Allylmetal-Based Alkene Isomerization as a Tool for Stereoselective Synthesis of Bioactive and Therapeutically Relevant Molecules

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ABSTRACT: The positional isomerization of alkenes is a well-known process mediated by various transition metal complexes. Nevertheless, systems which isomerize alkenes with complete regio- and stereoselectivity are rare. Most reported cases proceed through 1,3-hydrogen shift (allyl) mechanisms, rather than the generally more common 1,2-hydride shift (alkyl) mechanism, provoking consideration of the unique opportunities the former mechanism offers. Accordingly, the first part of this Perspective article will cover stereoselective alkene isomerization systems operating through 1,3-hydrogen shift mechanisms, with an emphasis on the origin of stereocontrol. Next, examples where these systems are employed in tandem with subsequent transformations to rapidly form complex molecular architecture will be discussed, illustrating the potential of alkene isomerization as a strategic tool in stereoselective synthesis.

Keywords: alkene isomerization, allylmetals, chain-walking, stereoselective synthesis, tandem processes

1. Introduction

Alkene isomerization has been traditionally regarded as an undesired side reaction in transition metal-catalyzed processes. However, recent advances involving this transformation have initiated a paradigm shift, leading to a growing interest in its strategic application in organic synthesis. In particular, the concept of remote functionalization,[1–3] which allows the transfer of chemical information between distant functional groups, often relies on a metal-based mediator to “travel” across the carbon skeleton of a molecule.[4,5]

Utilizing alkene isomerization in this context has resulted in powerful reactivity manifolds, enabling for example the convergent transformation of regioisomeric mixtures into valuable products,[6,7] the stereoselective formation of remote stereocenters,[8,9] or the unfolding of rigid cyclic systems into acyclic fragments featuring precisely controlled stereochemistry.[10,11]

As transition metal-mediated alkene isomerization is generally perceived as a fundamentally dynamic and reversible process, less attention has been given to this approach for the regio- and stereoselective preparation of highly substituted alkenes from their simpler regioisomeric counterparts. When used judiciously, this strategy should be able to dramatically simplify access to stereodefined alkenes which are otherwise challenging to prepare stereoselectively. In this Perspective, we will showcase examples where the strategic use of transition metal-based alkene isomerization epitomizes this idea, with focus on processes taking place through 1,3-hydrogen shift (allyl) mechanisms. After a brief survey of the underlying mechanistic aspects, with an emphasis on the sources of stereocontrol, exemplary catalytic alkene isomerization systems will be highlighted. Finally, processes where alkene isomerization is paired with subsequent stereoselective steps to enable powerful transformations will be covered.

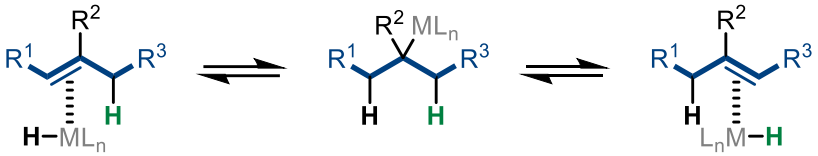
2. Stereoselective alkene isomerization through allylmetals

2.1. Mechanistic aspects

Transition metal-mediated alkene isomerization can proceed through several unique mechanisms.[12] From the standpoint of stereoselectivity, the most important distinction is between the 1,2-hydrogen shift (alkyl) and 1,3-hydrogen shift (allyl) mechanisms.

The most common 1,2-hydrogen shift mechanism (Scheme 1) requires a metal hydride and proceeds through the intermediacy of an alkylmetal species, generated through migratory insertion of the coordinated alkene into the M-H bond. Isomerization by the 1,2-hydride shift has been extensively reviewed elsewhere[13,14] and is not the focus of this Perspective.

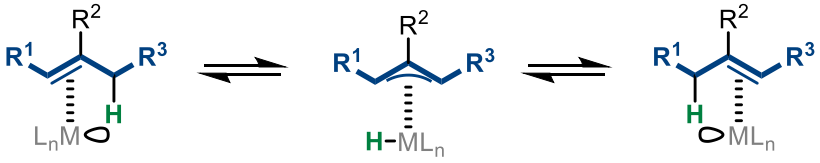
Scheme 1. The 1,2-hydride shift mechanism.



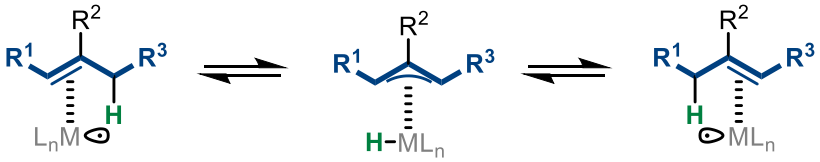
The second type of mechanisms includes the 1,3-hydride-, hydrogen atom-, and proton shift mechanisms, all of which proceed through an allylmetal intermediate which results from abstraction of the allylic hydrogen prior to insertion of hydrogen to the allylic system (Scheme 2). The 1,3-hydride shift mechanism, first proposed to operate in 1962 for iron pentacarbonyl-catalyzed alkene isomerization,[15–19] commences by coordination of an alkene to a coordinatively unsaturated metal center, followed by oxidative addition to the allylic C-H bond, yielding an allylmetal intermediate which can adopt one of several interconvertible conformations. Reinsertion of the hydride at the opposite terminus of the allylic system, followed by dissociation from the metal center, furnishes the isomerized alkene. The 1,3-H atom- and proton shift mechanisms proceed through analogous allylmetal intermediates, with the allylic hydrogen formally behaving as a hydrogen atom or a proton, respectively.

Scheme 2. The 1,3-hydrogen shift mechanisms.

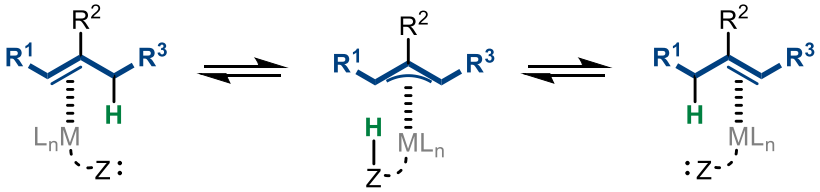
1,3-hydride shift



1,3-H atom shift



1,3-proton shift

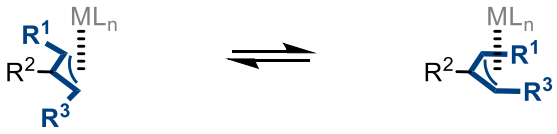


The fundamentally different nature of the intermediates involved in the 1,2- and 1,3-hydride shift mechanisms translates into different considerations regarding stereocontrol. During the 1,2-hydride shift mechanism, the intermediate alkylmetal may freely rotate along the C-C bond, resulting in a stereoisomeric product distribution that depends on the relative reactivity of different conformers towards β-hydride elimination. Moreover, the metal hydride species necessary for isomerization might induce geometrical isomerization of the product alkene, affording thermodynamic mixtures.

