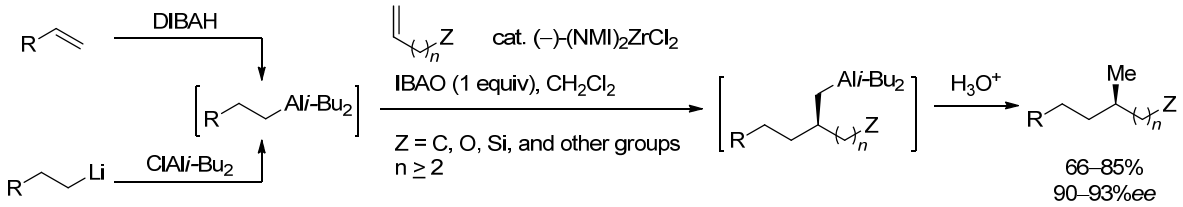


Scheme 6. Marked solvent effect in the reaction of 1-decene with Et_3Al in the presence of $(NMI)_2ZrCl_2$

Throughout the investigations, the authors' group was very much concerned about the third potential side reaction, i.e., Zr-catalyzed alkene polymerization of Ziegler and Natta.[21] However, this has hardly been of any serious concern. In retrospect, this is not surprising, if one considers (i) essentially 1:1 alkene-to-alane ratios and (ii) absence of highly efficient polymerization promoters, such as methylaluminoxane (MAO), typically required in large quantities relative to trialkylalanes. In the ZACA reaction,[18,19] the use of MAO and other promoters is not mandatory and typically not necessary, although addition of one equivalent or less of water or the corresponding amount of preformed MAO can significantly promote an otherwise slow ZACA reaction,[22,23] such as that of styrenes.

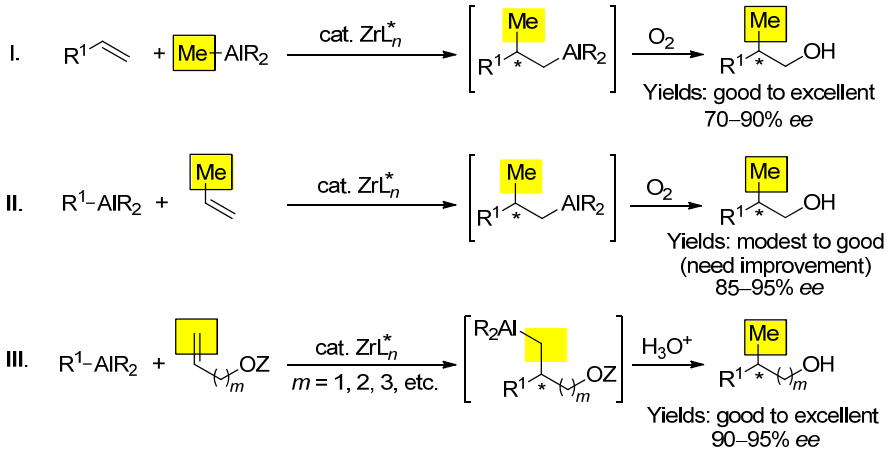
Having learned about three major pitfalls, namely (i) cyclic carbometallation, (ii) H-transfer hydrometallation, and (iii) Ziegler-Natta-type alkene polymerization as well as how to avoid them, the remaining major task was to find some satisfactory chiral zirconocene catalysts. In this respect, no systematic catalyst optimization involving catalyst design has as yet been made. Instead, a dozen to fifteen known chiral zirconocene complexes were initially screened. Widely used $(EBI)ZrCl_2$[24] and its partially hydrogenated derivatives[25] were less effective. The most effective among those tested thus far is Erker's $(NMI)_2ZrCl_2$.[20] Although methylalumination is singularly important from the viewpoint of the synthesis of natural products, it is ironically the uniquely unfavorable case where the *ee* figures are around 75%, as compared with ethylalumination and higher alkylalumination which proceeds in 90–95% *ee*. An attractive alternative has been developed by taking advantage of high enantioselectivity observed

in ethylalumination and higher alkylalumination (Scheme 7).[26,27] This new protocol provides methyl substituted alkanols in 90–93% *ee*. Two critical points are notable in this reaction. First, *β*-unbranched primary alkyl groups in mixed trialkylalanes, generated *in situ* by hydroalumination of alkenes with DIBAH (HAl*i*-Bu_2) or transmetallation of alkyllithium compounds with ClAl*i*-Bu_2, selectively react to produce the desired products containing the *β*-unbranched primary alkyl groups. Second, IBAO (isobutylaluminoxane), which is prepared by mixing equimolar quantities of *i*-Bu_3Al and H_2O in CH_2Cl_2, can be used as cocatalyst to accelerate the reaction. MAO has similar effects, but the reaction can be complicated by the formation of methylaluminated products.



Scheme 7. Hydroalumination/ZACA/hydrolysis process for the synthesis of methyl-substituted alkanols

There are currently three Zr-catalyzed asymmetric carboalumination protocols that can be used for the synthesis of methyl-branched 1-alkanols (Scheme 8). As indicated in Scheme 8, addition of the Me–Al bond via ZACA reaction leads to 70–90% *ee*, typically 70–80%.[27] The same products can be obtained in 85–95% *ee* by adding Et and higher alkyl groups and Al to propene and by using $(NMl)_2ZrCl_2$ of the opposite chirality. Both isomers of $(NMI)_2ZrCl_2$ are obtainable from the appropriate isomers of menthol with comparable ease. Moreover, addition of alkyl–Al bonds to free allyl[28,29] and homoallyl alcohols as well as longer *ω*-alken-1-ols by ZACA reaction is generally high-yielding and highly enantioselective, typically around 90% *ee*.[26,27] These three protocols can often be mutually complementary.[30]



Scheme 8. Three protocols for enantioselective synthesis of methyl-substituted 1-alkanols

2. SYNTHESIS OF CHIRAL HETEROCYCLIC COMPOUNDS VIA ZACA REACTION

2-1. ZACA–Pd-Catalyzed Cross-Coupling Sequential Processes for the Synthesis of Deoxypolypropionates and Related Heterocyclic Compounds

The ZACA reaction is a novel and as yet rare catalytic asymmetric C–C bond forming reaction of terminal alkenes of one-point-binding without requiring any other functional groups, even though various functional groups may be present. ZACA reaction has a high synthetic potential, since it provides organoaluminium intermediates which allow for a wide variety of further *in situ* transformations, such as oxidation, iodinolysis, hydrolysis, Pd-catalyzed cross-coupling, etc. Despite some room for improvement, especially (i) improvement of the enatioselectivity of carboalumination and (ii) realization of higher turnover numbers through elevation of the current level of 20–10^3 to ≥10^3–10^4 or higher, the ZACA reaction promises to provide a widely applicable, efficient, and selective asymmetric method for the synthesis of a variety of chiral organic compounds. In view of a large number of naturally occurring and biologically important deoxypolypropionates, intense efforts for the development of efficient and selective methods for their synthesis have been made.[31] Most of the currently known and widely used methods for the constructions of deoxypolypropionates are chiral auxiliary-mediated 1,4-conjugate additions[32] or enolate alkylations.[33] Only a few other transition metal-catalyzed methods are known, of which one that involves catalytic asymmetric conjugate addition by B. L. Feringa[34] is noteworthy. However, one homologation by one propylene unit appears to require typically three steps.

Despite the somewhat moderate *ee* values associated with methylalumination in ZACA reaction, the development of a few synthetic protocols and the exploitation of the well-known principle of statistical enantiomeric amplification have led to some efficient, selective, and practical processes for the synthesis of both α-monoheterofunctional and α,ω-diheterofunctional deoxypolypropionates and related compounds containing two or more asymmetric carbon atoms. According to the principle of statistical enantiomeric amplification, in the absence of internal chiral recognition, the stereochemical outcome of

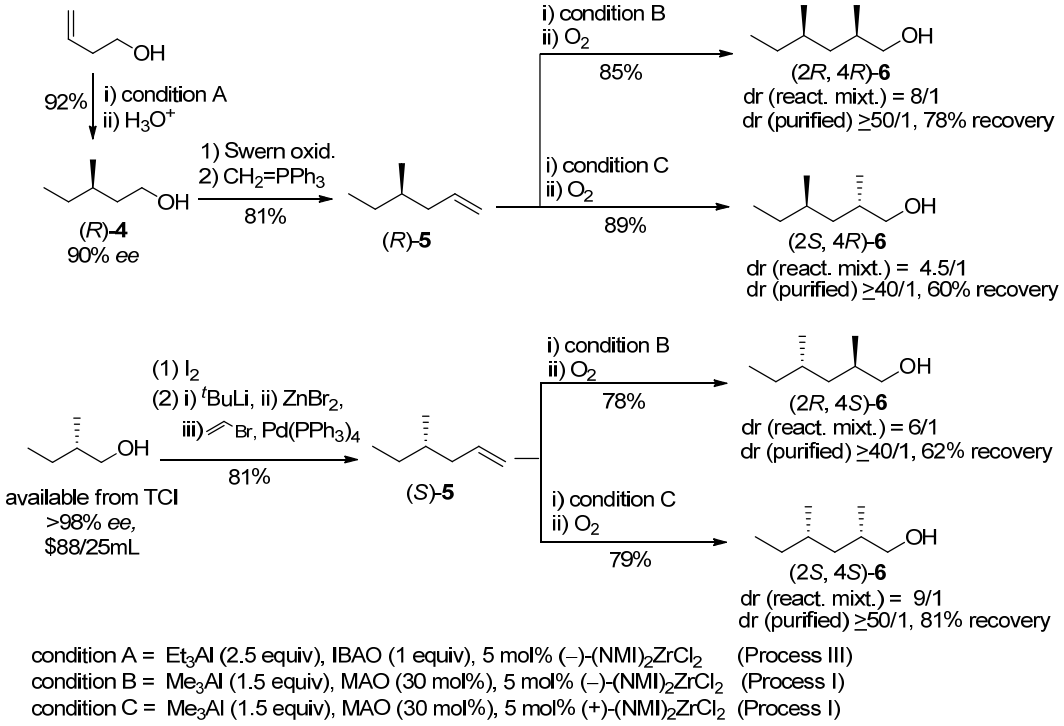
Table 1. Statistical enantiomeric amplification

ee in step or species I	*ee* in step or species II	Max. yield of major stereoisomer	Overall *ee*
70	70	74.5	94.0
80	80	82.0	97.6
90	80	86.0	98.8
90	90	90.5	99.4
99	99	99.0	99.995

Value shown are percentages. Max., maximum

combining two chiral species and/or asymmetric reactions may be predicted by resorting to the mass action law, as indicated for some representative cases in Table 1. For example, a process II of 80% *ee* followed by a process I of 90% *ee* would produce the desired product of 98.8% *ee* in a maximum 86% yield. The presence of three or more asymmetric carbon centers in the target molecules will make it possible to readily synthesize them in enantiomerically very pure forms (>99.9% *ee*).

