Account

Regulation of Stereoselectivity and Reactivity in the Inter- and Intramolecular Allylic Transfer Reactions

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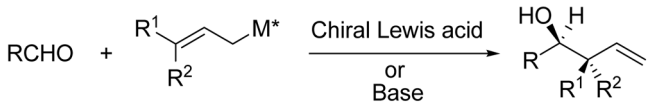
The preparation of enatiomerically enriched homoallylic alcohols through asymmetric addition of chiral allylic transfer reagents and allylating reagents with chiral catalysts to the carbonyl functionalities represents an important chemical transformation. Excellent progress has been made over past decade in the development and application of catalytic asymmetric allylic transfer reactions. In this account, our efforts for the various intermolecular allylic transfer reactions such as allylation, propargylation, allenylation, and dienylation utilizing accelerating strategy and sequential allylic transfer reactions to achieve multiple stereoselection mainly using transition metal catalysts are described.

Key Words : Allylation, Asymmetric synthesis, Catalyst, Selectivity, Stereochemistry

Introduction

The availability of efficient synthetic methods for achieving absolute stereoselectivity *via* catalytic process in the production of enantiomerically pure compounds is of considerable current interest because such products can be used as chiral building blocks for the synthesis of valuable chiral substances.[1] In the light of widespread advances in catalytic methods for the synthesis of chiral substances, the allylic transfer reactions of carbonyl functionalities using chiral auxiliaries or catalysts led to significant developments in the area of asymmetric synthesis.[2] Numerous successful methodologies using stoichiometric amounts of chiral reagents and catalytic amount of chiral Lewis acid or base have been developed and applied to organic synthesis (eq. 1).



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Subsequent early studies on the utilization of chirally modified allylic boranes to accomplish asymmetric induction by Hoffmann,[3] many research groups have been made important contributions to the extension of this protocol to achieve high levels of stereoselectivity.[4] The exceptional power of the allylic transfer reactions to aldehydes in forming enantioenriched alcohols has been enhanced by newly developed catalytic versions, especially chiral Lewis acids[5] or chiral Lewis bases[6] catalyzed addition of achiral reagents to a carbonyl functionality. Two typical mechanisms, Lewis acid- and Lewis base-catalyzed mechanism, can be considered for the allylic transfer reactions as illustrated in Scheme 1. If chiral metal catalysts shown in Scheme 1 act as a Lewis acid in the asymmetric allylation, an aldehyde is coordinated to this catalyst first and then reaction by an allylmetal (M = SiR_3 or SnR_3) takes place *via* an acyclic antiplanar model. On the other hand, chiral Lewis bases shown in Scheme 1 to activate allylmetal reagent (M = SiX_3) begins by coordination of the base to the central, electrophilic metal. The resulting complex retains sufficient Lewis acidity to coordinate the aldehyde, and the ternary complex of allylmetal, aldehyde, and chiral Lewis base reacts through a closed model. Reactive intermediates derived from chiral Lewis acid or bases could provide an opportunity to control stereoselectivity to realize asymmetric allylation.

This account describes our resent approaches an accelerating strategy to enhance reactivity and stereoselectivity for

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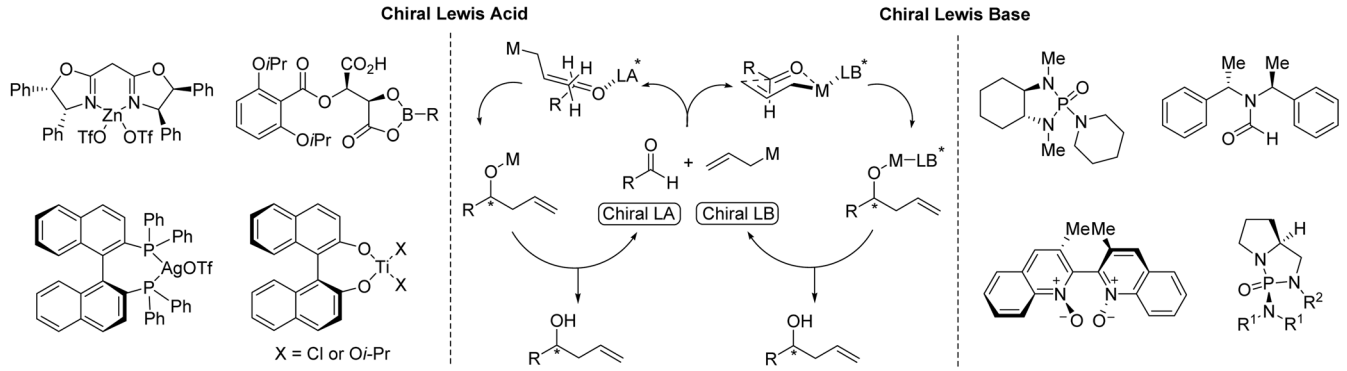


Scheme 1. Asymmetric allylations catalyzed by chiral Lewis acid and base.

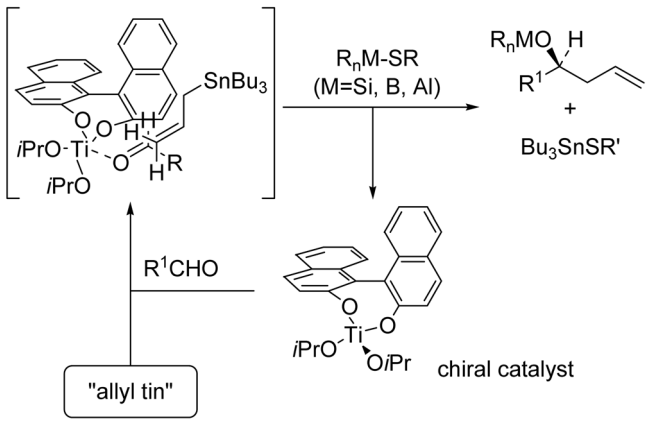
the intermolecular allylic transfer reactions of aldehydes to provide a variety of enatiomerically enriched alcohols and a sequential allylic transfer strategy mainly utilizing transition metal catalysis to achieve excellent stereoselectivities in short course.