In contrast, the stereochemical outcome of isomerization by the 1,3-hydrogen shift mechanisms depends on the conformational preferences of the intermediate allylmetal. The two competing steric factors at play are the steric interactions between the

substituents at the termini of the allylic system (R^1 and R^3) with the substituent at the central carbon R^2 (1,2-allylic strain), compared to the interactions of R^1 and R^3 with each other (1,3-allylic strain) and with the metal coordination sphere (Scheme 3). The balance between the two effects depends on the exact nature of the starting alkene and the catalyst used. Notably, catalysts operating through 1,3-hydrogen shift mechanisms rarely promote the geometrical isomerization of alkene products.

Scheme 3. Steric effects on the conformation of allylmetal intermediates.



1,2-allylic strain

steric clash with ML_n
1,3-allylic strain

By virtue of the greater rigidity of allylmetal intermediates, 1,3-hydrogen shift mechanisms sometimes allow for more pronounced stereocontrol than their 1,2-hydrogen shift counterparts. This is not to assert superiority of any mechanism over the other, as the intricacies of either can be capitalized upon in the right synthetic setting.

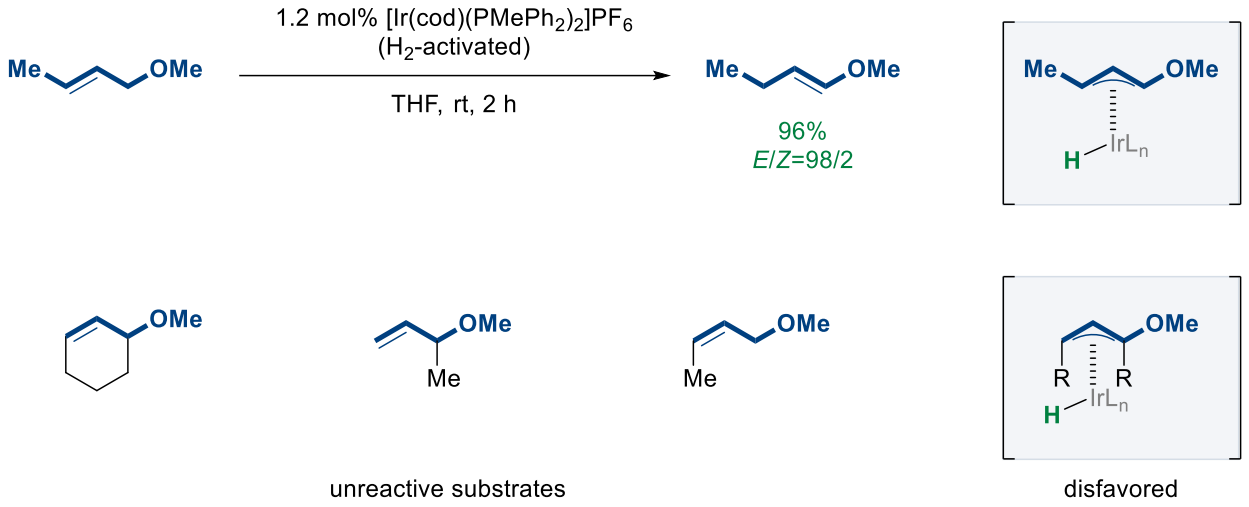
2.2. Selected alkene isomerization catalysts.

2.2.1. Iridium.

In 1978, Felkin and coworkers reported the stereoselective isomerization of allyl ethers to enol ethers catalyzed by hydrogen-treated cationic iridium complex $[Ir(cod)(PPh_2Me)]PF_6$ (Scheme 4),[20] previously reported by Crabtree to serve as a promising precatalyst for alkene hydrogenation.[21] While primary allylic ethers featuring

trans 1,2-disubstituted or 2,2-disubstituted alkenes smoothly underwent isomerization, secondary and primary ethers bearing *cis*-substituents failed to react.

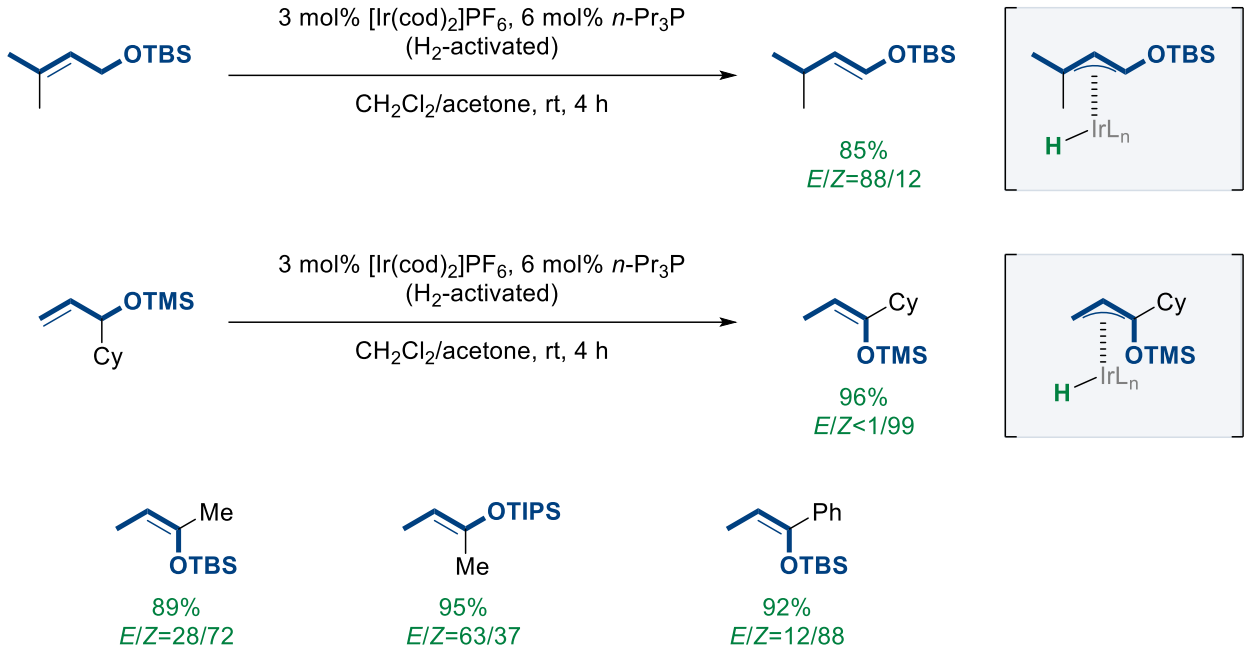
Scheme 4. Felkin (1978): Stereoselective isomerization of allyl ethers to enol ethers.