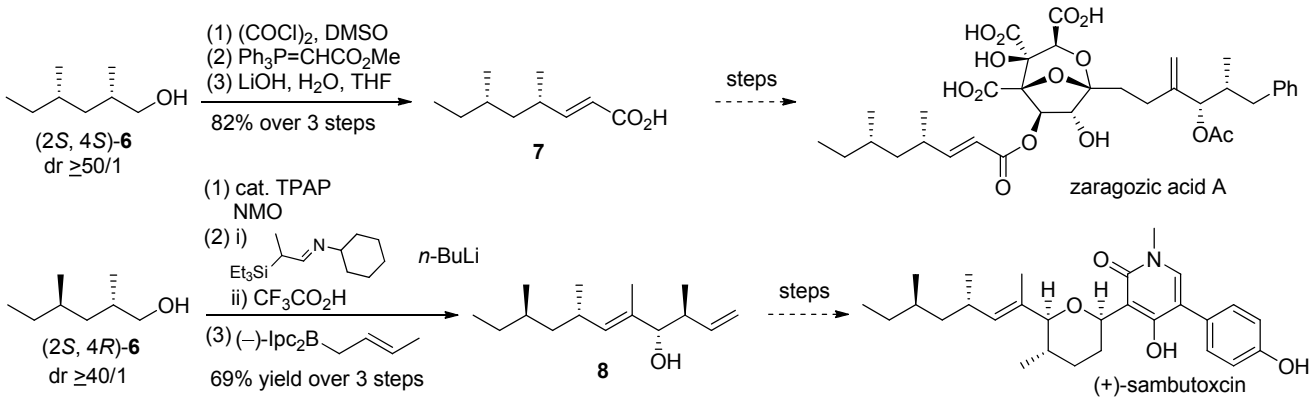
Because most, if not all, of the possible stereoisomers of reduced polypropionate fragments are present in various natural products, any general methods for their synthesis must be capable of synthesizing all possible stereoisomers with comparable ease and without extensive procedural modifications. To this end, two synthetic protocols for the conversion of monomethylsubstituted 1-alkanols into 2,4-dimethyl-1-alkanols have been developed (Scheme 9).[27] One is a three-step process involving (i) oxidation of alcohols to aldehydes, (ii) olefination by Wittig or other related reactions, and (iii) Zr-catalyzed methylalumination of alkene into 2,4-dimethyl-1-alkanols (2*R*, 4*R*)-**6** and (2*S*, 4*R*)-**6**. The other protocol for chain elongation shown in Scheme 9 also involves a three-step process consisting of (i) iodination of alcohols, (ii) zincation followed by Pd-catalyzed vinylation, and (iii) Zr-catalyzed asymmetric methylalumination followed by oxidation with O_2. This protocol is iterative, and it should be applicable to the synthesis of reduced polypropionates containing any number of branching methyl groups. An unexpected finding was that the diastereomeric separation of various 2,4-dimethyl-1-hydroxybutyl derivatives can be readily purified by one round of ordinary chromatographic separation



Scheme 9. Synthesis of all four possible stereosiomers of 2,4-dimethyl-1-hexanols (**6**)

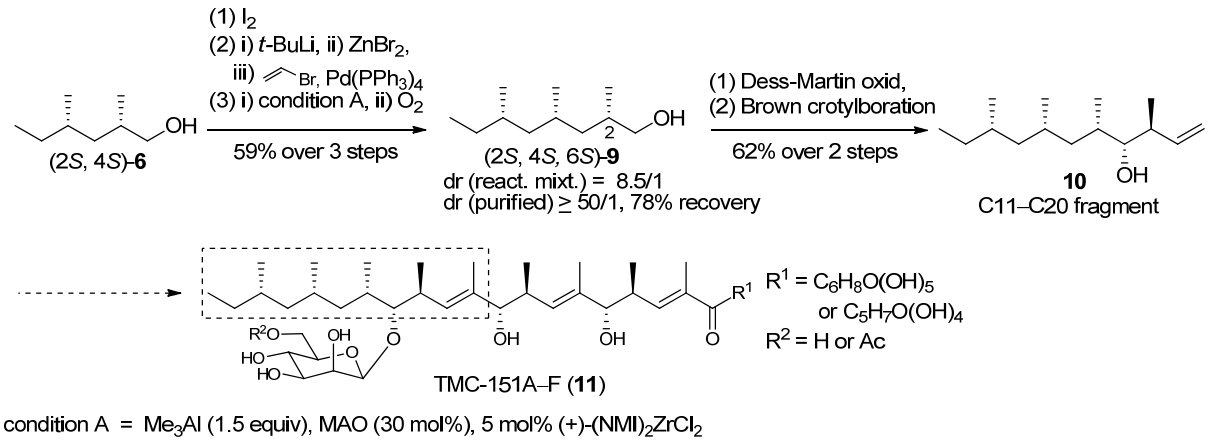
using silica gel and hexanes–EtOAc to provide the desired major stereoisomers to ≥97–98% pure compounds. The modest preference for the formation of *syn*-2,4-dimethyl-1-alkanols over that of *anti*-2,4-dimethyl-1-alkanols was observed in these cases where 1-alkenes containing chiral alkyl groups were subjected to the ZACA reaction.[27]

Stereoisomers of 2,4-dimethyl-1-hexanols (**6**) have been used for the syntheses of some natural products, such as zaragozic acid A[35] and (+)-sambutoxin[36,37] (Scheme 10). (*E*)-*α*,*β*-Unsaturated acid **7** was prepared by oxidation of (2*S*, 4*S*)-**6** under Swern conditions, condensation with $Ph_3P{=}CHCO_2Me$, and hydrolysis with lithium hydroxide in aqueous THF, which was an key intermediate for the synthesis of zaragozic acid A.[35] Compound **8**, which has been employed as a key intermediate in a recent synthesis of (+)-sambutoxin,[37] was synthesized in 69% yield over three steps from (2*S*, 4*R*)-**6**.



Scheme 10. Syntheses of **7** and **8** as key intermediates of zaragozic acid A and (+)-sambutoxin

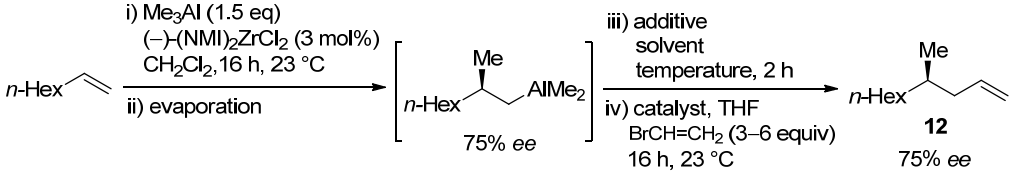
Since the three-step protocol of (i) iodination, (ii) Pd-catalyzed vinylation, (iii) ZACA reaction followed by oxidation is iterative, and it has been applied to the synthesis of higher reduced polypropionates as shown in Scheme 11.[27] 2,4-Dimethyl-1-alkanols **6** was readily converted to 2,4,6-trimethyl-1-alkanols **9**



Scheme 11. Synthesis of C11–C20 fragment (**10**) of antibiotics TMC-151 A–F (**11**)

by iterative three-step protocol. For this all-*syn* isomer case, dr of 8.5/1, corresponding to 89.5% stereoselectivity at C2, has been observed. The desired major stereoisomer (2*S*,4*S*,6*S*)-**9** was readily purified to >98% purity by one round of ordinary chromatographic separation. As discussed earlier, the overall enantiomeric excess for this trimethyl derivative **9** may safely be estimated to be 99.9%. This trimethyl trimethyl-1-octanol **9** was further converted to compound **10** in two steps, which corresponds to the C11–C20 fragment of antibiotics TMC-151 A–F (**11**) without the sugar moiety.

One-Pot ZACA–Pd-Catalyzed Vinylation Tandem Process for One-Step Iterative Homologation by a Propylene Unit. Initially, the author's group used a three-step iterative homologation cycle for incorporation of one propylene unit,[27] which consisted of (i) ZACA-oxidation, (ii) iodination, and (iii) metalation–Pd-catalyzed vinylation. Since the initial ZACA reaction product is an alkylalane, its direct use in the Pd-catalyzed vinylation was explored by skipping oxidation and iodination. Thus, a highly efficient one-pot ZACA–Pd-catalyzed vinylation tandem process for one-step iterative homologation by a propylene unit has been developed.[38] The isoalkyldimethylalanes, generated by ZACA reaction, was directly used for Pd-catalyzed vinylation under the condition of (i) $Zn(OTf)_2$ as an additive, (ii) $Pd(DPEphos)Cl_2$ and *i*-Bu_2AlH in a 1:2 molar ratio as a catalyst system, and (iii) DMF as a solvent. The ZACA reaction of 1-octene proceeded in 75% *ee* (Mosher ester analysis of 2-methyl-1-octanol after oxidation). After Pd-catalyzed vinylation at elevated temperature (even at 120 °C), the product **12** was formed in 75% *ee*, which was determined by HPLC analysis of the amide derivative of its oxidation product 3-methylnonanoic acid. Thus, no racemization took place under the conditions of the Pd-catalyzed vinylation.

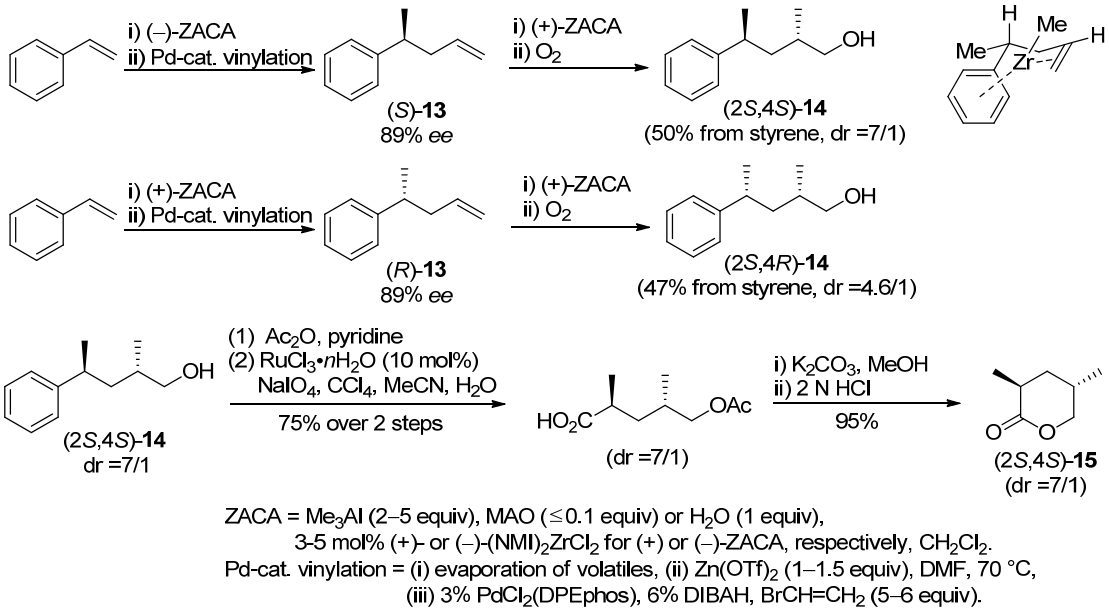


additive (equiv)	solvent	temp. (°C)	catalyst (%)	Yield (%)
$ZnBr_2$ (1)	THF	60	$Pd(PPh_3)_4$ (5)	14
$ZnBr_2$ (1)	DMF	120	$Cl_2Pd(DPEphos)$ (5) + *i*-Bu_2AlH (10)	36
$ZnBr_2$ (3)	DMF	120	$Cl_2Pd(DPEphos)$ (5) + *i*-Bu_2AlH (10)	63
$Zn(OTf)_2$ (1)	**DMF**	**70**	**$Cl_2Pd(DPEphos)$ (3) + *i*-Bu_2AlH (6)**	**71**

Scheme 12. "One-pot" ZACA–Pd-catalyzed vinylation tandem process

This one-pot ZACA–Pd-catalyzed vinylation tandem process has been used to the synthesis of α,ω-diheterofunctional deoxypolypropionates and related compounds containing two or more asymmetric

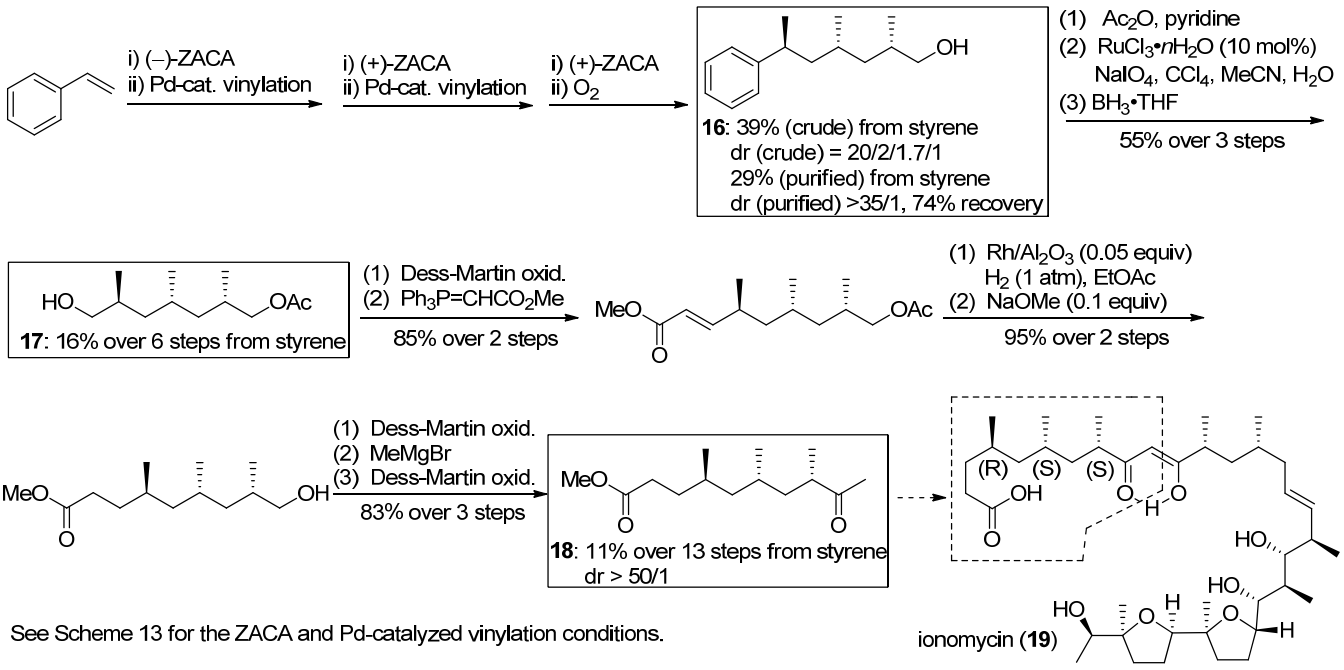
carbon atoms. Compound **13** was prepared by ZACA reaction of inexpensive (<$1/mol) styrene followed by Pd-catalyzed vinylation of the *in situ* generated isoalkylalane promoted by $Zn(OTf)_2$ (Scheme 13).[38] Compound (*S*)-**13** was then converted to (2*S*,4*S*)-2-methyl-4-phenyl-1-pentanol **14** by (+)-ZACA reaction followed by *in situ* oxidation with O_2 in 50% yield over two steps from styrene. Since the first ZACA reaction gave 2-phenyl-1-propanol of 89% *ee*, the diastereomeric ratio (dr) of 7.0/1 observed by ^{13}C NMR spectroscopy for (2*S*,4*S*)-**14** before purification, indicated that the enantiomeric selectivity in the second (+)-ZACA reaction was 92% and that **14** should be 99% *ee* according to the principal of statistical enantiomeric amplification (Table 1). The undesired diastereomers of **14** could be separated by ordinary column chromatography. Compound (2*S*,4*S*)-**14** was converted to tetrahydro-2*H*-pyran-2-one **15** by acetylation, Ru-catalyzed oxidation with $NaIO_4$, and lactonization. Similarly, a *syn* isomer of (2*S*,4*R*)-**14** was prepared in 47% yield over two steps as a 4.6/1 diastereomeric mixture by using (+)-$(NMI)_2ZrCl_2$ for both ZACA reaction steps. It is noteworthy that the diastereomeric ratio is higher for the formation of the *anti* isomer of **14**, i.e., (2*S*,4*S*)-**14** (dr = 7.0/1) than that of the *syn* isomer of **14**, i.e., (2*S*,4*R*)-**14** (dr = 4.6/1). The observed *anti* preference may be rationalized in terms of preferred equatorial disposition of the preexisting Me group in a putative pseudochair-like conformation arising from double π-complexation of a 14-electron $MeZr(NMI)_2$ complex.[38]