Intermolecular Allylic Transfer Reactions

Catalytic Asymmetric Allylation and Propargylation. The first example of catalytic asymmetric allylations was reported by Yamamoto using chiral acyloxyl borane (CAB) as a chiral Lewis acid.[7] One of the most extensively studied chiral Lewis acid catalyzed reactions employs titanium complexes of the BINOL (1,1'-binaphthalene-2,2'-diol).[8] The application of BINOL-Ti(IV) complexes in enantioselective allylation was first reported by Mikami in the addition of allylsilane or allylstannane to glyoxylates.[9] The extension of the BINOL-Ti(IV) system to normal aldehydes was independently reported to realize high enantioselectivities by Tagliavini and Keck.[10] Nonetheless each of known methods has exhibited the problems, for instance, restriction of reagents and substrates, longer reaction time, and inefficient catalytic ability. The development of synthetic methods for achieving absolute stereoselectivity by the utilization of chiral catalysts increasingly requires precise control of the reaction pathway based on the mechanistic behavior and rational design of new reagents and processes. Of particular interest is chiral modified ligand accelerating strategy mainly due to the stereoselective pathway could dominate over the nonselective route.[11] Furthermore, this system can be allowed to use extra reagent to regulate reaction pathway. The BINOL-Ti(IV) complex prepared from the reaction of BINOL and Ti(O*i*-Pr)$_4$ has proven to be ligand accelerating catalyst in comparison with Ti(O*i*-Pr)$_4$ as a role of Lewis acid catalyst.[12] This enhanced Lewis acidity may be interpreted by assuming that the favorable angular change of Ti(IV) species caused by chelation of sterically demanding BINOL into the pentacoordinate from the tetracoordinate resulted in the formation of vacant orbital to accommodate aldehyde. Even though there have been several elegant reports regarding chiral Lewis acid promoted allylation reaction in the literature, the lack of data concerning the synergistic additive effects to increase catalytic ability surprised us, in view of the expected similarity of such system to the well defined catalytic carbonyl addition reactions.[13] During the course of our research program aimed at finding new catalytic system for the stereoselective addition of an activated dihydropyran to aldehydes,[14] we became quite interested in the systematic study on the effect of additives into the BINOL-Ti(IV) catalyst system to increase reactivity and stereoselectivity.

Rationale for the introduction of a synergistic reagent into the catalytic system was based on simple speculation as illustrated in Scheme 2. In order to increase catalytic ability, regeneration of chiral catalyst as a consequence of dissociation of product from the reaction complex must be achieved. Thus, if a bifunctional synergistic reagent, R_nMSR' (M = Si, B, Al), could control the catalytic allylation process *via* the Sn-S (enhancement of Sn-C bond breaking) and M-O (dissociation of product) bond forming steps to reinforce regeneration of catalyst, practical and efficient catalytic asymmetric allylic transfer reactions might be realized in a predictable fashion. The key to our approach was the strong Sn-S and M-O bonds relative to the weaker M-S bond.

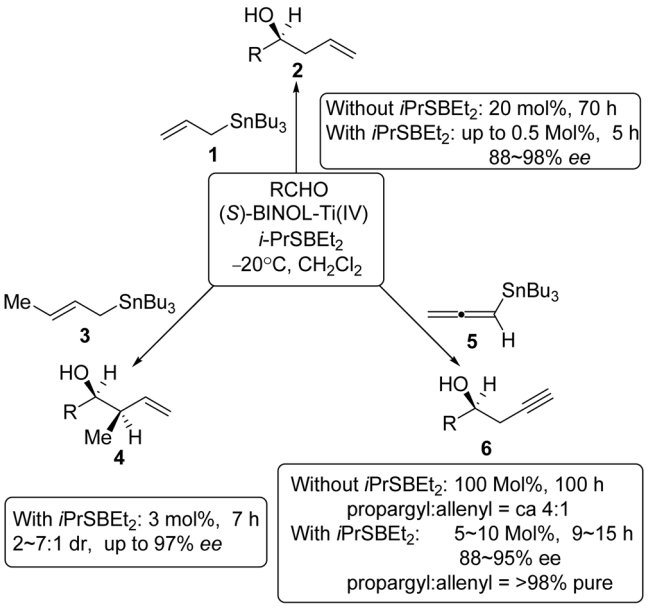
Indeed, we observed that the reaction rate could be enhanced by addition of a synergistic reagent such as *i*PrSSiMe$_3$, *i*PrSBEt$_2$, and *i*PrSAlEt$_2$; *i*PrSBEt$_2$ was generally superior and was chosen for systematic studies (Scheme 3).[15] In general, the allylation reaction of aldehydes with allystannane **1** catalyzed by the BINOL-Yi(IV) complexes is



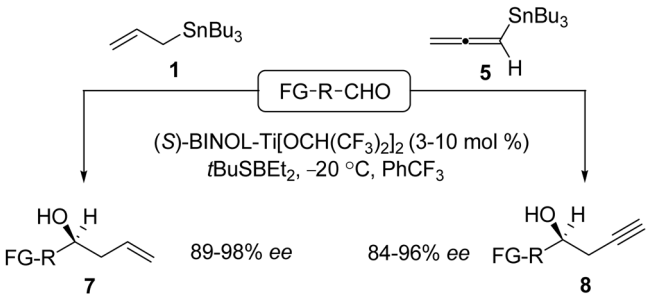
Scheme 2. Mechanistic aspect in catalytic allylic transfer reaction.