The observed stereoselectivity and reactivity could be explained by a 1,3-hydride shift mechanism, proceeding through a π-allyliridium intermediate which prefers a zig-zag conformation where the substituents at the termini of the allylic system avoid steric interaction with the metal coordination sphere. This pioneering study was the first to uncover a highly stereoselective alkene isomerization catalyst.

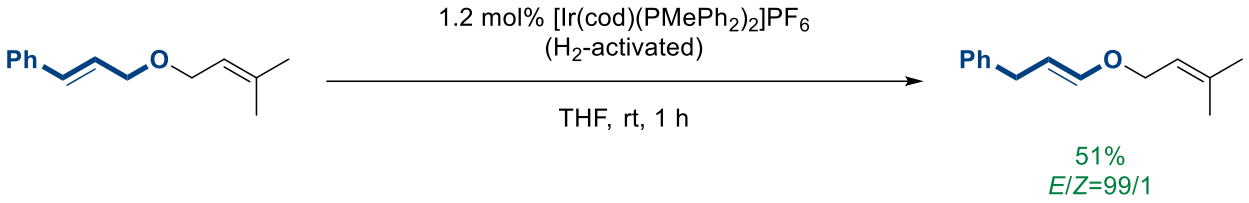
Inspired by these efforts, Miyaura and coworkers extended the scope of the approach to the stereoselective generation of synthetically valuable silyl enol ethers (Scheme 5).[22,23] Importantly, by identifying a more active catalytic system, previously unreactive substrates such as secondary allyl silyl ethers were also isomerized, albeit with non-uniform stereoselectivity, strongly dependent on the substituent α to oxygen.

Scheme 5. Miyaura (1999): Stereoselective isomerization of allyl silyl ethers to silyl enol ethers.

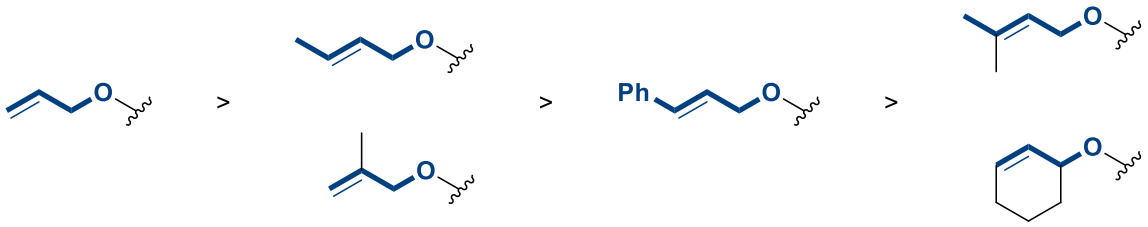


Subsequent work by Miyaura[24] concerned the regio- and stereoselective isomerization of unsymmetrical diallyl ethers to allyl vinyl ethers (Scheme 6). This study established a qualitative reactivity scale of differently substituted allyl fragments towards isomerization by the Felkin catalytic system. Significantly, the product allyl vinyl ethers serve as substrates for the aliphatic Claisen rearrangement (see section 3.2.1).

Scheme 6. Miyaura (2000): Selective mono-isomerization of unsymmetrical diallyl ethers.

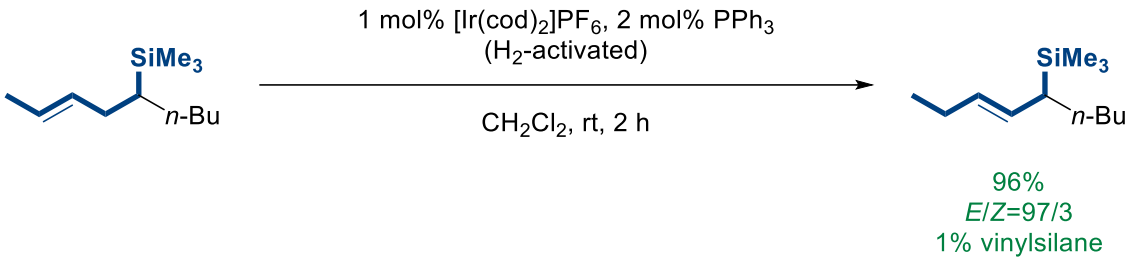


Reactivity order observed:



Matsuda applied an Ir-based catalytic system to the regio- and stereoselective isomerization of alkenes to allylsilanes (Scheme 7).[25] Over-isomerization is avoided thanks to the 1,3-hydride shift mechanism, which disfavors isomerization towards branched positions in the chain (see Scheme 4).

Scheme 7. Matsuda (1986): Regio- and stereoselective isomerization towards allylsilanes.

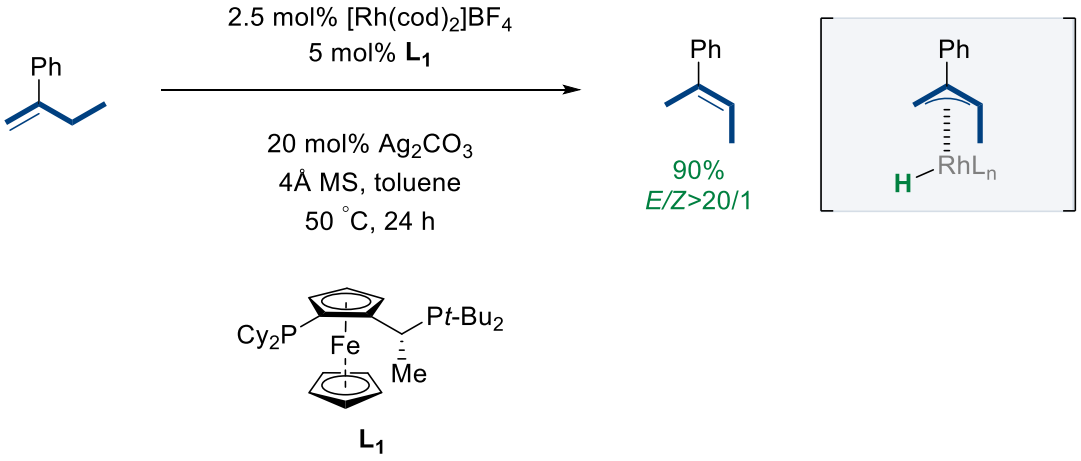


A polymer-supported analogue of the Felkin catalyst has been developed by the Ley group and employed in the total synthesis of the natural product carpanone.[26–28]