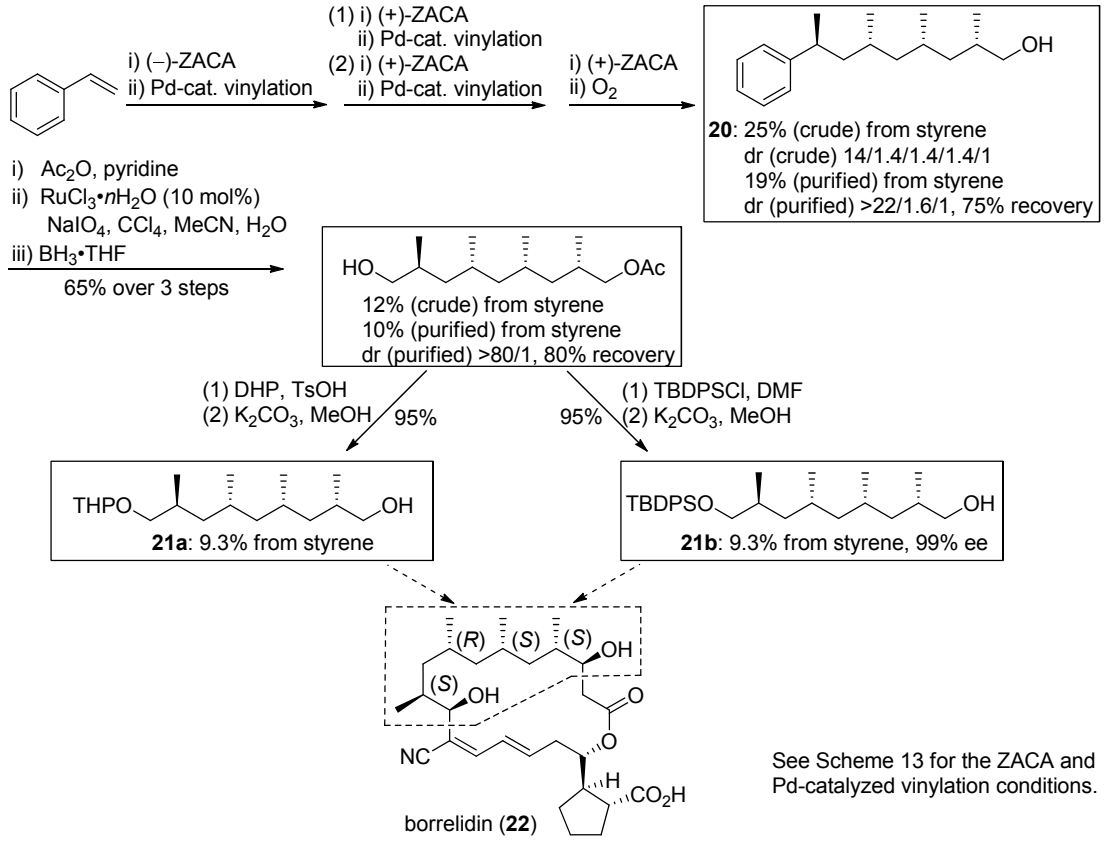
Scheme 13. Styrene-based protocol for the synthesis of tetrahydro-2*H*-pyran-2-one (**15**)

α,*ω*-Diheterofunctional deoxypolypropionates tri- and tetramethyl-branched intermediates **16** and **20** have also been synthesized by this highly efficient all-catalytic asymmetric protocol (Schemes 14 and 15).[38] The key point is to repeat the ZACA–Pd-catalyzed vinylation. The undesired diastereomers could be removed by ordinary column chromatography. Compounds **16** and **20** were transformed to compounds **18**

and **21**, respectively, which are the key intermediates employed in the previous syntheses of reduced polypropionate natural products ionomycin (**19**)[39] and borrelidin (**22**).[40]

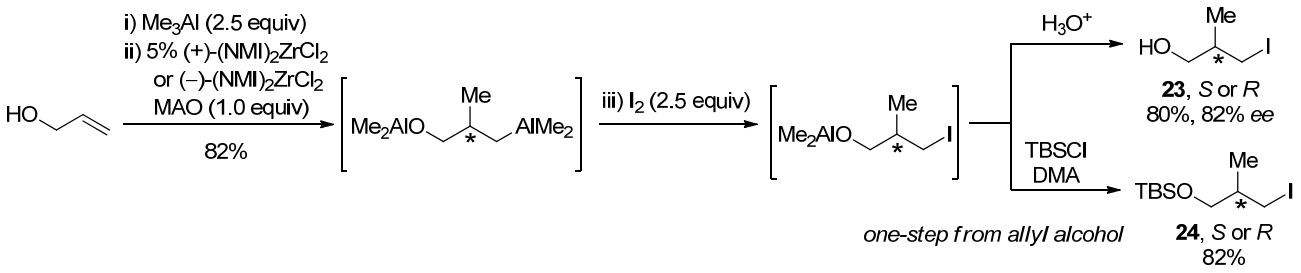


Scheme 14. Styrene-based protocol for the synthesis of **18** as a key intermediate of ionomycin (**19**)



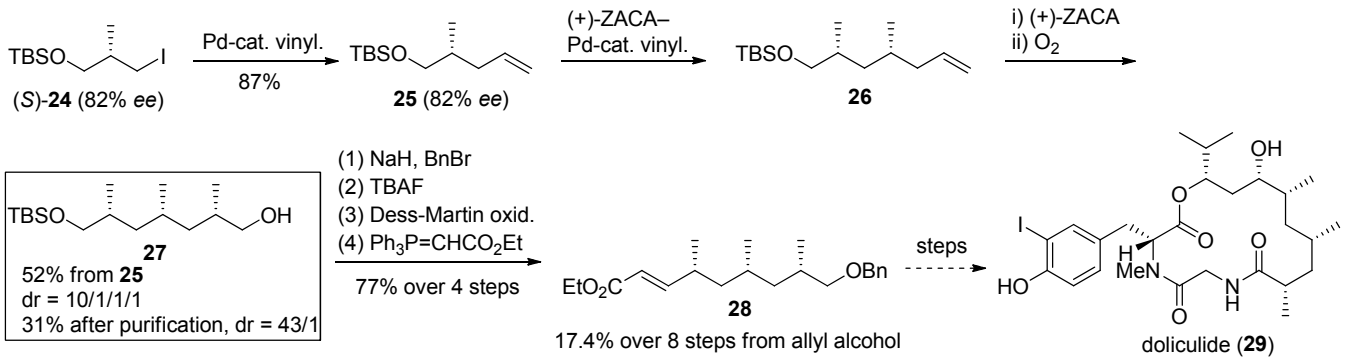
Scheme 15. Styrene-based protocol for the synthesis of **21** as a key intermediate of borrelidin (**22**)

In 2006, we developed a novel "one-pot" conversion of inexpensive allyl alcohol to TBS-protected (*R*)- or (*S*)-3-iodo-2-methyl-1-propanol (**24**) via (i) ZACA reaction of allyl alcohol with Me_3Al, (ii) *in situ* iodinolysis with I_2, and (iii) *in situ* protection with ^{t}BuMe$_2$SiCl (Scheme 16**)**.[28] The entire one-pot reaction gave either *R* or *S* isomer of **24** in 82% isolated yield by using (–)- or (+)-(NMI)$_2$ZrCl$_2$, respectively. (*R*)- or (*S*)-3-Iodo-2-methyl-1-propanol (**23**) were also readily prepared in 80% isolated yield with 82% *ee* by the same protocol except hydrolysis with H_2O was used instead of *in situ* protection with ^{t}BuMe$_2$SiCl. It should be noted that iodinolysis of the *in situ* generated isoalkylalane leading to the synthesis of **23** and **24** in high yields was a crucial finding since neither oxidation nor protonolysis of the isoalkylalane intermediate would lead to chiral products.



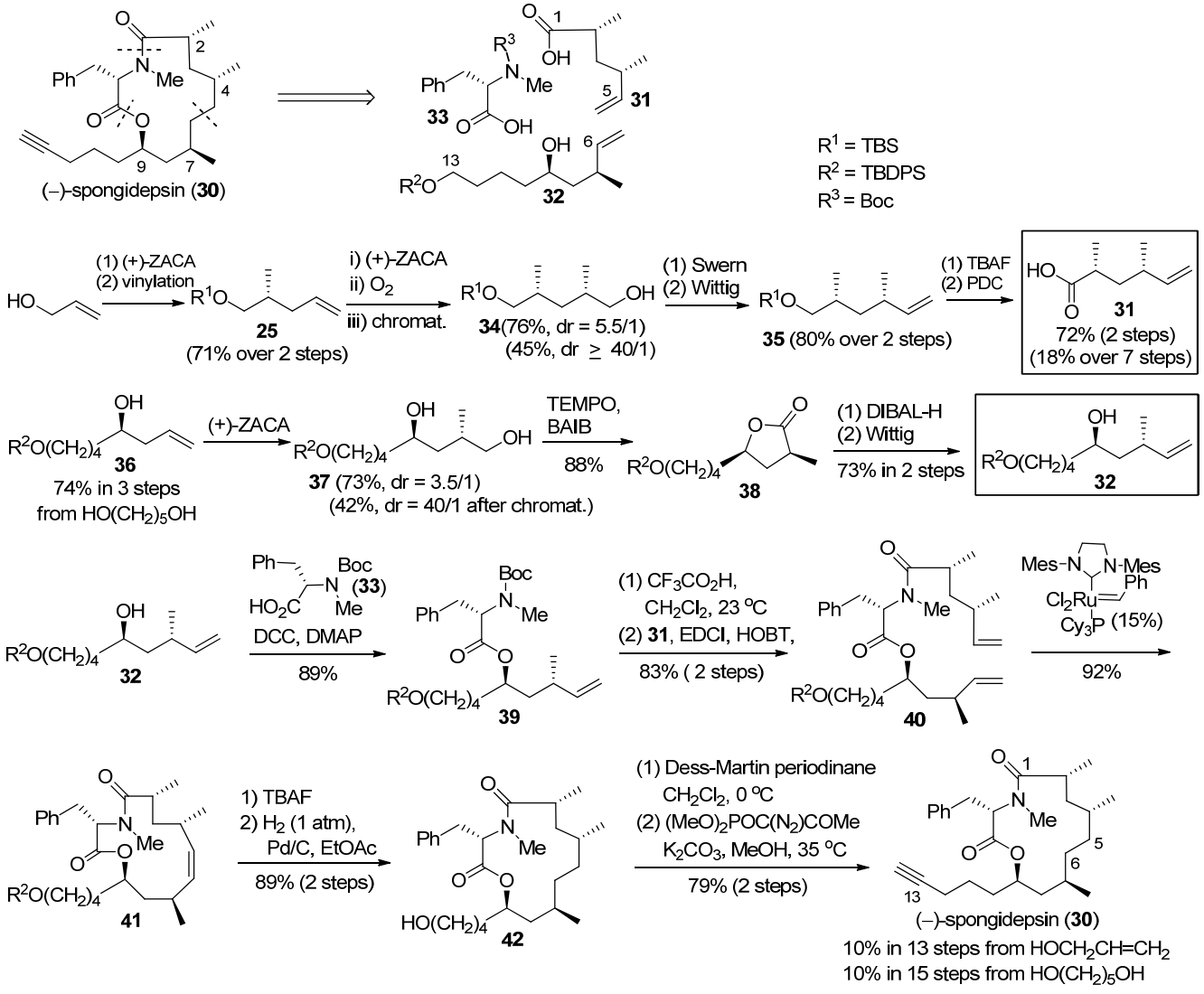
Scheme 16. ZACA of allyl alcohol–iodinolysis process for the synthesis of **23** and **24**