very slow and often requires extended reaction time, leading to irreproducibility. Research results revealed that efficient allylation was realized with *i*PrSBEt$_2$ at –20 °C for 5 h ($PhCH_2CH_2CHO$, 93% yield, 97% *ee*); this result is superior to the control system without using the synergistic reagent (–20 °C for 70 h, 78% yield, 94% *ee*). This result clearly indicated that the synergistic reagents is thought to dissociate the product by taking advantage of the strong affinities of Sn-S and M-O bonds to facilitate regeneration of the catalyst. We also found that the use of *i*PrSBEt$_2$ as a synergistic reagent accelerates the chiral BINOL-Zr(IV) asymmetric allylation reaction and suppresses the concomitant Meerwein-Pondorf-Verley reduction with aldehyde presumably due to an acceleration of the reaction rate for the allylic transfer.[15c] Always with the goal of enhancement of reaction rates and greater selectivity, we found more practical synergistic reagent $B(OMe)_3$, but with limited applicability.[15d] Yields and enanatioselectivitie comparable to those with other additives have been obtained. This method has been often employed in the synthesis of natural products.[16] Extension of this protocol to the addition of crotylstannane **3** with *i*PrSBEt$_2$ in the presence of BINOL-Ti(IV) complex revealed that the products are obtained with high enanatioselectivities, but somewhat lower *syn* selectivities to be 3-7 : 1 (Scheme 3).

In view of similarity of mechanistic behavior, the addition of allenic reagent **5** to aldehydes to afford the homopropargylic alcohols **6** closely resembles the corresponding reaction with allylic reagents. However, reactivity of allenylstannane **5** has been known to be less reactive than allylstannane **1** due to the development of positive charge at an sp carbon during the electrophilic addition to the allenyl moiety.[17] The enantioselective propargylation of aldehydes with allenylstannane **5** required the use of nearly stoichiometric amounts of BINOL-Ti(IV) complex and longer reaction time (100 h at –20 °C).[18] Even though enantioselectivities turned out to



Scheme 3. Catalytic asymmetric allylation and propargylation.



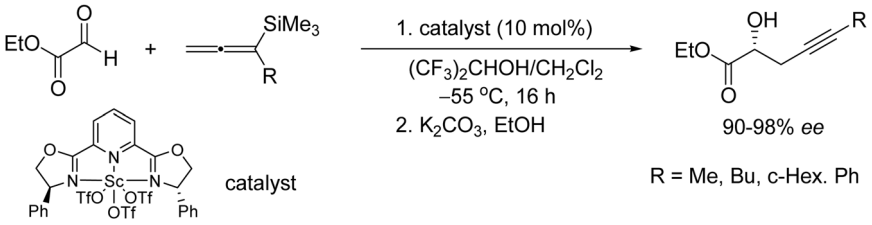
Scheme 4. Catalytic allylic transfer reactions of functionalized aldehydes.

be high, reaction also produced isomeric allenic alcohols (*ca* 4 : 1 ratio). However, the reaction rate of propargylation is significantly enhanced when *i*PrSBEt$_2$ is added.[19] Furthermore, we observed that the reaction produced only homopropargyl alcohols **6** with high levels of enantioselectivity. Both BINOL-Ti(IV) and BINOL-Zr(IV) complexes could be employed in the addition, although the BINOL-Ti(IV) catalyst provided marginally higher enanatioselectivities.

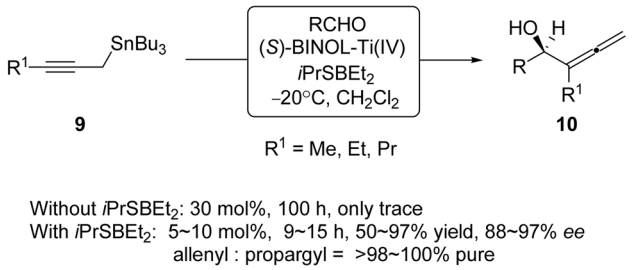
Interesting observations were made when this protocol applied to the allylic transfer reactions of functionalized aldehydes as shown in Scheme 4.[20] Remarkable effects caused by synergistic reagent were observed, which expedites the catalytic process for asymmetric allylation and propargylation of a variety of aldehydes containing additional carbonyl unit with high levels of enantioselectivity. The coordination of the boronyl product with a normal aldehyde could retard reaction rates. Surprisingly, allylic transfer reactions of functionalized aldehydes were superior to those of normal aldehydes in terms of reaction times and catalytic ability. The enhanced reactivity of functionalized aldehydes especially for propargylation might be explained by the intramolecular coordination of an additional carbonyl unit with the boronyl group in product.

Recently, Evans showed allenyltrimethylsilanes could be a function as propargylation reagent.[21] The addition of allenyltrimethylsilane to ethyl glyoxylate in the presence of chiral catalyst (10 mol%) based on the scandium triflate complex resulted in the formation of the homopropargylic alcohols in high yields and enanatioselectivity. This reaction underwent under milder conditions and provided the product with high regioselectively.