2.2.2. Rhodium.

While investigating the enantioselective isomerization of alkenyl alcohols using a Rh-based catalytic system, Zhao reported an impressive example of stereocontrolled alkene isomerization toward trisubstituted alkenes (Scheme 8).[29] The authors propose a 1,3-hydride shift mechanism proceeding through an allylrhodium intermediate which avoids the 1,2-allylic strain between the adjacent substituents on the allyl system, resulting in the *E*-alkene.

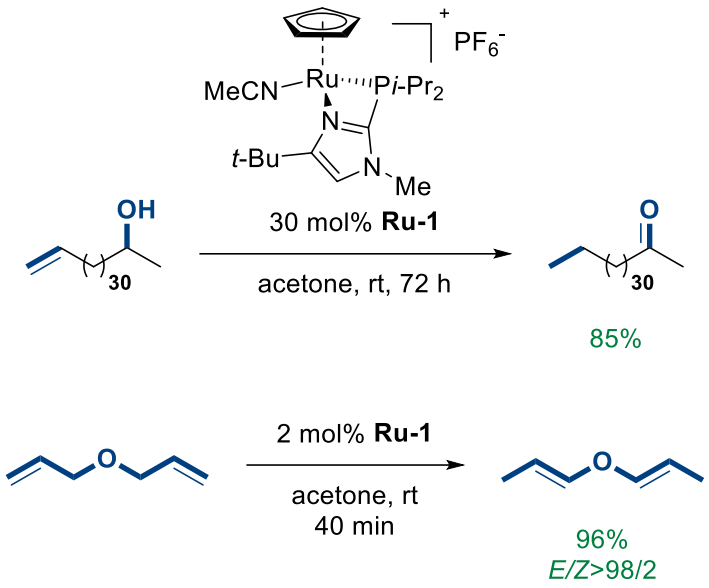
Scheme 8. Zhao (2018): Stereoselective isomerization towards trisubstituted alkenes.



2.2.3. Ruthenium.

In 2007, Grotjahn and coworkers reported[30] a highly active ruthenium-based alkene isomerization catalyst, capable of long-distance isomerization of alkenyl alcohols to the corresponding ketones (Scheme 9). The observed regio- and stereoselectivity are typical of an allyl mechanism.

Scheme 9. Grotjahn (2007): Long-distance alkene isomerization.

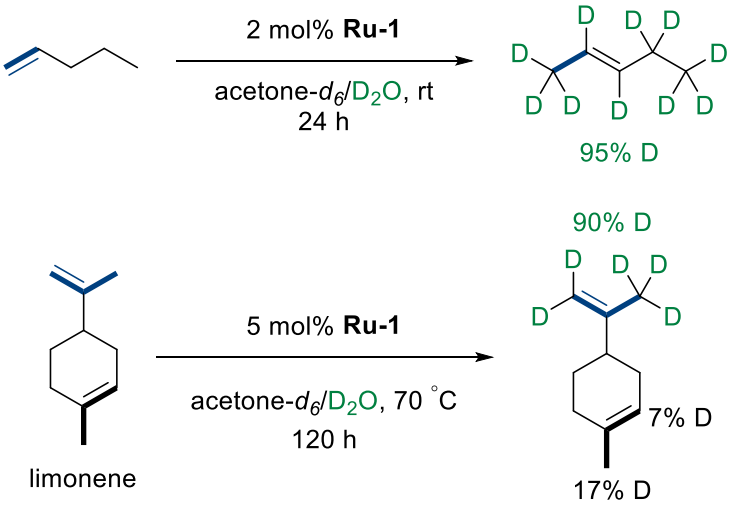


An analogous complex devoid of the imidazole moiety displayed significantly lower catalytic activity, which lead the authors to propose a 1,3-proton shift mechanism, where the imidazole acts as a Brønsted base, abstracting the allylic hydrogen as a proton and directly leading to the key allylruthenium intermediate. A subsequent computational investigation by Tao[31] suggested instead that oxidative addition into the C-H bond by Ru precedes deprotonation by the imidazole, meaning the mechanism is in fact a 1,3-hydride shift with the imidazole acting as an internal proton shuttle.

In any case, a clear protic behavior of the allylic hydrogen during the mechanism is uncovered when conducting isomerization in the presence of D_2O, which leads to deuterium incorporation in the product.[32] This finding enables deuterium-labeling of aliphatic C-H bonds under mild conditions and using inexpensive heavy water as a deuterium source (Scheme 10). For example, 1-pentene furnished fully deuterated *trans*-2-pentene after 24 hours of reaction at room temperature. More complex molecules such as limonene could be selectively deuterated at the positions accessible to the catalyst,

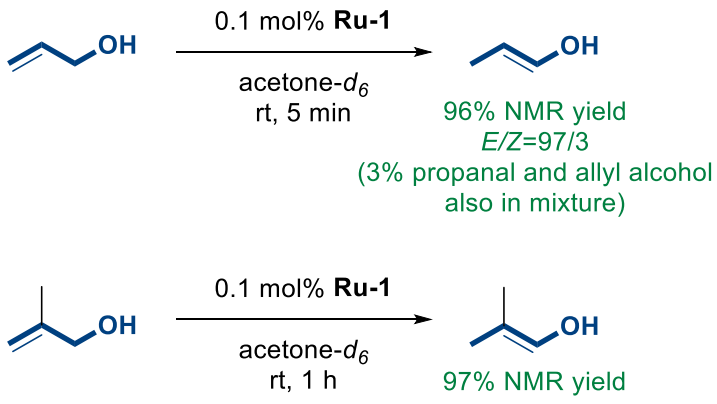
with the 2-substituted propenyl group primarily labeled over the more hindered endocyclic trisubstituted alkene.