Compound **24**, readily prepared from inexpensive allyl alcohol by one step, is a very useful intermediate to synthesize a wide variety of chiral compounds since it contains two functional groups, e.g. (i) substituting iodine with various carbon groups via Pd- or Cu-catalyzed cross-coupling, (ii) converting OTBS group to desired groups. For the synthesis of deoxypolypropionates and other chiral compounds containing two or more asymmetric carbon centers, compound **24** can be converted to alkene **25** by Pd-catalyzed vinylation in 87% yield. One-pot ZACA–Pd-catalyzed vinylation tandem process for one-step iterative homologation by a propylene unit can be also applied. It should be noted that since the ZACA reaction of **24** has been shown to be more *syn*-selective (*syn*/*anti* = 13/1) than *anti*-selective (*anti*/*syn* = 8/1),[41] this protocol nicely complements an *anti*-selective styrene-based protocol discuss above.[38] To demonstrate its synthetic utility, a key intermediate **28** for the synthesis of doliculide (**29**)[42] have been prepared as summarized in Schemes 17.[28] For the synthesis of compound **27**, **25** (82% *ee*) was subjected to one round of the (+)-ZACA–Pd-catalyzed vinylation followed by the second (+)-ZACA reaction and oxidation with O_2. The crudely isolated **27** (52% from **25**) could be purified by ordinary column chromatography. Thus, **27** (dr = 43/1, >99% *ee*) was prepared in mere four isolation steps and one chromatographic purification from allyl alcohol in 25% overall yield.[28] Compound **27** was further converted to **28** in 77% yield over 4 steps.



Scheme 17. Allyl alcohol-based protocol for the synthesis of **28** as a key intermediate of doliculide (**29**)

(–)-Spongidepsin (**30**), isolated from the Vanuatu marine sponge *Spongia* sp., displays cytotoxic and antiproliferative activities against J774.A1, HEK-293, and WEHI-164 cancer cell lines.[43] We reported an efficient total synthesis of (–)-spongidepsin (**30**) by using **31**, **32**, and **33** through application of the

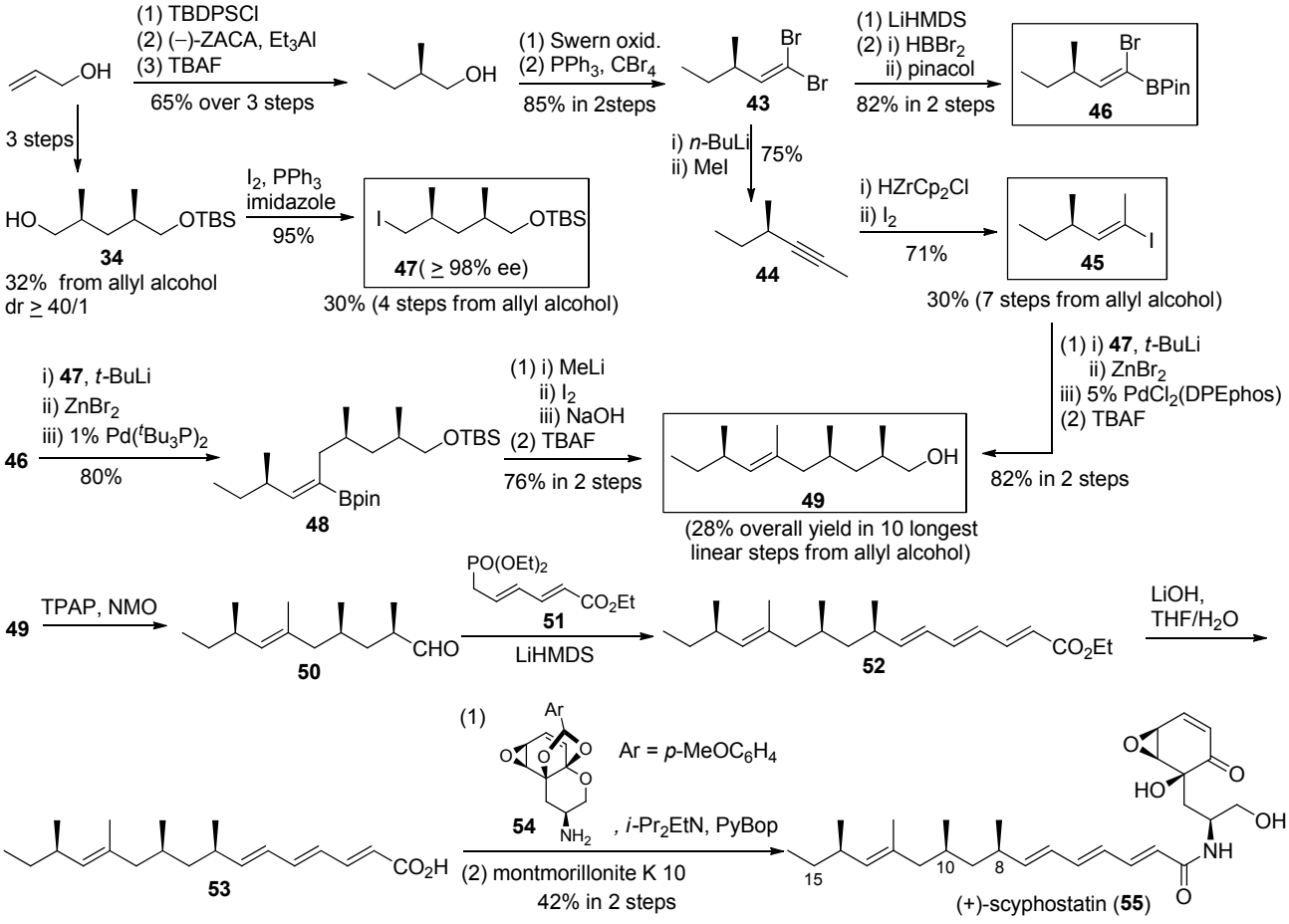


Scheme 18. Total synthesis of (–)-spongidepsin (**30**)

esterification–amidation–ring closing metathesis[44] strategy employed in the previous syntheses[45] (Scheme 18).[46] The C1–C5 fragment (**31**) and the C6–C13 fragment (**32**) were synthesized via ZACA reaction as key steps. The synthesis of **31** was achieved via the two-step conversion of allyl alcohol into **25** via **24** in 71% yield and 82% *ee*, followed by one-pot ZACA–oxidation tandem process and chromatographic purification to give **34** in 32% overall yield (dr ≥ 40/1) from allyl alcohol (Scheme 18). Compound **34** was converted to **35** via Swern oxidation and Wittig olefination, and **35** was then converted to **31** via desilylation with TBAF, followed by PDC oxidation (18% over 7 steps from allyl alcohol).[46] Compound **32** was synthesized from inexpensive 1,5-pentanediol in 20% overall yield via TBDPS-protection, Swern oxidation and Brown allylboration[47] to give **36** in 74% over 3 steps. Conversion of **36** via ZACA reaction followed by *in situ* oxidation with O_2 gave **37** (dr = 3.5/1) in 73% yield (43% after chromatographic purification to dr = 40/1). Oxidation of **37**, followed by reduction with DIBAL-H and olefination by the Wittig reaction provided **32** in 64% yield in 3 steps (20% yield from 1,5-pentanediol over 7 steps). The final assembly of (–)-spongidepsin (**30**) was summarized in Scheme 18.

(+)-Scyphostatin (**55**), a naturally occurring ceramide analogue, is a promising pharmacological target for the treatment of inflammation, immunological and neurological disorders.[48] We have developed one efficient and convergent total synthesis of (+)-scyphostatin (**55**)[49] and two different routes to the side-chain (**49**).[41,50] (+)-Scyphostatin (**55**) has been synthesized in the high level of convergency by amidation of compounds **53** and **54**, followed by one step of deprotection (Scheme 19).[49] Synthesis of compound **53** was performed by (i) oxidation of **49** with TPAP and NMO, (ii) olefination of the resultant aldehyde with **51**, and (iii) hydrolysis with LiOH. For the synthesis of the side-chain (**49**), two different routes have been developed via ZACA reaction by treatment of **47** with two different intermediates **45** and **46**, respectively (Scheme 19). Compound **47** was synthesized by iodination of **34** which was prepared by two rounds of ZACA reaction as discussed in Scheme 18 (30% over 4 steps from allyl alcohol). Compound **44** was prepared by asymmetric ethylalumination of TBDPS-protected allyl alcohol, desilylation, Swern oxidation, and Corey-Fuchs reaction. Hydrozirconation/iodinolysis of **44** provided (2*E*,4*R*)-2-iodo-4-methyl-2-hexene (**45**) of ≥98% isomeric purity in 71% yield. The C7–C16 side-chain (**49**) was then prepared by $PdCl_2$(DPEphos)-catalyzed Negishi coupling of **45** with zinc derivative of **47** generated via treatment of **47** with *t*-BuLi (2.1 equiv) and dry $ZnBr_2$ (0.65 equiv), followed by desilylation with TBAF.[41] Our recently developed 1-halo-1-alkyne hydroboration–Negishi coupling–organoborate migratory insertion protocol has been used in another route to the side-chain **49** (Scheme 19).[50] (*Z*)-1-Bromo-1-alkenylboranes **46** was prepared by treatment of **43** with LiHMDS and then with $HBBr_2$ followed by addition of pinacol. Conversion of **46** with zinc derivative of **47** by Negishi coupling provided (*Z*)-alkenylborane **48** in ≥98% retention of configuration. Side-chain (**49**) was then

synthesized by further transformation of **48** via (i) "ate" complexation with MeLi, (ii) I_2-induced methyl migration, and (iii) hydroxy-induced *anti*-deiodoboration, followed by removal of the TBS group with TBAF (76% yield in two steps).[50]



Scheme 19. Total synthesis of (+)-scyphostatin (**55**)

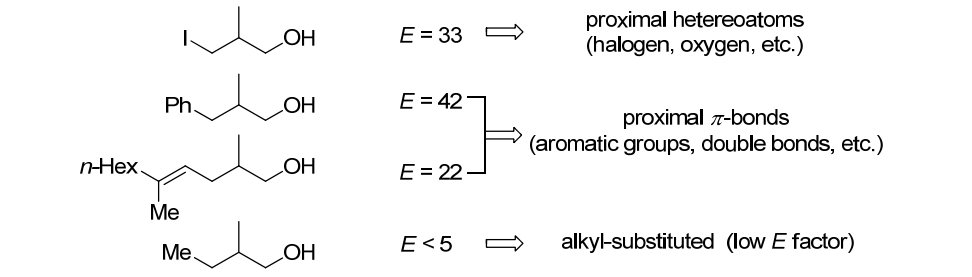
2-2. ZACA–Lipase-Catalyzed Acetylation–Pd- or Cu-Catalyzed Cross-Coupling Synergy to Chiral Heterocyclic Compounds

Having developed unprecedentedly efficient methods for the synthesis of deoxypolypropionates with two or more stereogenic carbon centers as discussed above, it was acutely realized that, only if ZACA products containing just one stereogenic carbon center can be readily and predictably purified, the ZACA-based asymmetric synthetic method would become much more widely applicable. The senior author recently became fully aware of the following strengths and weaknesses of the previously known lipase-catalyzed (*S*)-selective acetylation: (i) Enantiomerically pure (*R*)-2-methyl-1-alkanols can be reliably obtained from their racemic mixtures, although the maximally attainable yield (or recovery) of (*R*)-alcohols of ≥98% *ee* is limited to 50% or, more specifically ≤25% if E = 10, ≤35% if E = 20, and