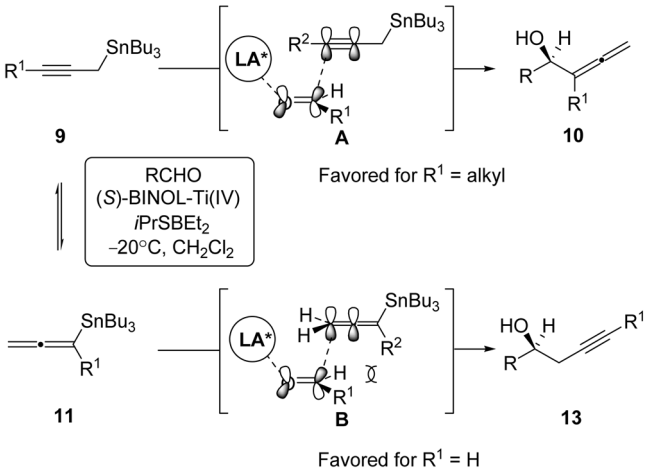
Catalytic Asymmetric Allenylation. The accessibility of practical methods for the synthesis of allenic alcohols is often limited by the tendency of propargylic reagents to couple with carbonyl units to produce allenic alcohols mainly with the lack of regiochemical selectivity.[22] Recently, an efficient method in the enantioselective synthesis of allenic alcohols *via* self-immolative transfer of chirality employing stoichiometric amount of non-racemic propargylstannanes with aldehydes has been reported.[23] While a couple of propargylboranes employing stoichiometric chiral auxiliaries have been developed to achieve a highly enantio- and regioselective synthesis of allenic alcohols,[24] a catalytic version of allenylation of aldehydes had not been realized.



Scheme 5. Catalytic asymmetric propargylation with allenylsilane.



Scheme 6. Catalytic asymmetric allenylation.

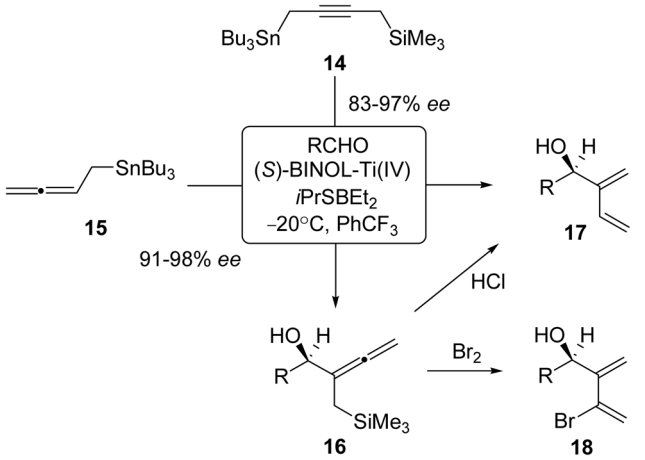


Scheme 7. Reaction pathways *via* equilibrium of tin reagents.

We felt that our strategy could prove to be effective for the catalytic allenylation of achiral aldehydes. Under similar conditions as described for propargylation, propargylic stannanes **9** successfully add to aldehydes to provide the allenic alcohols **10** in high yields and selectivities as shown in Scheme 6.[25] However, sterically bulk aldehyde such as isovaleraldehyde provided relatively lower yield and enantioselectivity (50-70% yield, 81-90% ee).

An interesting regioselectivity convergence was observed in these reactions using either allenic or propargylic stannanes. For example, the remarkable regulation of equilibrium between allenyl- and propargylstannane reagents under the reaction condition was observed. We were surprised to find that the reaction of **11** (R^1 = Me, 87 : 13 mixture) with hydrocinnamaldehyde under the same conditions afforded the alcohol **10** in 75% isolated yield and 92% *ee*. This high regio- and enantioselectivity in the formation of allenyl alcohol **10** from allenyltin **11** (R^1 = Me) at –20 °C mediated by BINOL-Ti(TV) complex is virtually identical to that observed with propargyltin **9**. This is not a common case because allenyltin usually converted to propargyl alcohol with aldehyde mediated by a Lewis acid catalyst in the absence of equilibrating reagents such as $BuSnCl_3$. On the other hand, both propargyltin **9** (R^1 = H) and allenyltin **11** (R^1 = H) under identical conditions were shown to produce the same propargyl carbinol **13** (R^1 = H) as a major component. In general, allenic stannane reagents lead to the formation of propargylic adduct and propargylic isomers to allenic adduct *via* S_E2' addition to aldehyde. These apparent contradictions could be accounted that the reaction produced products originated from the equilibrium between allenyl- and propargyltin reagents under the reaction condition. Since antiperiplanar attack would lead to the particular product **10** or **13** *via* transition state **A** or **B**, the major reaction pathway could be dependent on the stability in the transition state under kinetic control such as orientations and steric factors without a necessary link to product stability as depicted in Scheme 7. Thus, we believe that the origin of regiochemical outcomes for these transformations might be a thermodynamic factor of tin reagents rather than original concentration as well as subtle geometrical preferences for orientation in the transition states offered by the three dimensional catalytic system.

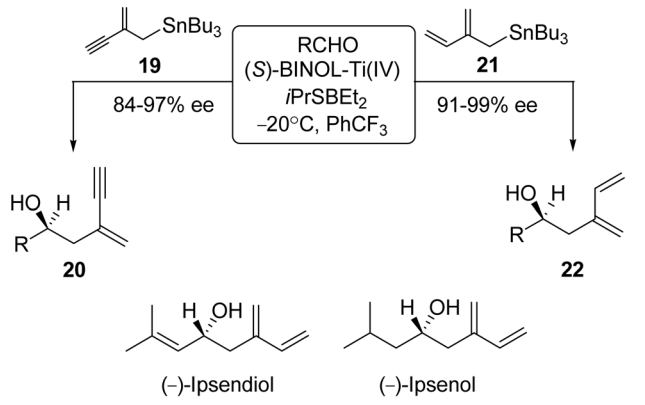
Catalytic Asymmetric Dienylation. The efficiency of our protocol of an acceleration strategy in terms of enantioselectivity and catalytic ability has encouraged us to apply the extension of this method to more versatile systems which would expand the scope and utility of allylic transfer reactions. Even though the enantioselective synthesis of dienyl alcohols using stoichiometric chiral reagents was documented in the literature, a catalytic version of dienylation had not been reported until we set out the program.[26] Eventually, two versions of the catalytic asymmetric dienylations have been developed. We demonstrated the enantioselective synthesis of dienyl alcohols by two step sequence employing new tin reagent **14** as depicted in Scheme 1.[27] In this study we focused on the sequential addition of a bifunctional reagent to aldehydes followed by second electrophiles to form dienyl carbinols. Catalytic enanatioselective addition of **14** to aldehydes provides **16** under the similar conditions described for the allylation in high levels of enantioselectivitiy, which can be converted with second electrophiles such as HCl and Br_2 to the corresponding dienyl alcohols **17** and **18** respectively. To provide direct access to the dienyl alcohols **17**, we considered the allenyltin compound **15** as an allylating reagent. Indeed, reaction with **15** under identical