Scheme 10. Grotjahn (2009): Isomerization-deuteration using D_2O.



The mild conditions employed for isomerization by **Ru-1** enable exciting applications. For example, allylic alcohols are smoothly isomerized to the corresponding enols (Scheme 11),[33,34] which are sufficiently resistant to tautomerization under the reaction conditions to be directly observed by NMR.

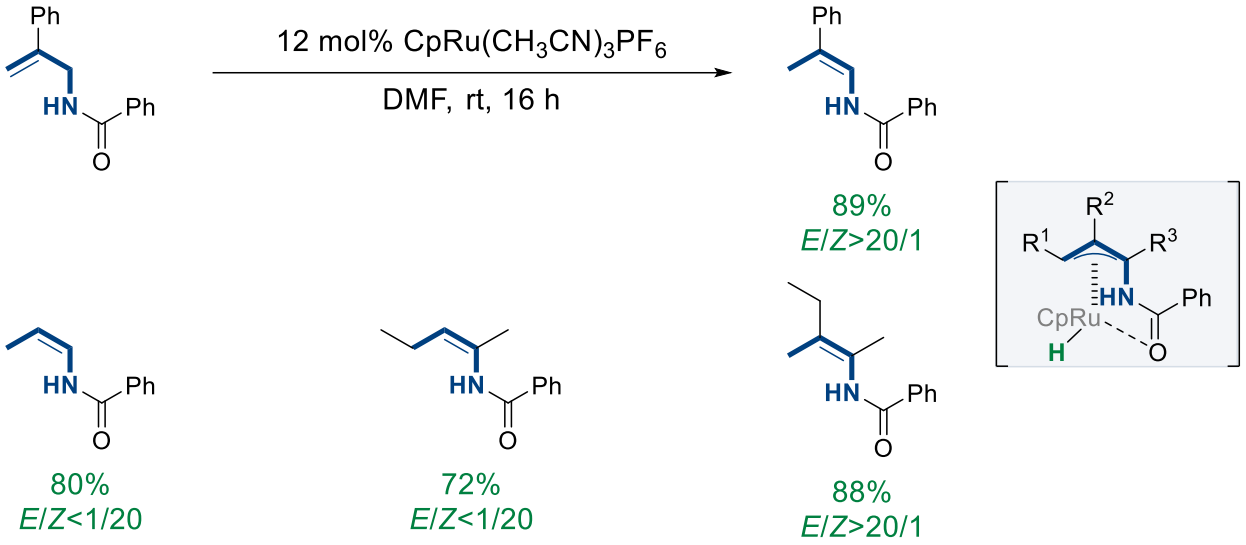
Scheme 11. Grotjahn (2012): Generation and direct observation of enols.



The Grotjahn catalyst has gained popularity in the synthetic community and is widely used for applications involving alkene isomerization, some of which will be discussed in the next section. In addition to the first-generation catalyst, a polymer-supported variant has been developed,[35,36] as well as analogs featuring a bulkier Cp* ligand, capable of regio- and stereoselective mono-isomerization of linear terminal alkenes.[37,38]

In 2017, Trost reported a highly stereoselective Ru-catalyzed isomerization of *N*-allyl amides to enamides featuring various substitution patterns (Scheme 12).[39] Most impressively, a tetrasubstituted enamide could be generated with complete stereoselectivity, the only known example of alkene isomerization leading to a stereodefined tetrasubstituted alkene. This approach provides access to previously elusive stereodefined enamides, which serve as useful synthetic building blocks and are also found in numerous pharmaceutically relevant compounds. Mechanistic experiments suggest that the stereoselectivity of isomerization is determined by chelation of the amide to the cationic ruthenium center, which fixes the conformation of the intermediate allylruthenium species.

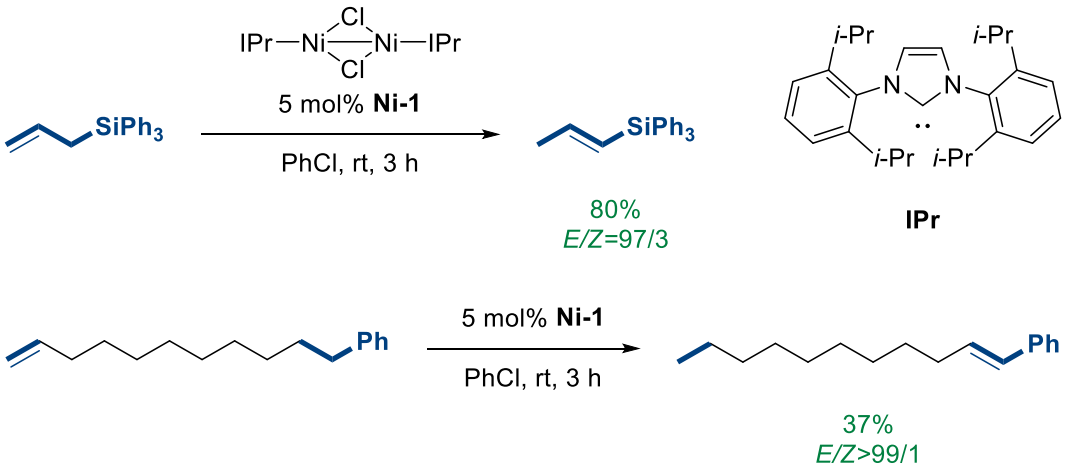
Scheme 12. Trost (2017): Stereoselective isomerization of *N*-allylamides to enamides.

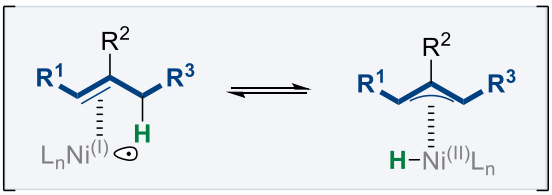


2.2.4. Nickel.

A rare type of allyl mechanism is the 1,3-hydrogen atom shift mechanism, the first example of which was recently reported by Schoenebeck.[40] The active catalytic species, a Ni^{I} metalloradical, generated by dissociation of the dimeric precatalyst **Ni-1**, is proposed to abstract the allylic hydrogen as a hydrogen atom, leading to an allylnickel intermediate. This system is notable for its mechanistic novelty and mild conditions of operation. Various alkenes were isomerized with high stereoselectivity, generating useful compounds such as stereodefined vinylsilanes (Scheme 13). The catalytic system is also capable of isomerizing terminal alkenes over long distances (up to 9 positions).