≤45% if E = 100, where E (enantiomeric ratio or selectivity factor) = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)] and C and ee are the extent of conversion and the enantiomeric excess of the unreacted alcohol, respectively.[51] As such, it is not an attractive method, especially if the starting 2-methyl-1-alkanols are very expensive; (ii) Much more striking and important is that the lipase-catalyzed acetylation method is practically incapable of providing the ≥99% pure acetates of (*S*)-2-methyl-1-alkanols from their racemic mixtures in one cycle, since it can be predicted that the maximally attainable yields of ≥99% pure acetates would be ≤1–2% (E≤100).[51] Consequently, iterative purification processes, in which the purity of desired compound must be gradually elevated, will be required. This theoretical prediction also points to a significant advantage in being able to start with enantiomerically enriched (*S*)-2-methyl-1-alkanols as shown in Table 2. Some maximally attainable yields of ≥99% pure acetates of (*S*)-2-methyl-1-alkanols can be predicted as follows: ≤80% if the initial ee_o is 70% and E is 50; ≤85% if ee_o is 80% and E is 30; ≤95% if ee_o is 90% and E is 20.[51] It is clear that neither the ZACA reaction alone nor the lipase-catalyzed acetylation alone is capable of providing a satisfactory method for the synthesis of either *R* or *S* isomer of 2-methyl-1-alkanols of ≥99% isomeric purity but that a combination of the two would be, provided that (i) the ZACA reaction is sufficiently enantioselective, preferably 80–90% *ee* but minimally ≥70% *ee* and

Table 2. The maximally attainable yields of (*S*)-2-alkyl-1-alkanols of >98% *ee* from the racemic and enantiomerically enriched mixtures[51]

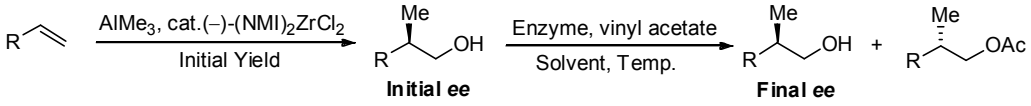
Initial ee_o (%)	E[a]	Max. yield (%)	Initial ee_o (%)	E[a]	Max. yield (%)
0 (racemic)	100	≤2	70	100	≤85
	90	0		50	~80
				30	~60
20	100	≤35		20	~25
	80	~20		10	0
	60	0			
			80	100	≤90
50	100	≤70		30	~85
	50	~55		20	~70
	40	~25		10	0
	30	0			
60	100	≤80	90	100	≤95
	50	~65		20	≤95
	30	~25		10	80
	20	0		5	0



[a] E (enantiomeric ratio or selectivity factor) = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)]
C and ee are the extent of conversion and the enantiomeric excess of the unreacted alcohol, respectively

(ii) the *E* values are sufficiently high, preferably ≥20–30. The ZACA–lipase-catalyzed acetylation sequential process has indeed been successfully applied to the purification of either *R* or *S* isomers of 2-methyl-1-alkanols, as represented by the results shown in Table 3.[52] Thus, 2-alkyl-1-alkanols, even in some cases of lacking any proximal π-bonds or heterofunctional groups, have been efficiently synthesized in ≥98% *ee* by ZACA–lipase-catalyzed acetylation sequential protocol.

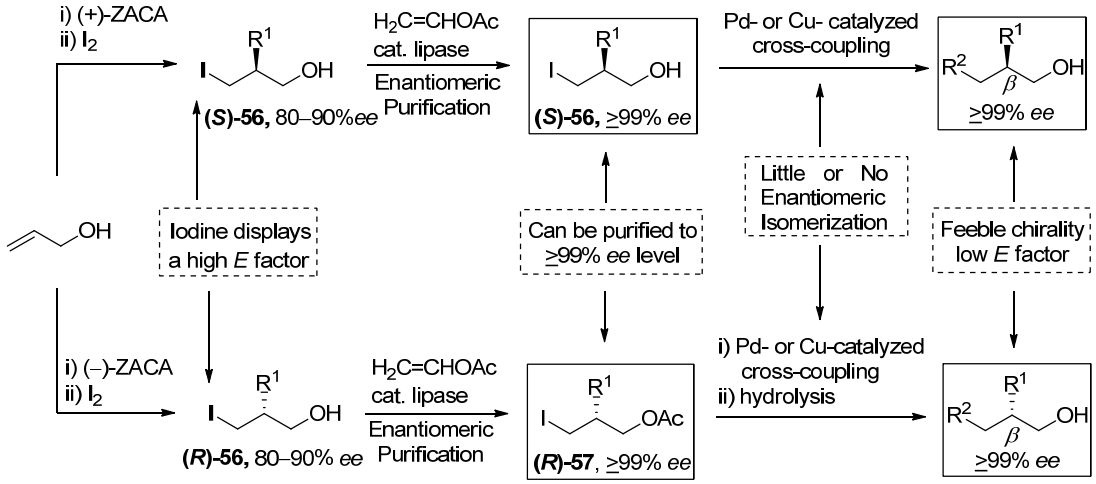
Table 3. ZACA–lipase-catalyzed acetylation sequential processes for the synthesis of 2-methyl-1-alkanols



R	Initial Yield (%)	Intial ee (%)	Enzyme	Solvent	Temp [°C]	Conversion (%)	Recovery (%)	Final ee (%)
Ph	85	89	Amano PS	THF/H_2O	23	22	68	93
			Amano PS	THF/H_2O	23	50	43	96
			PPL	THF/H_2O	23	**31**	**62**	**99**
$PhCH_2$	85	76	PPL	THF/H_2O	23	48	51	77
			Amano PS	THF/H_2O	23	**40**	**59**	**99**
$Ph(CH_2)_2$	85	78	PPL	THF/H_2O	23	**30**	**64**	**99**
			Amano PS	THF/H_2O	23	38	56	99
n-Hex, Me	76	75	Amano PS	CH_2Cl_2	0	**16**	**80**	**98**
n-Hex	71	72	Amano PS	CH_2Cl_2	0	**38**	**60**	**98**

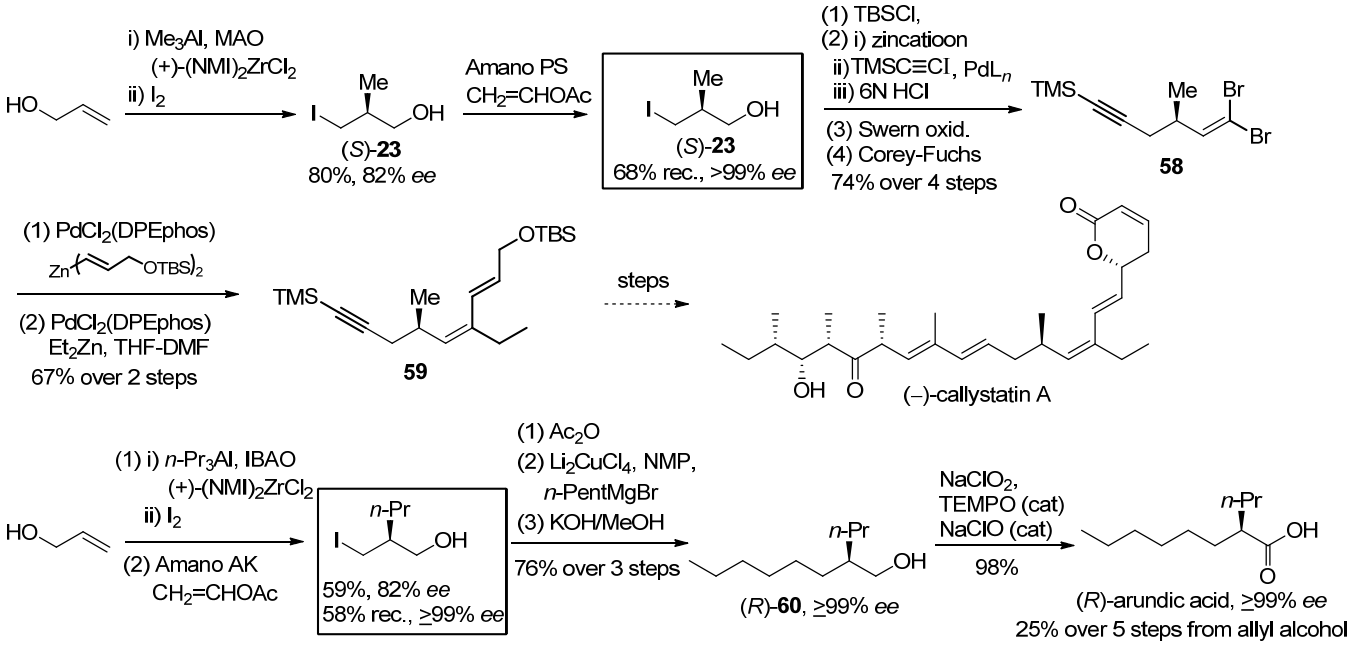
As discussed above, the efficiency of the lipase-catalyzed acetylation heavily depends on the *E* factor. In more demanding (feebly chiral) cases, especially when two alkyl groups are very similar, it is difficult to purify to >98% *ee* even from enantiomerically enriched mixtures by lipase-catalyzed acetylation. To overcome this difficulty, the ZACA–lipase-catalyzed acetylation–Pd- or Cu-catalyzed cross-coupling sequential process was considered and developed for the synthesis of various feebly chiral 2-alkyl-1-alkanols of >99% *ee* as outlined in Scheme 20.[29] The first step involves a "one-pot" conversion of inexpensive allyl alcohol to various 2-substituted (*R*)- or (*S*)-3-iodo-1-propanols (**56**) by ZACA reaction followed by iodinolysis. The introduction of iodine here is based on two considerations: (i) iodides serve as excellent cross-coupling partners and (ii) iodine displays a high *E* factor which makes both (*S*)- and (*R*)-**56** readily purifiable to the level of ≥99% *ee* by lipase-catalyzed acetylation. Moreover, enantiomerically pure (>99% *ee*) **56** and **57** can be readily and efficiently transformed further into a wide

variety of feebly chiral 2-substituted 1-alkanols by Pd- or Cu-catalyzed cross-coupling to introduce various carbon groups with >99% retention of all carbon skeletal features.



Scheme 20. General strategy for the synthesis of feebly chiral 2-substituted 1-alkanols of ≥99% *ee*

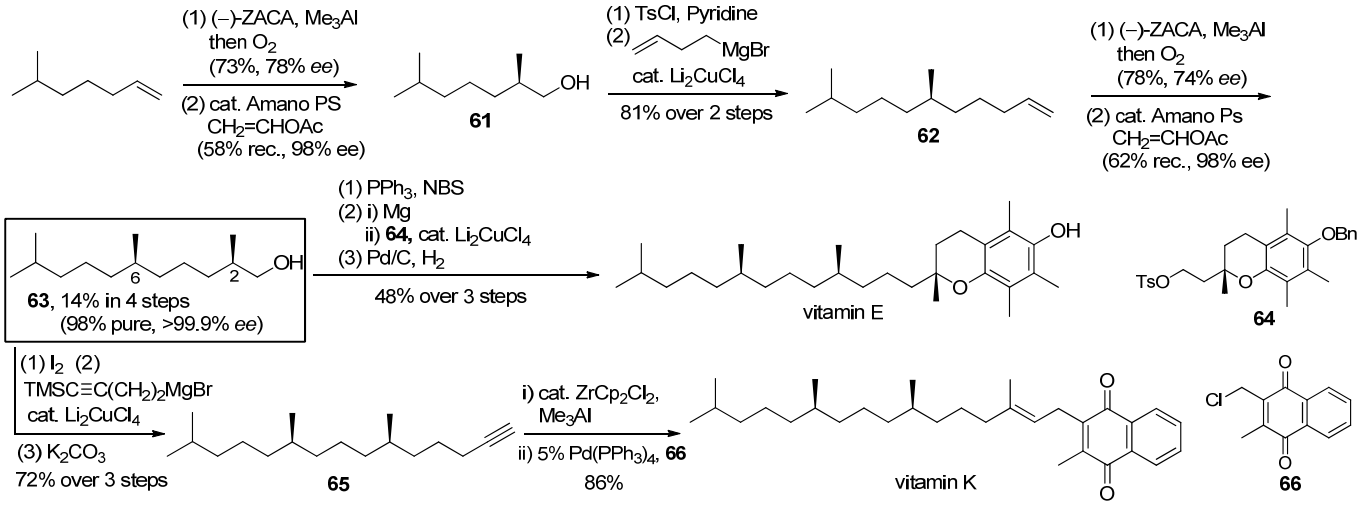
This ZACA–lipase-catalyzed acetylation–Pd- or Cu-catalyzed cross-coupling synergy has been applied to highly efficient and enantioselective synthesis of various chiral compounds.[28,29] Thus, (*S*)-**23** of >99% *ee*, obtained by ZACA/iodolysis–lipase-catalyzed acetylation, was converted to 1,1-dibromo-alkene **58** of >99% *ee* in 74% yield over four steps. Compound **58** was further transformed to **59**, a potential intermediate for the synthesis of callystatin A, by $PdCl_2$(DPEphos)-catalyzed Negishi coupling reactions