Scheme 8. Catalytic asymmetric dienylation.

conditions provided **17** in high enantioselectivities as shown in Scheme 7.[28] Again, the utilization of synergistic reagent *i*PrSBEt$_2$ turned out to be crucial to enhance reactivity in both cases.

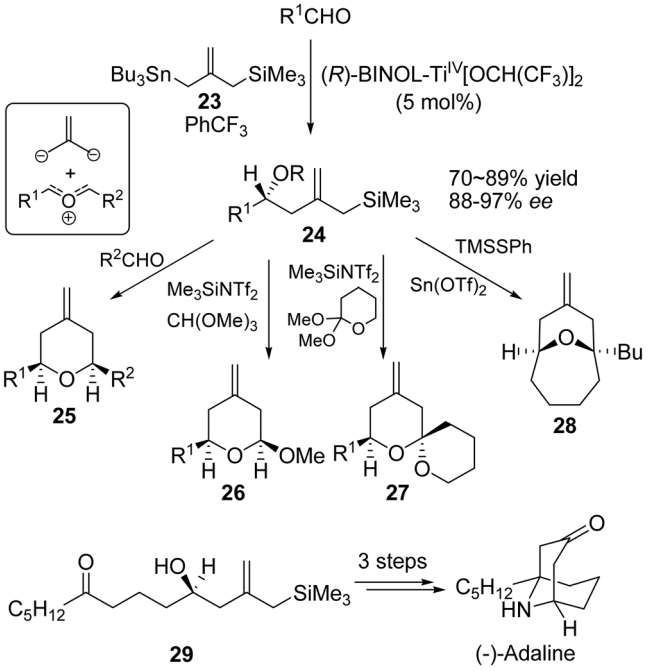
With these observations in hand, we extended the scope to one carbon homologated systems such as **20** and **22**. The realization of an efficient method for the synthesis of **20** and **22** should be valuable because the structures are featured in biologically relevant substances, and the many useful functional group transformations can be foreseen for enynyl and dienyl moieties. Our approach for the catalytic asymmetric enylation of new tin reagent **19** involving the use of (*S*)-BINOL-Ti(IV) complex along with *i*PrSBEt$_2$ has shown to provide highly enantioselective version of allylic transfer reactions of achiral aldehydes in the production of enantio-enriched alcohols **20**.[29] Key to this success was an availability of the new reagent **19**, which was prepared from commercially available 2-methyl-1-buten-3-yne by a single operation. With this research results, we turned our attention to examine possibility of this approach with dienyltin reagent for the catalytic asymmetric dienylation reaction of aldehydes. Asymmetric homodienylations of **21** were conducted on a variety of aldehydes to furnish the alcohols **22** with excellent enantioselectivities.[29] The direct synthetic application of catalytic asymmetric homodienylation was exemplified by the enantioselective syntheses of naturally occurring (–)-Ipsdienol and (–)-Ipsenol involving the use of (*R*)-BINOL-Ti(IV) complex, which are two of the aggregation pheromones isolated from the bark beetles *Ips paraconfusus*.



Scheme 9. Catalytic asymmetric enylation and homodienylation.

Sequential Allylic Transfer Reactions

Stepwise Sequential Allylic Transfer Reactions. Development of stereo-controlled consecutive processes can offer advantages over the multi step transformations by increasing chemical efficacy and saving efforts due to a simple operation.[30] In this study we concentrated on the sequential addition of a bifunctional reagent to aldehyde and then second aldehyde to form asymmetric tetrahydropyran system as outlined in Scheme 10. We have disclosed several crucial points including the development of new catalysts and reagents for the sequential allylic transfer reaction, the introduction of highly efficient promoter for the tetrahydropyran ring formation, and the highly stereoselective synthesis of four different tetrahydropyrands containing exocyclic olefin. After exploring various conditions, we were delighted to find that the use of alcohol free BINOL-Ti^{IV}[OCH(CF$_3$)$_2$]$_2$ as a chiral promoter in PhCF$_3$ always led to best results in terms of chemical yields and enantioselectivities. Furthermore, the new catalytic process was usually complete at –20 °C within 12 h with catalyst alone without using synergistic reagent. The second challenge in this study was the development of synthetic routes from **24** to a variety of tetrahydropyran unit as demonstrated in Scheme 10. Nonetheless, each of the published approaches suffers from major disadvantages such as low chemical conversion and diastereoselectivity, and often partial

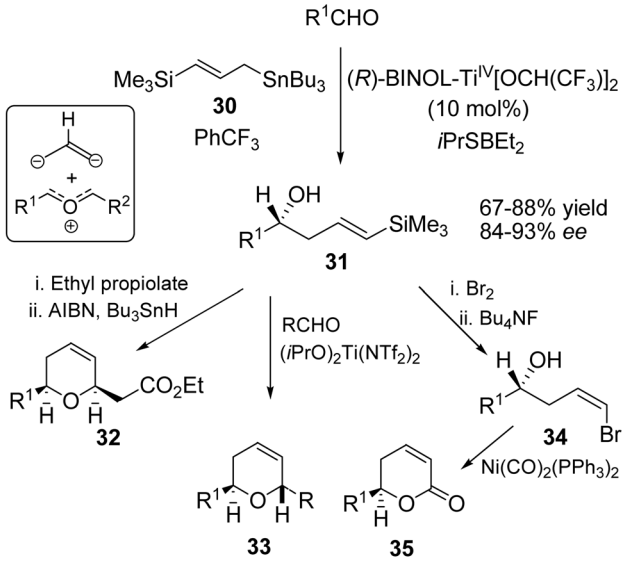


Scheme 10. First version of the stepwise sequential allylic transfer reaction.