Scheme 13. Schoenebeck (2019): 1,3-H atom shift alkene isomerization.





H-atom abstraction by $Ni^{(I)}$ metalloradical

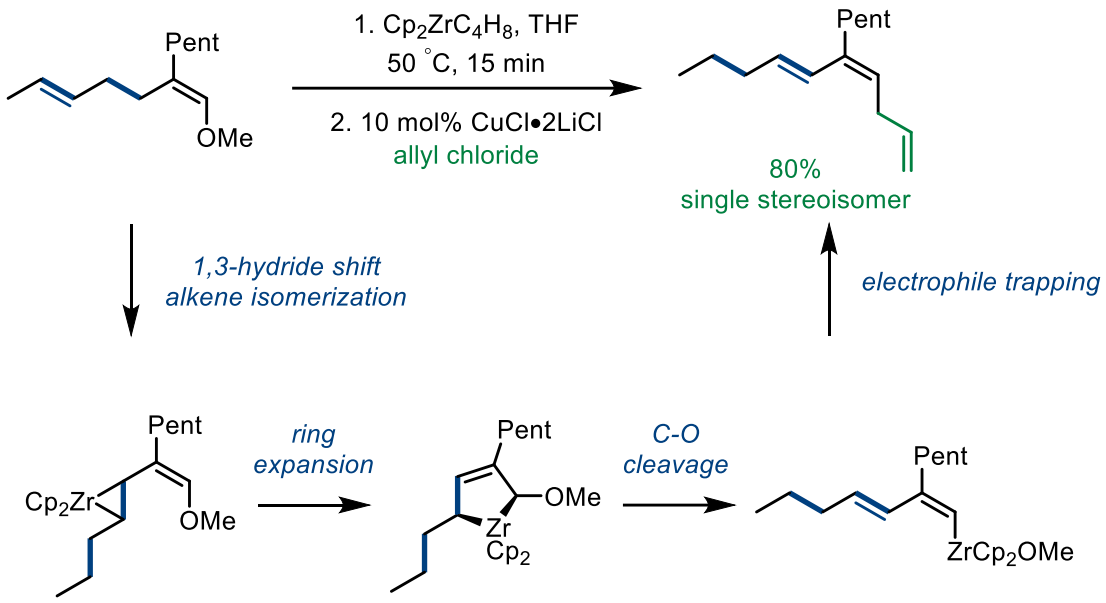
3. Applications to tandem processes

3.1. Isomerization-C-X insertion.

Building on the pioneering work of Negishi,[41] our group has developed new transformations based on zirconocene-mediated alkene isomerization coupled with subsequent steps, which are challenging to realize using other metals.[42]

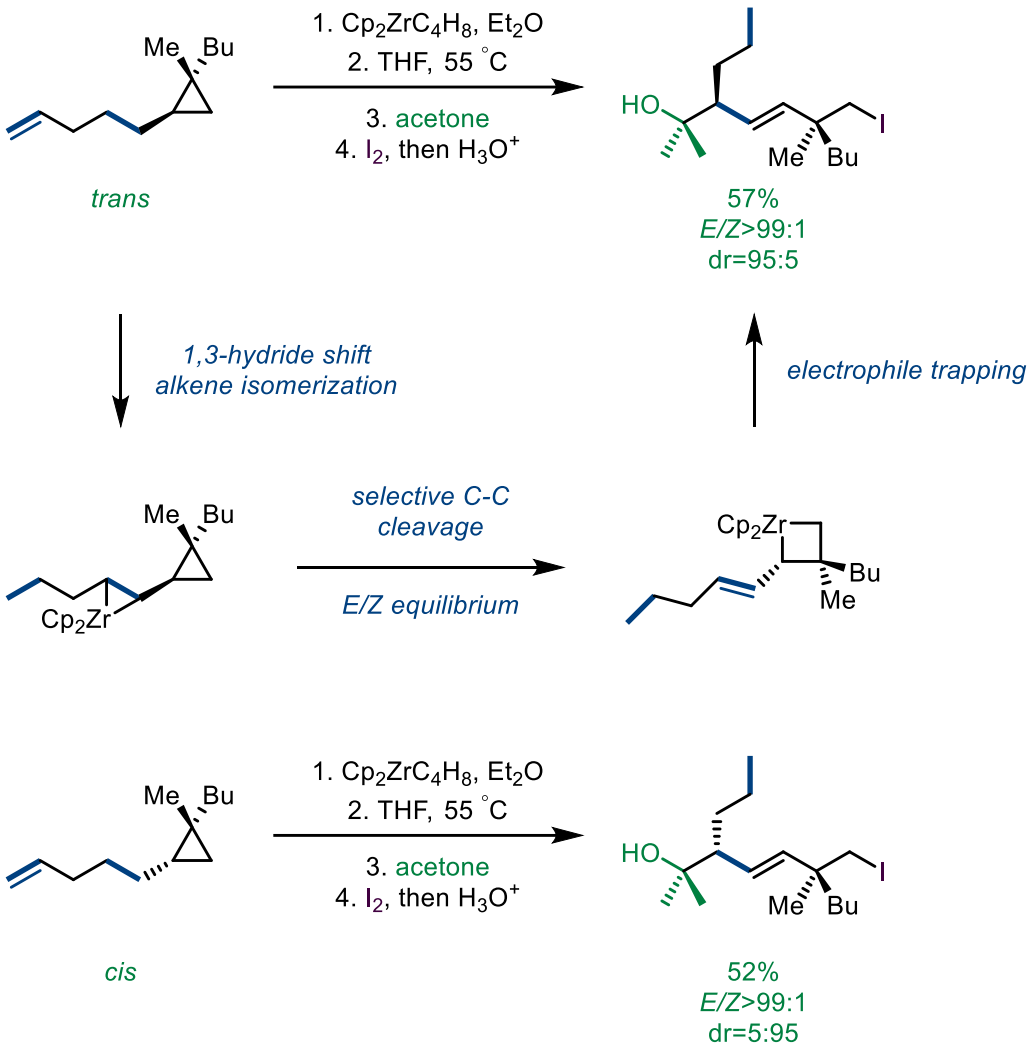
In the presence of $Cp_2ZrC_4H_8$, also known as the Negishi reagent,[43] ω-ene-enol ethers were found to undergo a sequence of stereoselective alkene isomerization and stereospecific C-O cleavage, resulting in regio- and stereodefined dienylzirconocene species, which are amenable to reaction with various electrophiles, yielding polysubstituted 1,3-dienes (Scheme 14).[44] Notably, the less substituted alkene is selectively isomerized over up to 6 positions with complete stereoselectivity.[45]

Scheme 14. Marek (2003): Regio- and stereoselective isomerization-C-O insertion sequence.