Scheme 21. ZACA–lipase-catalyzed acetylation–Pd- or Cu-catalyzed cross-coupling synergy for the syntheses of **(–)**-callystatin A and (*R*)-arundic acid

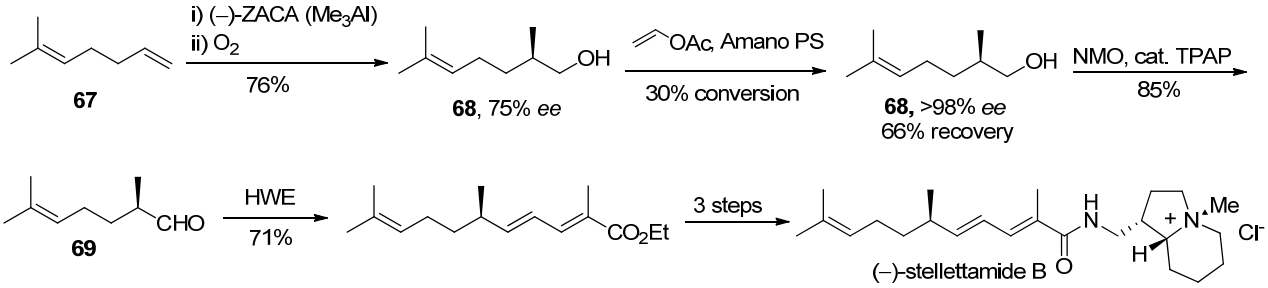
where the second Negishi coupling proceeding with a clean stereoinversion.[28] (*R*)-Arundic acid is a drug candidate for the treatment of acute ischemic stroke, as well as clinical development in other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.[53] For the synthesis of (*R*)-arundic acid, (*R*)-**60** of ≥99% *ee*, prepared by ZACA–lipase-catalyzed purification–Cu-catalyzed cross-coupling synergy (Scheme 21), was transformed into (*R*)-arundic acids in 98% yield by oxidation with $NaClO_2$ in the presence of catalytic amounts of NaClO and 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO).[29]

The ZACA–lipase-catalyzed acetylation synergy has been widely applied to the syntheses of a variety of monochiral natural products as well as those multichiral compounds in which the chiral centers do not effectively interact among them for allowing efficient isomeric purification by ordinary column chromatography. This synergy was applied to an efficient synthesis of (2*R*,6*R*)-2,6,10-trimethylundecan-1-ol (**63**), which is a key intermediate[54] for the synthesis of vitamins E and K as shown in Scheme 22.[52] In our previous synthesis,[54] the preparation of **63** as a stereoisomerically pure substance was achieved via three-step purification process involving formation–repeated recrystallization–hydrolysis of a bisurethane derived from **63** and *p*-phenylene diisocyanate, which was rather laborious and of unpredictable applicability. In the recent synthesis,[52] 1-alkanol **61** of 78% *ee*, prepared by ZACA reaction of the corresponding alkene followed by oxidation, was readily purified to 98% *ee* by Amano PS lipase-catalyzed acetylation in 58% recovery yield. After two-step conversion of **61** to **62** in 81% yield, a second ZACA–oxidation provided crude **63** in 78% yield (74% *ee* at C-2), which can also be purified to 98% *ee* at C-2 by Amano PS lipase-catalyzed acetylation. Thus, **63** (dr > 50/1 and >99.9% *ee*) was synthesized in 14% yield (4 steps and two purification operations from 6-methylhept-1-ene), which was readily converted to vitamins E and K as shown in Scheme 22.[54]



Scheme 22. Total synthesis of vitamins E and K

The ZACA–lipase-catalyzed acetylation process was also applied to an efficient and enantioselective synthesis of (–)-stellettamide B as shown in Scheme 23. Crude alcohol **68** prepared by the ZACA reaction of the corresponding terminal alkenes **67** in 76% and 75% *ee*, was purified by Amano PS lipase-catalyzed acetylation to >98% *ee* in 66% recovery.[52] Oxidation of **68** of >98% *ee* with *N*-methylmorpholine *N*-oxide (NMO) and catalytic amount of tetrapropylammonium perruthenate (TPAP) produced aldehyde **69** which has been converted to the antifungal and cytotoxic (–)-stellettamide B.[55]



Scheme 23. Synthesis of (–)-stellettamide B

A large number of natural products and related compounds of biological and medicinal interest contain 2,4-dimethyl-1-penten-1,5-ylidene moieties and derivatives thereof. Nafuredin (**70**),[56] a selective NADH-fumarate reductase inhibitor, milbemycin β_3 (**71**),[57] a macrolide antibiotics, (–)-bafilomycin A_1 (**72**),[58] a potent vacuolar H^+-APTase inhibitor, are some of the representatives examples containing an (*E*)-trisubstituted alkene moiety, while discodermolide (**73**),[59] an anticancer marine natural product, for example, contains a (*Z*)-trisubstituted alkene. Others including (–)-callystatin A (**74**),[60] a potential antitumor polyketide, contain a disubstituted (*E*)-alkene.

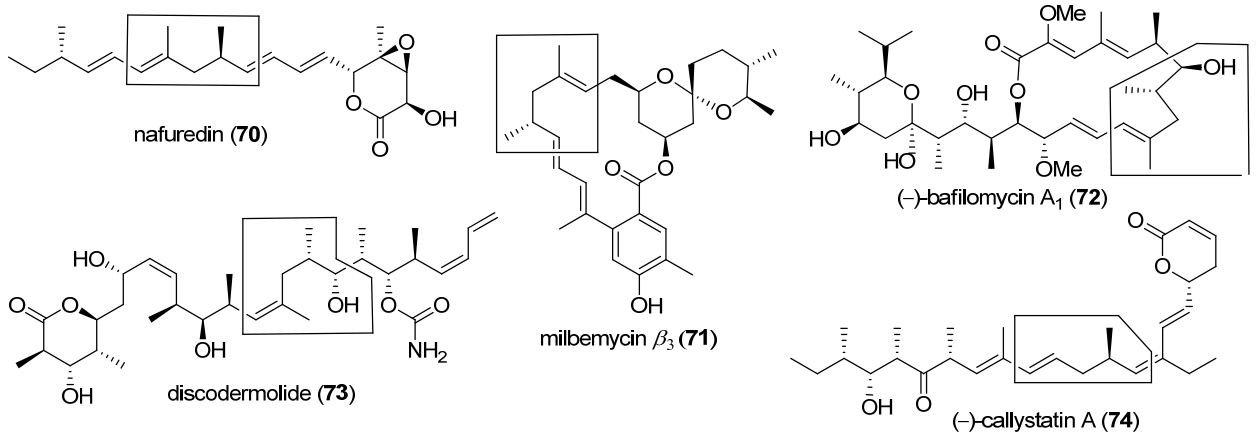
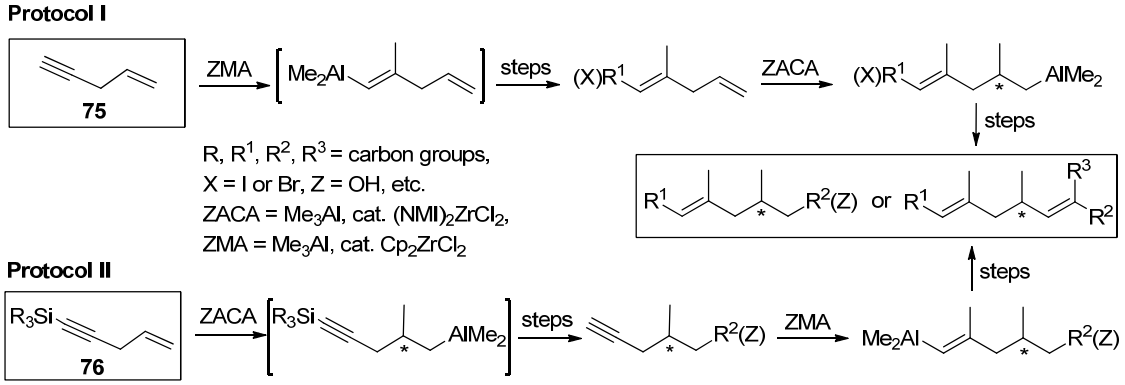


Figure 1. Some naturally occurring 2,4-dimethyl-1-penten-1,5-ylidene moieties of biological and medicinal importance

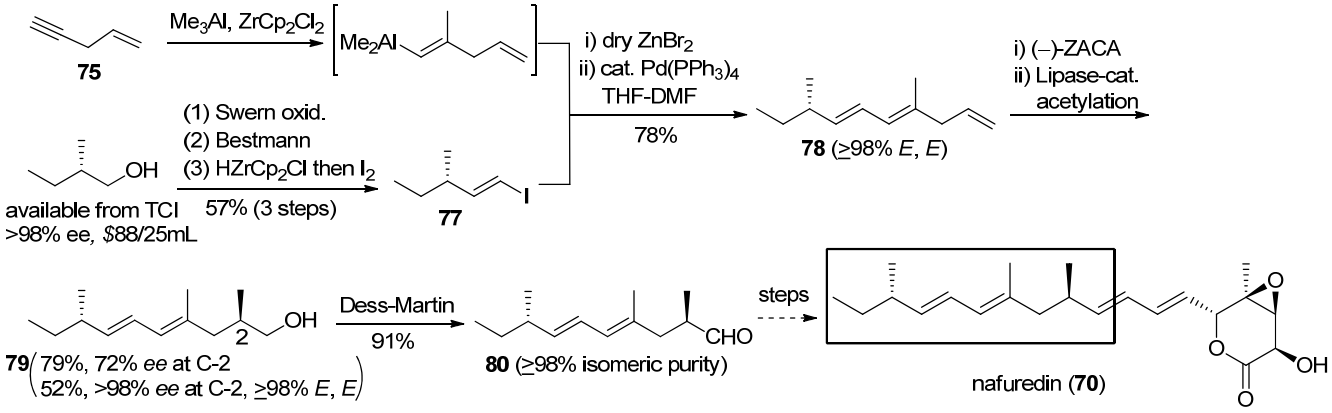
With the goal of developing widely applicable, efficient, and stereo- and regioselective synthetic protocols, two protocols with 1,4-pentenyne (**75**) and its silyl derivatives (**76**) as five-carbon synthons

have been developed for constructing 2,4-dimethyl-1-penten-1,5-ylidene derivatives via ZMA reaction and ZACA reaction (Scheme 24).[61]



Scheme 24. Two protocols to 2,4-dimethyl-1-pentene and 2,4-dimethyl-1,5-hexadiene derivatives

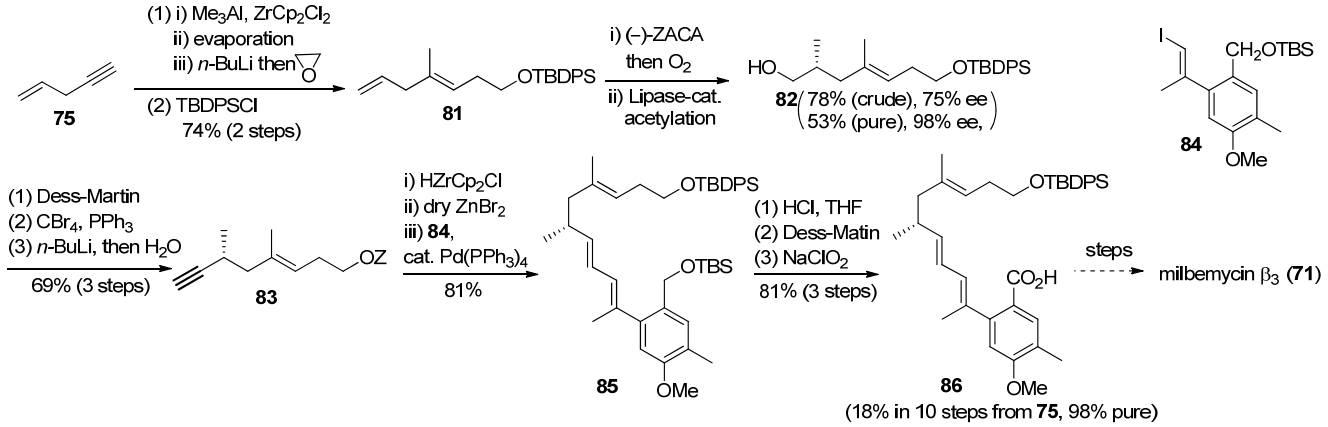
(2*R*,4*E*,6*E*,8*S*)-2,4,8-Trimethyldeca-4,6-dienal (**80**), a key intermediate for synthesis of nafuredin (**70**),[56] was prepared according to *Proctocol I* from **75** as shown in Scheme 25.[61] The conjugated diene **78** (≥98% *E*,*E*) was synthesized via Pd-catalyzed cross-coupling of **77** with alkenylaluminum intermediate obtained from ZMA reaction of **75**. Its ZACA reaction with (–)-$(NMI)_2ZrCl_2$ as a catalyst followed by oxidation with O_2 provided **79** in 79% yield and 72% *ee* (C-2). Although this compound contains two asymmetric carbon centers with a relatively rigid (*E*,*E*)-diene moiety between them, it was difficult to purify **79** by column chromatography. On the other hand, **79** of ≥98% *ee* (C-2) was prepared by lipase-catalyzed acetylation using Amano PS lipase in 52% overall yield from **78**. Oxidation of **79** with Dess-Martin periodinane provided **80** of ≥98% isomeric purity in 91% yield.