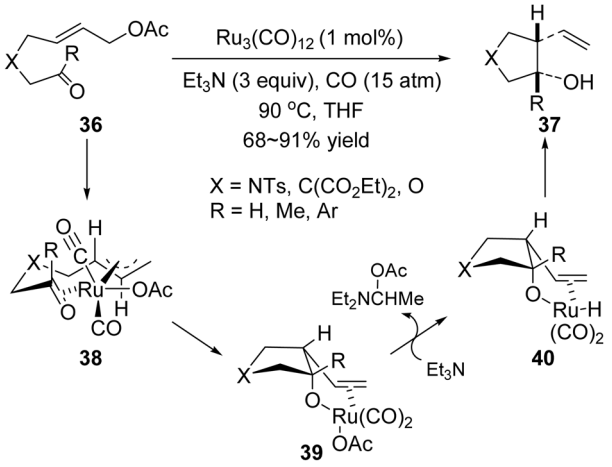
isomerization of exo-olefin to endo form. Fortunately, when $Me_3SiN(SO_2CF_3)_2$ (TMSNTf$_2$) was employed as a promoter, the cyclization process was greatly improved in terms of chemical yields and diastereoselectivity.[31] The synthetic application of this approach was achieved by the enantioselective synthesis of (–)-adaline.[32]

These results for the stepwise allylic transfer reactions led to the extension of stannyl reagent utilizing 3-trimethylsilyl-2-propenyltributylstannane **30** as a bifunctional allylating reagent. Although the reaction proceeded under similar conditions described for allylation, products were formed as an isomeric mixture and low chemical yield. Subsequently, we observed that the utilization of catalyst BINOL-Ti(IV)[OCH(CF$_3$)$_2$]$_2$ along with *i*PrSBEt$_2$ in the presence of 4 Å molecular sieves in PhCF$_3$ proved to be the most effective conditions.[33] Surprisingly the catalytic process always produced the 1,2-carbonyl addition adduct **31** as a single regioisomer (*E*)-vinylsilane instead of the usual 1,3-adduct. This observation could be accounted by a equilibrium of isomeric tin reagents regulated by an external chiral Lewis acid catalyst through the transition state based on the Curtin-Hammett principle. The products **31** are readily amenable for further conversion into useful synthetic intermediates by functional group transformations of vinylsilane as demonstrated in Scheme 11.

Intramolecular Allylic Transfer Reactions Promoted by Transition Metal Catalysts. The availability of efficient synthetic methods in the construction of cyclic systems *via* organotransition metal catalysts is of considerable current interest in organic chemistry.[34] Intramolecular allylic transfer reactions has proved to be useful transformations in the construction of five, six, and even larger rings for the synthesis of carbocyclic and heterocyclic biologically active molecules mainly through electrophilic cyclizations mediated by Lewis acid catalysts.[35] It was anticipated that the cyclization with proper modifications of substrates for



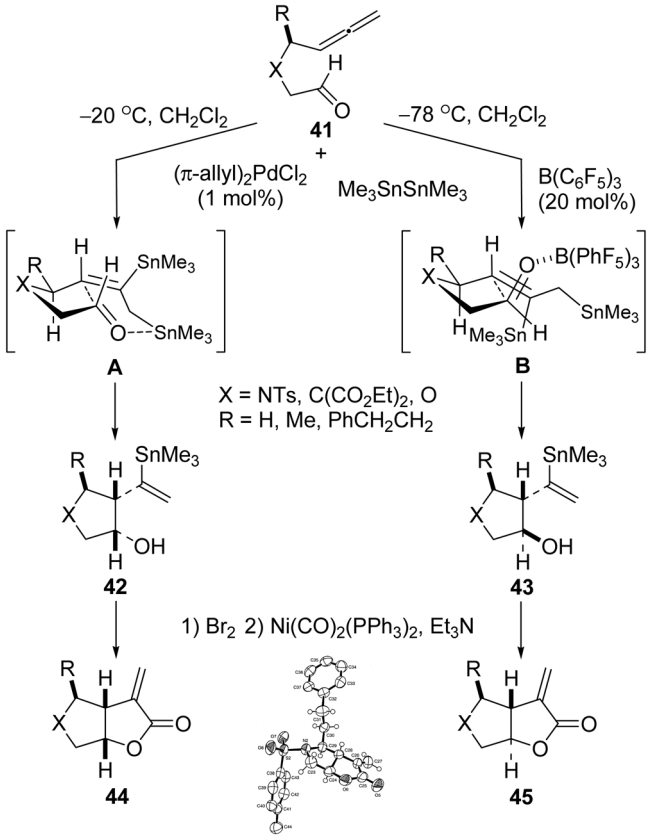
Scheme 11. Second version of the stepwise sequential allylic transfer reaction.