A second application of the Negishi reagent involving alkene isomerization is its reaction with ω-ene-cyclopropanes,[46,47] which proceeds through alkene isomerization up to the reactive vinylcyclopropane intermediate, which readily undergoes regioselective C-C bond cleavage.[48,49] The resulting allylzirconium species exists as a mixture of *E* and *Z* stereoisomers at the nucleophilic alkene. Fortunately, heating the reaction mixture in THF for a few hours yields the more stable *E*-allylzirconium exclusively, which diastereoselectively reacts with electrophiles such as acetone. The remaining alkylzirconium moiety is less reactive than the allylzirconium, enabling the selective incorporation of a second electrophile such as iodine (Scheme 15). Either diastereomer of the product is accessible, starting from the appropriate diastereomer of the starting ω-ene-cyclopropane.

Scheme 15. Marek (2014): Isomerization-selective C-C bond cleavage sequence.



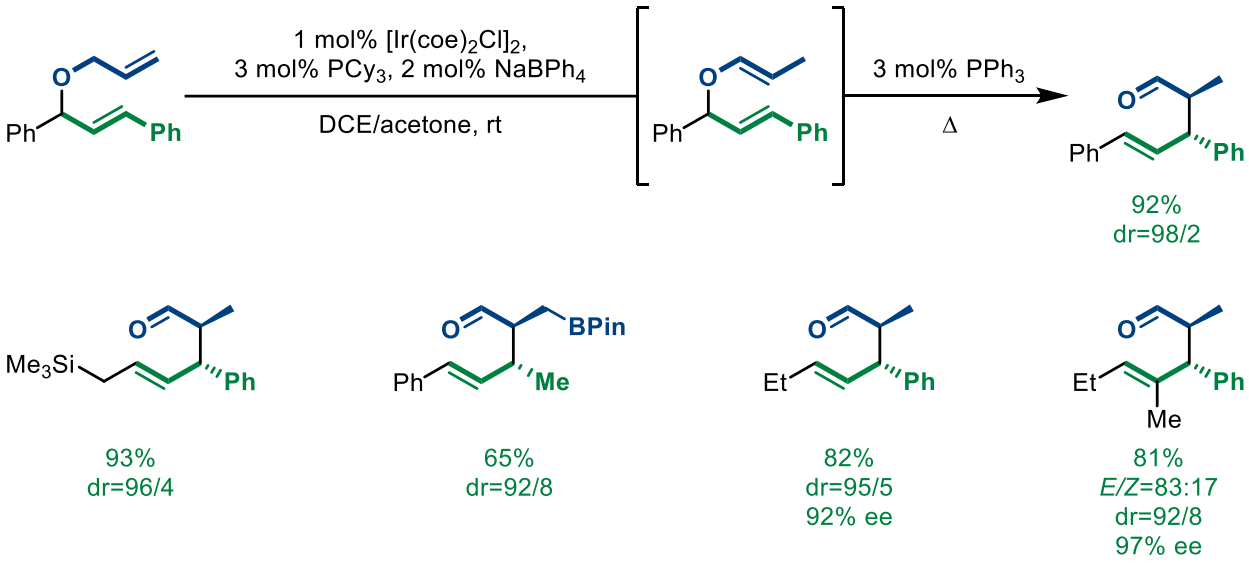
3.2. Isomerization-sigmatropic rearrangement

3.2.1. Isomerization-Claisen rearrangement

Following Miyaura's preliminary work on Ir-catalyzed mono-isomerization of unsymmetrical diallyl ethers to allyl vinyl ethers and subsequent Claisen rearrangement,[24] Nelson developed an isomerization-Claisen rearrangement (ICR) sequence, using a similar Ir-based catalytic system, which affords the rearrangement products with high

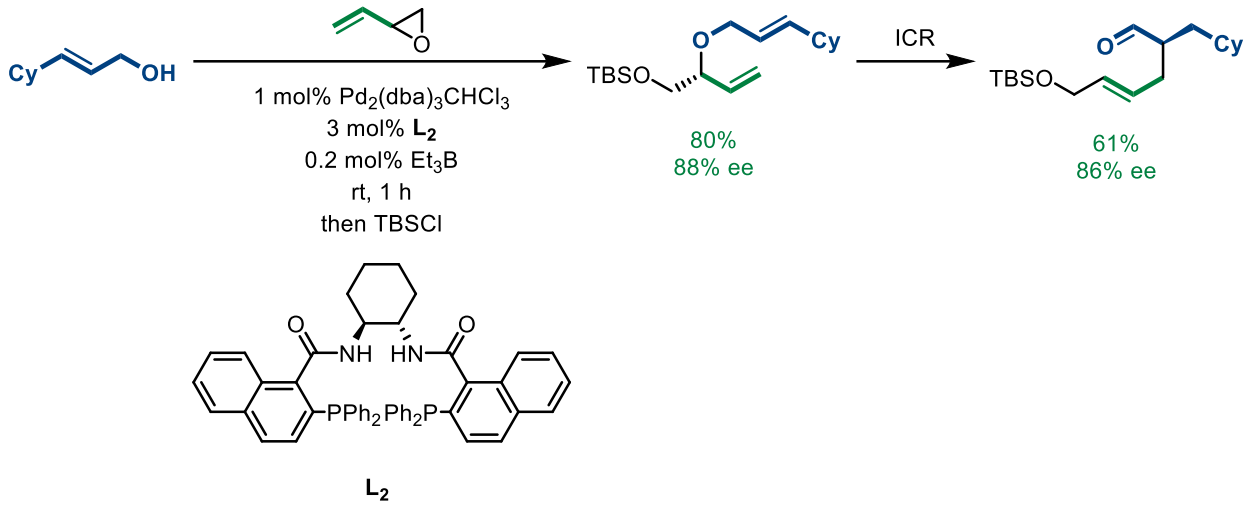
yield and diastereoselectivity in one step from simple diallyl ethers (Scheme 16).[50–52] The development of enantioselective access to the starting ethers renders this approach even more attractive.[53]

Scheme 16. Nelson (2003): Isomerization-Claisen rearrangement sequence.