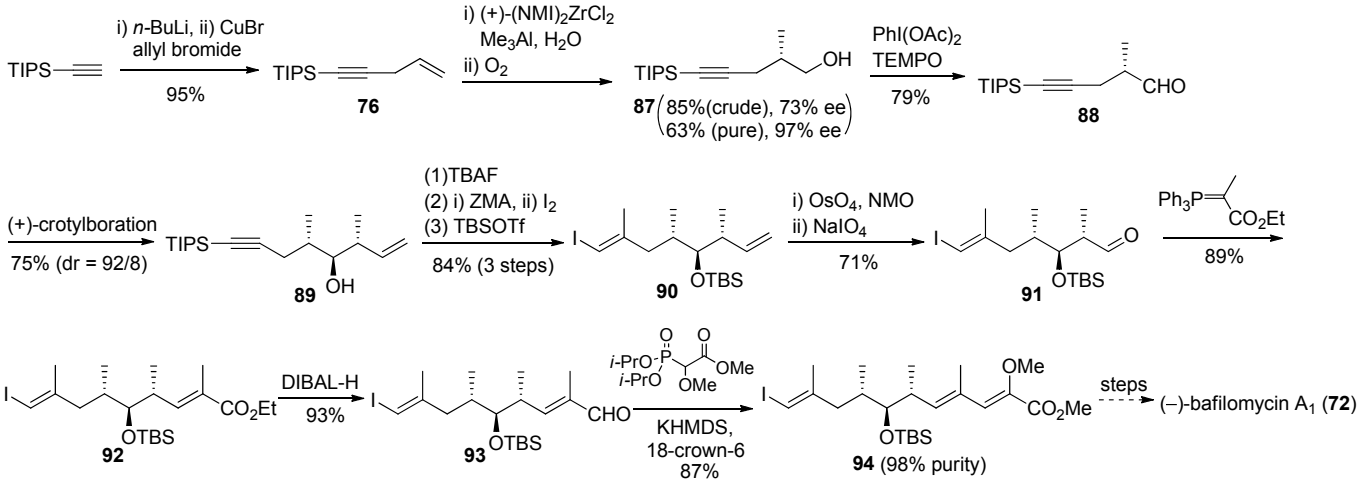
Scheme 25. Synthesis of **80** as a key intermediate of nafuredin (**70**)

For an efficient and selective synthesis of **86**, a potential key intermediate for the synthesis of milbemycin β_3 (**71**),[57] a 10-step synthesis converting **75** into **86** in 18% overall yield has been developed (Scheme 26).[61] Zr-catalyzed methylalumination of **75**, evaporation of the volatiles, ate complexation of the alane with *n*-BuLi, and addition of ethylene oxide in one pot produced **81** in 74% yield, after protection with

TBDPSCl. The ZACA reaction of **81** with Me_3Al (2.5 equiv) and 1% of (–)-$(NMI)_2ZrCl_2$ gave crude **82** of 75% *ee* in 78% yield. Its purification by lipase-catalyzed acetylation using Amano PS lipase provided **82** of 98% *ee* in 53% overall yield from **81**. After conversion of **82** into **83** in 69% yield over 3 steps, hydrozirconation–transmetallation–Pd-catalyzed alkenyl-alkenyl coupling with alkenyl iodide **84** produced **85** in 81% yield, which was further converted to **86** of ≥98% isomerical purity in 81% yield over three steps.[61] Alkenyl iodide **84** was prepared from commercially available 3-methyl-4-methoxybenzaldehyde in 36% overall yield over 5 steps with Pd-catalyzed Negishi alkynylation and Zr-catalyzed methylalumination as key steps.[61]



Scheme 26. Synthesis of **86** as a key intermediate of milbemycin β_3 (**71**)

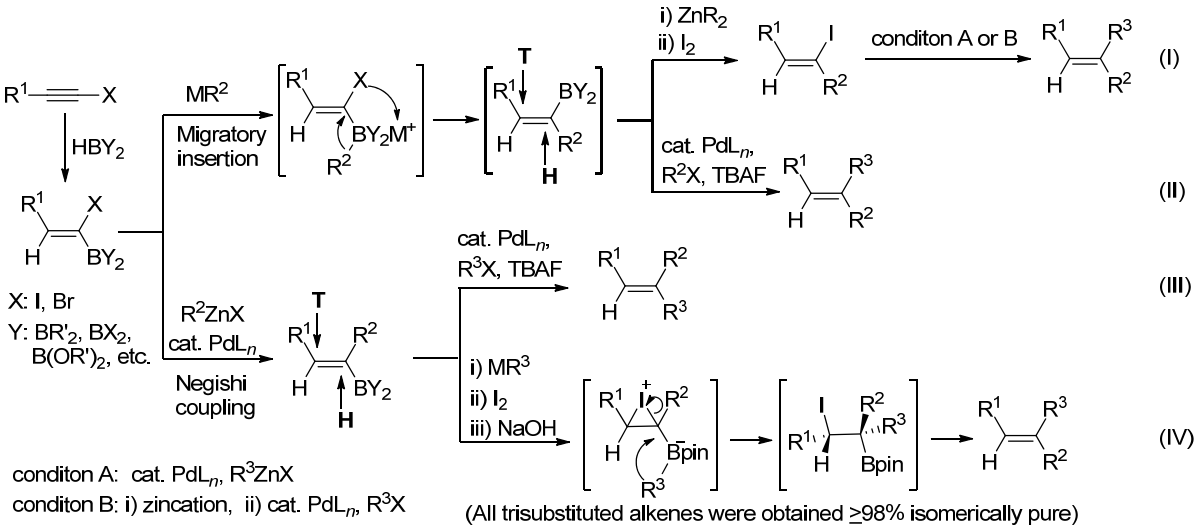


Scheme 27. Synthesis of **94** as a key intermediate of (–)-bafilomycin A_1(**72**)

Synthesis of intermediate **94**[58] for the synthesis of (–)-bafilomycin A_1 has been achieved as shown in Scheme 27.[61] TIPS-protected 1,4-pentenyne **76**, prepared by CuBr-catalyzed allylation of lithio derivatives of TIPS-protected ethynes with allyl bromide, was subjected to the ZACA reaction to produce crude **87** in 85% yield and 73% *ee*, which was readily purified to 97% *ee* by lipase-catalyzed acetylation. After conversion of **87** into **90** in 50% yield over five steps by oxidation, Brown crotylboration,

desilylation, ZMA/iodolysis, and protection with TBSOTf, oxidation of **90** with NMO/OsO_4 and $NaIO_4$ produced **91** in 71% yield, which was converted to **94** of >98% purity in 72% yield over 3 steps.[61]

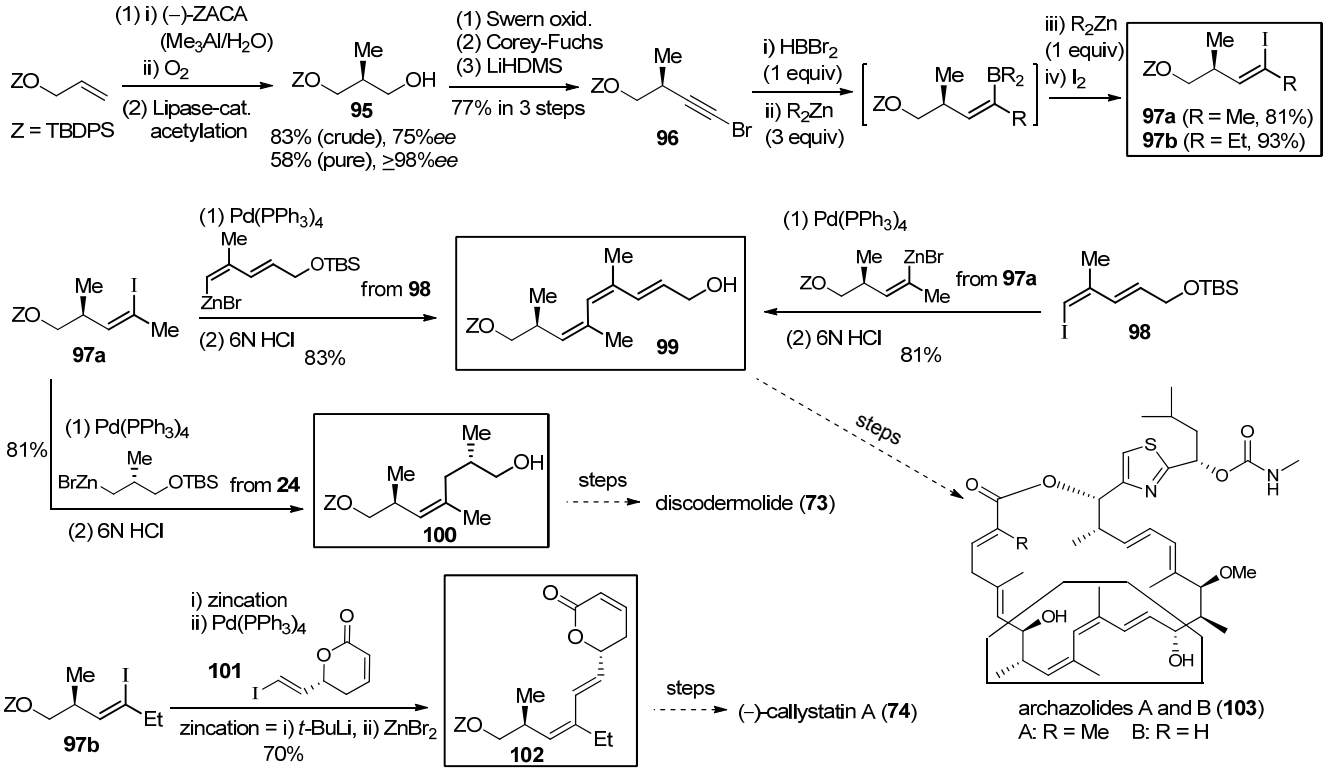
Trisubstituted alkenes including monoalkenes, conjugated dienes and oligoenes represent a wide variety of natural products. We have developed several simple and highly satisfactory procedures for synthesis of trisubstituted alkenes including both tail-to-head (**T**-to-**H**)[50,62,63] and head-to-tail (**H**-to-**T**)[64] construction directions. Four **T**-to-**H** routes have been developed for highly stereo- and regioselective synthesis of trisubstituted alkenes via (*Z*)-1-halo-1-alkenylboranes as key intermediates, prepared via hydroboration of 1-halo-1-alkynes (Scheme 28).[50,63] Route I consists of (i) 1-halo-1-alkyne hydroboration, (ii) migratory insertion of 1-halo-1-alkenylboron derivatives, (iii) Zn-promoted transmetalative iodinolysis, and (iv) Pd-catalyzed Negishi cross-coupling with alkenylzincs.[63] This protocol has been applied to the syntheses of the key intermediates of several natural products including archazolid A and B (**103**),[65] discodermolide (**73**),[59] and (–)-callystatin A (**74**).[60]



Scheme 28. T-to-**H** construction routes to stereodefined trisubstituted alkenes