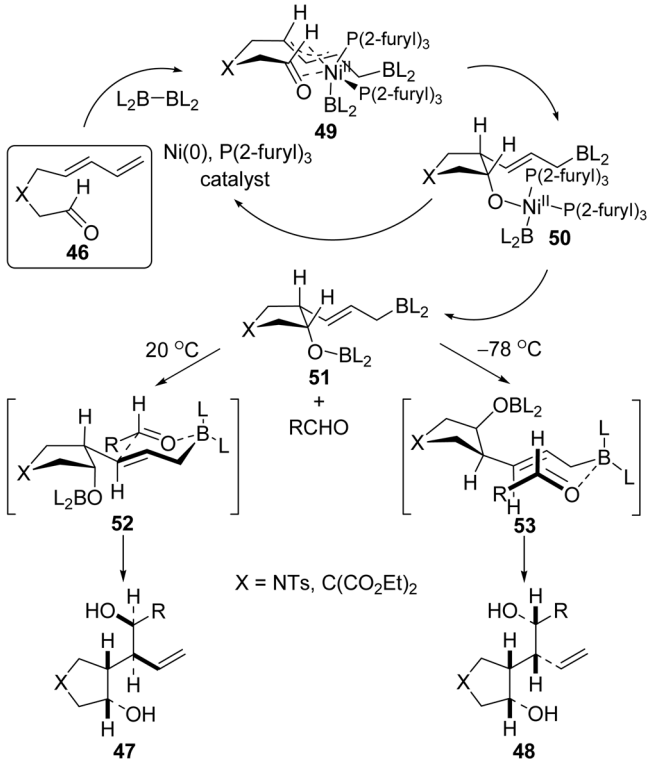
Scheme 12. Intramolecular allylic transfer reaction catalyzed by Ru complex.

metalation, especially π-allylmetals with catalysts, could be realized without using additional reagents. Unlike most other π-allylmetal complexes,[36] the wide range of oxidation states energetically accessible to ruthenium allows π-allylruthenium complexes to show nucleophilic character as well as electrophilic behavior.[37] With this issue in mind, our investigations began with **36** and a variety of transition metal complexes. Initial attempts to an intramolecular allylic transfer reaction of **36** indicated that the conversion to the corresponding **37** could not be realized with a variety of metal carbonyls including Rh, Mo, and Ni complexes under various reaction conditions mainly due to a lack of reactivity. Fortunately, we found that ruthenium complex could be effective catalyst for this purpose. Attempts on the catalytic carbocyclization of **36** with Ru$_3$(CO)$_{12}$ (1 mol%) in the presence of Et$_3$N at 90 °C under CO atmosphere (15 atm) in THF afforded **37** with optimal results through the reaction sequence as illustrated in Scheme 12.[38]

Recently we reported our discovery of several cyclization methods using allene functionalities by transition metal catalysis, as a part of the allylic transfer strategy. However, a majority of the methods in the cylization of an allene-aldehyde by transition metal catalysis provided the *cis* isomer as a major component.[39] Therefore, the development of synthetic route to the *trans* isomer under appropriate reaction conditions would expand the scope of the reaction. To solve the problems, our investigations began with **41** (X = NTs) and $Me_3SnSnMe_3$ and palladium complexes. Treatment of **41** with $Me_3SnSnMe_3$ in the presence of (π-allylPd)$_2$Cl$_2$ (1 mol%) at –20 °C for 30 min in CH_2Cl_2 afforded **42** as a sole product in 91%. Based on the reaction conditions for *cis* **42**, we carried out experiments to realize a reversal of distereoselectivity under various conditions. From the mechanistic perspective, major functions for the stereoselectivity are immediately discernable in the catalytic process. Scheme 13 could illustrate possible stereochemical routes for *cis* and *trans* stereoisomers. We reasoned that if the model **A**, assembled from the stereochemical route in addition of a bisstannane to **41** by transition metal catalyst,



Scheme 13. Reversal of stereochemistry by using a Lewis acid additive.



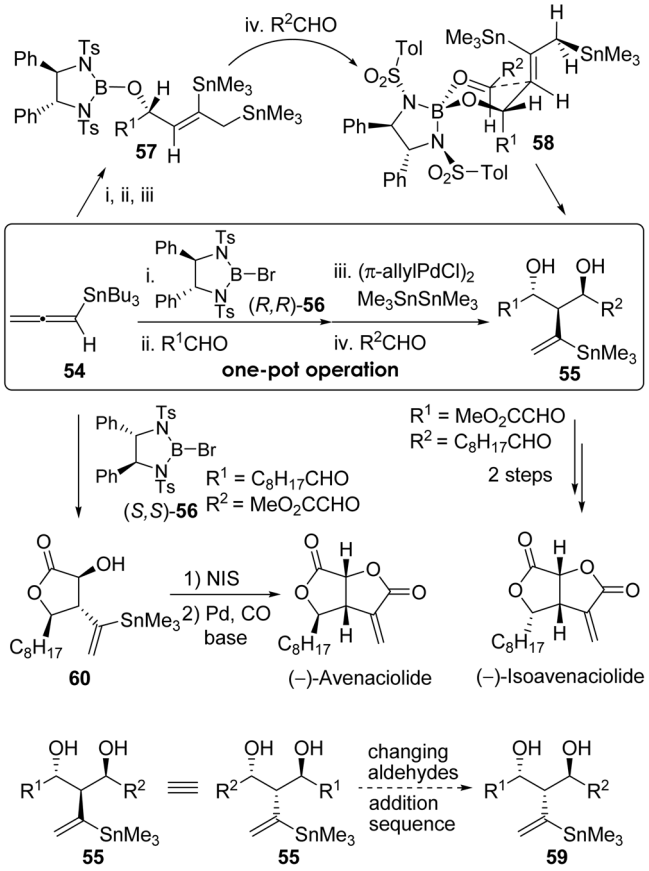
Scheme 14. Double Allylic Transfer Reaction.

was an intermediate on the reaction pathway, then it might be possible to reverse π-facial selectivity to yield *trans* **43** under a Lewis acidic condition *via* the model **B**. To prove this speculation, our investigations began with **41**, $Me_3SiSnMe_3$ and palladium complexes. After surveying numerous reaction conditions, we were delighted to find proper conditions to realize a reversal of stereoselectivity. A highly diastereoselective synthesis of **43** is achieved from the reaction of **41** with hexamethylditin catalyzed by palladium complex in the presence of 20 mol% tris-(pentafluorophenyl)borane as a Lewis acid additive for the reversal of diastereoselectivity.[40] The method is successful with various substrates **41** in good yields and high levels of diastereoselectivity.