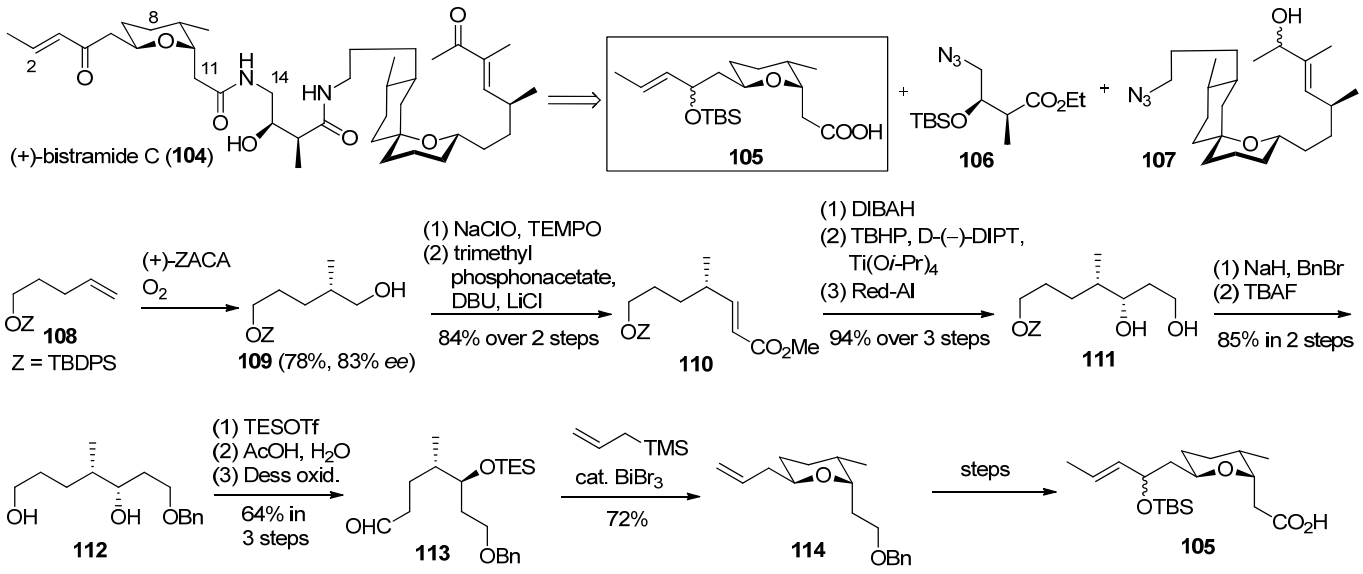
As shown in Scheme 29, the (–)-ZACA/oxidation of TBDPS-protected allyl alcohol produced crude **95** of 75% *ee* in 83% yield, which was readily purified to >98% *ee* by Amano PS lipase-catalyzed acetylation due to the notable selectivity-enhancing effect of proximal heterofunctional TBDPS group. After conversion of **95** to 1-halo-1-alkyne **96** in 77% yield over 3 steps, hydroboration of **96** followed by migratory insertion with dialkylzincs (3 equiv) gave alkenylboranes. Although their Pd-catalyzed Suzuki coupling had been problematic, their *in situ* transmetallation to the corresponding Zn derivatives with additional dialkylzincs (1 equiv) and sequential iodinolysis gave alkenyl iodide **97**, which have been shown to readily undergo highly demanding Pd-catalyzed Negishi coupling, as exemplified by the synthesis of potential intermediates **99**, **100**, and **102** for archazolid A and B (**103**),[65] discodermolide (**73**),[59] and (–)-callystatin A (**74**)[60] (Schemes 29), respectively. More recently, three other simple and

highly efficient routes II, III, IV have also been developed in the authors' group, which promise to provide ultimately satisfactory protocols to trisubstituted alkenes.[50] Route IV has been applied to highly selective synthesis of side chain (**49**) of scyphostatin (**55**) from allyl alcohol as discussed in Scheme 19.[50]



Scheme 29. Syntheses of **99**, **100**, **102** as key intermediates of archazolid A and B (**103**), discodermolide (**73**), and (–)-callystatin A (**74**), respectively

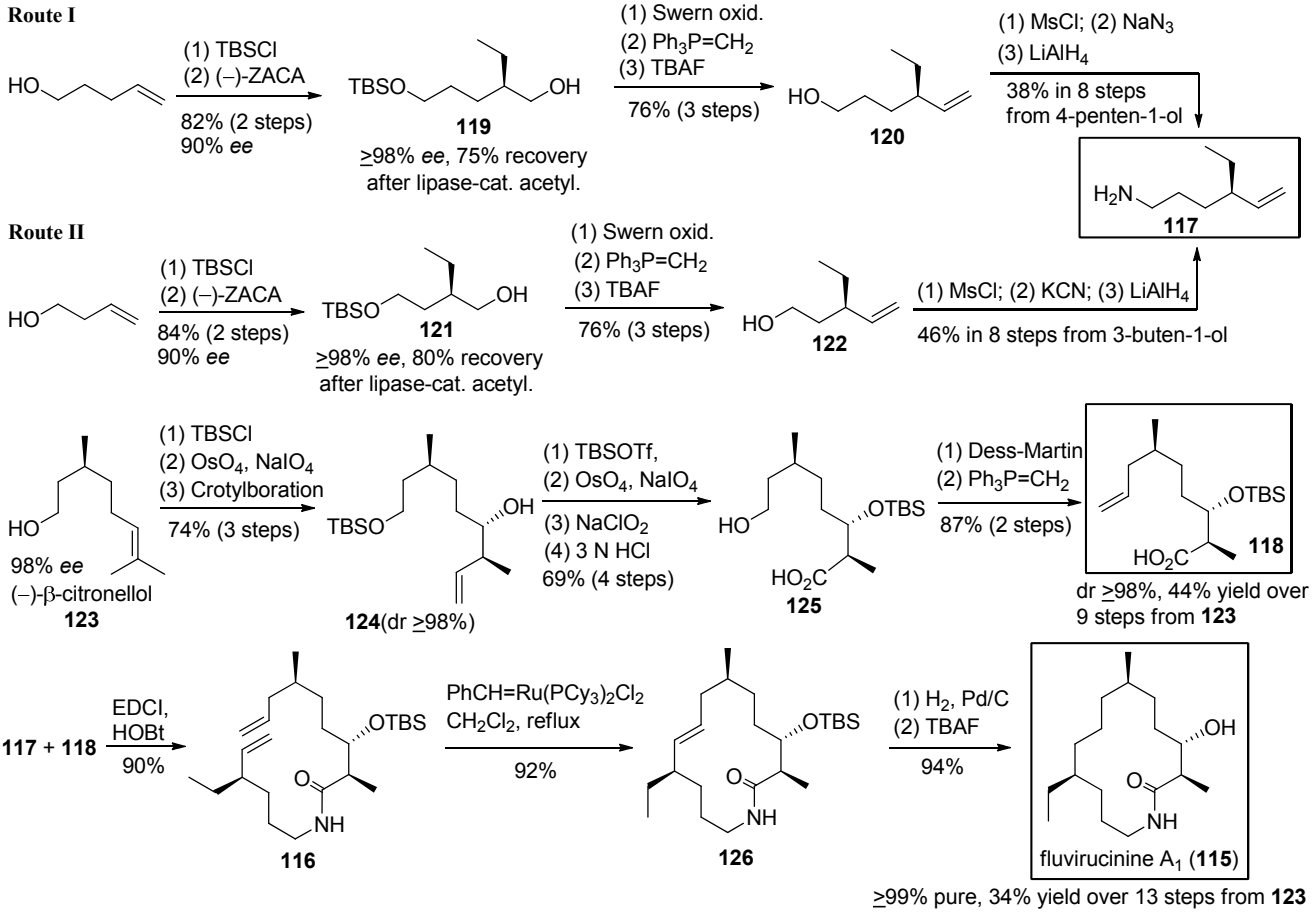
Wipf and co-worker reported the first total synthesis of a marine natural product (+)-bistramide C (**104**) via a triple convergency and a late-stage linkage of acid **105** to ester **106** and spiroketal **107** by azide couplings (Scheme 30).[66] The preparation of segment **105** began with the ZACA reaction of terminal alkene **108** in the presence of 2.8 mol% of (+)-$(NMI)_2ZrCl_2$, $AlMe_3$ (4.3 equiv) and MAO (1.5 equiv) providing **109** in 78% yield and 83% *ee*. Oxidation of **109** with NaOCl and a catalytic amount of TEMPO, followed by a HWE reaction provided enoate **110** in 84% yield. After conversion of enoate **110** into 1,3-diol **111** via a DIBAH reduction followed by a Sharpless asymmetric epoxidation and reductive opening of the resulting epoxy alcohol with Red-Al, the 1,3-diol **111** was converted to 1,5-diol **112** by selective protection and desilylation with TBAF. The 1,5-diol **112** was further transformed into the aldehyde **113** in 64% over three steps. The construction of *trans*-2,6-substituted tetrahydropyrans **114** was achieved via a tandem bismuth(III)-initiated etherification–allylation process[67] in 72% yield and >5:1 diastereomeric ratio. The key intermediate **105** was then prepared from **114** in six additional steps, which was used in the final assembly of (+)-bistramide C (**104**).[66]



Scheme 30. Synthesis of **105** as a key intermediate of (+)-bistramide C (**104**)

Fluvirucinine A_1 (**115**) is an aglycone of fluvirucin A_1 exhibiting considerable inhibitory activity against influenza A virus.[68] A convergent and highly efficient synthesis of fluvirucinine A_1 (**115**) via **116**, which was obtained from **117** and **118**, has been achieved as shown in Scheme 31.[69] Two enantioselective routes to **117** were achieved in a similar manner with ZACA–lipase-catalyzed acetylation as key steps. In Route I, crude **119** was obtained by the ZACA reaction of TBS-protected 4-penten-1-ol with Et_3Al (2 equiv), isobutylaluminoxane (IBAO, 1 equiv), and just 0.1 mol% of (–)-$(NMI)_2ZrCl_2$ in 82% yield and 90% *ee*. Its lipase-catalyzed acetylation with Amano PS lipase gave **119** of ≥98% *ee* in 75% recovery. After six additional steps, including formation and reduction of an azide, (*R*)-**117** of ≥98% *ee* was obtained in 38% yield over 8 steps from 4-penten-1-ol (Route I in Scheme 31). Similarly, 3-buten-1-ol was protected with TBSCl and was subjected to the ZACA reaction with Et_3Al, IBAO, and 0.1 mol% of (–)-$(NMI)_2ZrCl_2$. The crude **121** was obtained in 84% yield and 90% *ee*, which was readily purified to the level of ≥98% *ee* in 80% recovery by Amano PS lipase-catalyzed acetylation. These results clearly indicate that the ZACA–lipase-catalyzed acetylation protocol promises to provide a very favorable route to 2-alkyl-1-alkanols, where the 2-alkyl group is ethyl or a higher primary alkyl group in high enantiomeric purity. After six additional well-known steps including cyanation and reduction with $LiAlH_4$ of the formed nitrile, **117** of ≥98% *ee* was produced in 46% yield over 8 steps from 3-buten-1-ol (Route II in Scheme 31). The higher overall yield and the use of less expensive 3-buten-1-ol make Route II somewhat more attractive than Route I. Preparation of the other key intermediate **118** was achieved by conversion of (–)-(*S*)-*β*-citronellol (**123**) in 44% yield over nine steps, including the Brown crotylboration, OsO_4-catalyzed oxidative alkene cleavage with $NaIO_4$ used twice, Swern oxidation, and Wittig olefination. The final assembly of fluvirucinine A_1 (**115**) was performed by amidation of **117** with **118**,

Ru-catalyzed ring closing metathesis (RCM), hydrogenation, and desilylation with TBAF. Thus, fluvirucinine A_1 (**115**) was prepared in 34% yield over 13 steps from commercially available (–)-(*S*)-*β*-citronellol.[69]



Scheme 31. Total synthesis of fluvirucinine A_1 (**115**)

3. CONCLUSION

The ZACA reaction is a novel and as yet rare catalytic asymmetric C–C bond forming reaction of terminal alkenes of one-point-binding without requiring any other functional groups, even though various functional groups may be present. Since it provides organoaluminium intermediates which allow for a wide range of *in situ* transformations, ZACA reaction has a high synthetic potential. Despite some room for improvement, especially (i) improvement of the enatioselectivity of carboalumination and (ii) realization of higher turnover numbers through elevation of the current level of $20–10^3$ to $\geq 10^3–10^4$ or higher via systematic rational design and screening of chiral ligands, even at the current level of development, ZACA reaction provides a widely applicable, efficient and selective method for catalytic asymmetric C–C bond formation, which has already been used to significantly modernize and improve syntheses of natural products including deoxypolypropionates, isoprenoids, and other heterocyclic

compounds of biological and medicinal interest. We believe that ZACA reaction will be widely embraced by the organic synthetic community in the near future.

4. ACKNOWLEDGEMENTS

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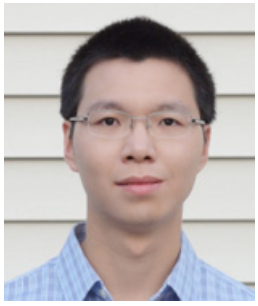

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