Double Allylic Transfer Reactions Promoted by Transition Metal Catalyst. In order to achieve multiple stereoselectivity in one operation, we developed a doulbe allylic transfer reaction from a diene and diboronyl reagent with two aldehydes by a transition metal catalysis to form **47** and **48** with the generation of four contiguous stereogenic centers as depicted in Scheme 14. It was envisaged that the sequential allylic transfer reaction of **46** with two different aldehydes leading to the formation of **47** could be realized through a reaction route as described in Scheme 14.

To provide direct access to product **47**, we considered the potent precursor **49**, which would be obtained *via* a reductive p-allyl complex formation and a diboration from diene promoted by transition metal catalysis. However, initial attempts of a reaction of **46** with benzaldehyde and diboronyl reagent in the presence of transition metal complexes mainly employed for the diboration of an unsaturated bond indicated that the conversion to the desired **47** could not be satisfied with platinum, palladium, and rhodium complexes under the standard reaction conditions. Fortunately, we found that the use of Ni^0 complex led to the best results in terms of reactivity and stereoselectivity.[41] Eventually, we have developed the nickel-catalyzed sequential allylic transfer reaction of a diene with two aldehydes to establish four contiguous stereogenic centers in one-operation. This highly regio- and stereocontrolled protocol involves the nickel catalyzed metalloboration of diene, the intramolecular allylation in the construction of cyclic system, and the intermolecular crotylboration of aldehydes. In each case, the observed products indicate that the sterochemical outcomes of this transformation depend on the reaction temperature as shown in Scheme 14. The method is extended to the synthesis of 6-membered rings with up to 10 : 1 diastereomeric ratio.[42]

Asymmetric Sequential Allenylation-Allylation Using Palladium Catalyst with Bisstannane. With our observations of a series of sequential allylic transfer reactions, we concentrated on designing another sequential allylic transfer reaction from **54** with two aldehydes to form *acyclic* 2-(1-stannylvinyl)-1,3-diols **55** possessing versatile functional groups as shown in Scheme 15. It was expected that the sequential allylic transfer reactions starting from **54** with two different aldehydes in the formation of **55** could be achieved by the three steps sequence as described in Scheme 15.



Scheme 15. Asymmtric sequential allenylation/allylation process in one pot operation.

To explain this results, the distannyl compound **57** was considered as a crucial intermediate. This transformation involves the propargylboration with an aldehyde to yield the allenic species, the distannylation of an allene moiety using palladium catalyst to form the allylic tin reagent **57**, and the second allylic transfer reaction with another aldehyde by activation of the existing boronyl group. Indeed, the method is successful with a variety of aldehydes to yield the 2-(1-stannylvinyl)-1,3-diols **55** in good yields with exceptional diastereo- and enantioselectivities. The stereochemical outcome for the transformations can be explained by the analysis of stereochemical models as depicted in Scheme 15. Therefore, the preference for absolute and relative configurations for adducts from (*R,R*)-**57** with aldehydes could be predicted on the basis of a chair like stereochemical model **58**. The stereochemical course of this process for **55** is likely to be due to a geometrical preference for **58** offered by (*R,R*)-bissulfonamidyl ligand in **58** as illustrated in Scheme 15. Thus, the stereoselectivity for both first and second allylic transfer reactions must be controlled by the chiral ligand. The exceptional stereoselectivity can also be explained by assuming that the tight coordination of aldehyde to the boronyl moiety must be required for the new C-C bond formation by the overlap between carbonyl and olefin with optimum stereoelectronics and minimum steric repulsions. With these results for the sequential transformation in the production of 2-(1-stannylvinyl)-1,3-diols **55** *via* four components assembly in one-pot operation with the generation of three contiguous stereogenic centers in exceptional stereoselectivity, the application of this approach to the syntheses of naturally occurring (–)-avenaciolide and (–)-isoavenaciolide have been carried out.[43] It is interesting to comment that the two diastereomers **55** and **59** can be obtained simply by changing the addition sequence of aldehydes as shown in Scheme 15. To take this advantage, the enantioselective syntheses of (–)-avenaciolide and (–)-isoavenaciolide were achieved by the addition sequence of aldehydes and the selection of the chiral bromoborane **56** for the absolute configurations as illustrated in Scheme 15. The concise syntheses of these natural products starting from **54** in three step demonstrate the utility of this synthetic method.[44]

Conclusions

In this account, we documented our struggles, accidental findings, and preliminary success in our search of a variety of allylic transfer reactions through inter- and intramolecular fashions. Excellent progress has been made over past decades in the development and application of stereoselective allylic transfer reactions as appeared in the literature. The outlook for the chemistry of the allylic transfer reactions of carbonyl functionality is very promising to solve still existing problems. What about endeavors in the allylic transfer reactions? This account is by no means written to announce an end to this effort. Ideal approach to realize more practical and efficient ways is still ahead. To complete this goal, we need continued efforts in both probing for reactivities and improving synthetic accessibility of allylic transfer reactions with rational designing of reagents, catalysts, and reaction routes.

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