Trost has shown that the starting diallyl ethers can be prepared in enantioenriched form from simple vinyl epoxides and allylic alcohols by a Pd-catalyzed asymmetric allylic alkylation reaction (Scheme 17).[54] Interestingly, since the Ir-based catalyst is reluctant to isomerize branched allyl fragments, only the 1,2-disubstituted alkene undergoes isomerization, with the terminal alkene untouched by the catalyst.

Scheme 17. Trost (2006): Enantioselective allylic alkylation to access ICR substrates.

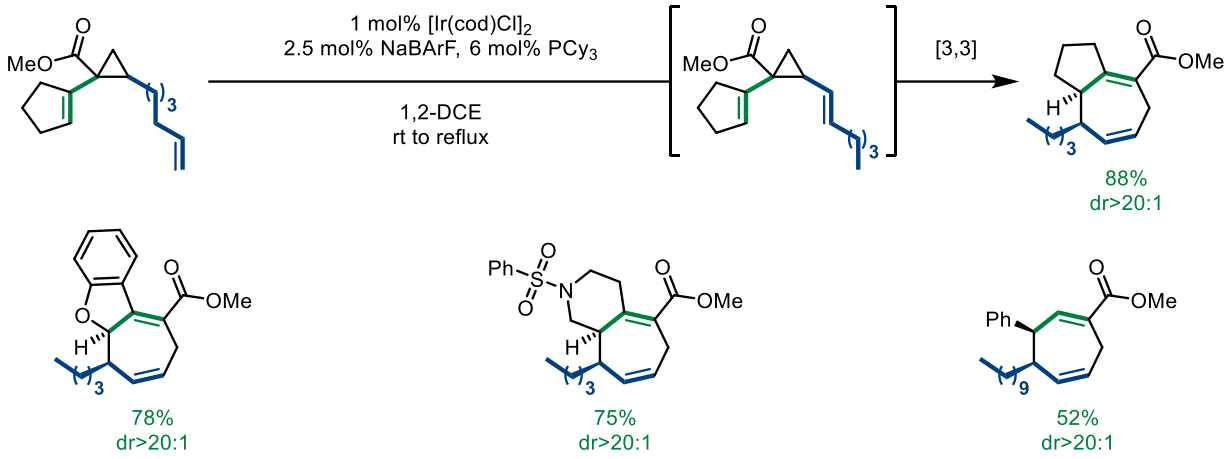


The limited accessibility of stereodefined allyl vinyl ethers required for the aliphatic Claisen rearrangement has significantly limited its use in synthesis. Clearly, forming these substrates by selective alkene isomerization of the readily available diallyl ether isomers greatly enhances the synthetic potential of this transformation.[55] It is therefore not surprising that the isomerization-Claisen rearrangement (ICR) strategy has found applications in the demanding field of total synthesis.[56,57]

3.2.2. Isomerization-Cope rearrangement

In 2019, our laboratory reported a tandem chain-walking-Cope rearrangement sequence, where the reactive divinylcyclopropanes are formed *in-situ* by alkene isomerization of the readily available alkenyl ω-ene cyclopropanes.[58] This process affords useful substituted cycloheptadiene scaffolds with complete stereocontrol (Scheme 18).

Scheme 18. Marek (2019): Isomerization-Cope rearrangement cascade



While the isomerization-Claisen rearrangement strategy benefits from the fact that the process can be performed sequentially, usually with quenching of the catalyst prior to heating, the isomerization-Cope rearrangement sequence does not enjoy this simplifying element, since the divinylcyclopropane leading to rearrangement is energetically comparable to its non-productive regioisomers. Fortunately, the Ir-catalyst can equilibrate the different isomers so that the Cope rearrangement simultaneously drives the equilibrium, all while staying completely *E*-selective and compatible with the rearrangement products (unlike in the case of the Claisen rearrangement).

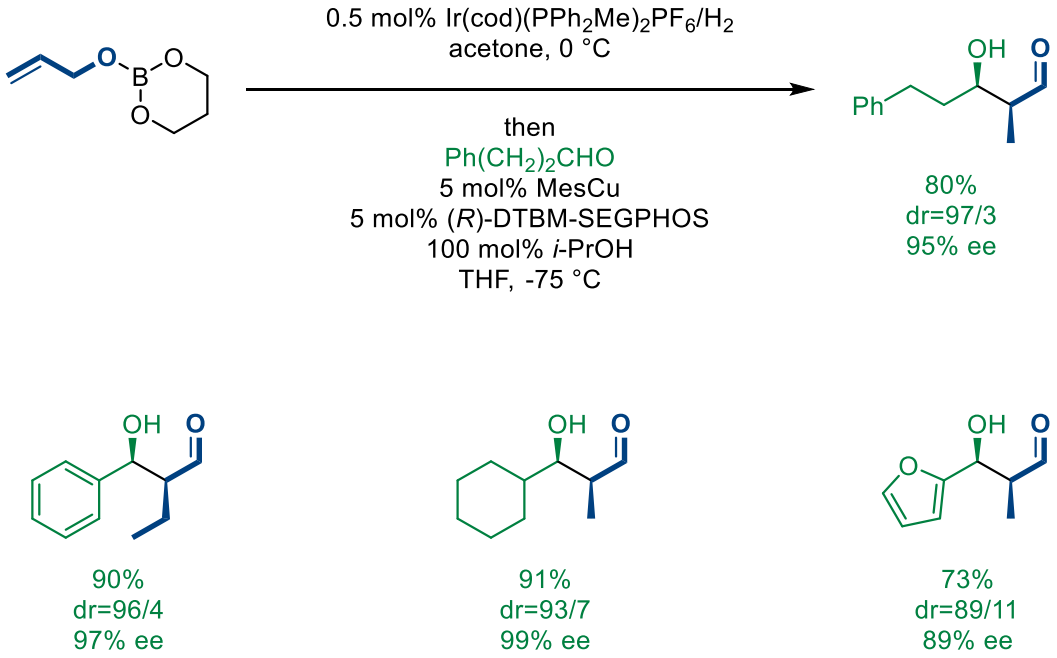
3.3. Isomerization-carbonyl addition sequences

3.3.1. Isomerization-aldol addition

The efficient and stereoselective generation of aldehyde enolates is challenging, considering their tendency to generate self-condensation products when generated by classical deprotonation of the corresponding aldehyde. Alternative approaches towards the generation of these enolates are therefore sought after. A particularly attractive way

to generate these enolates is through alkene isomerization from the corresponding allylic alcohols.[59–61] In 2015, Kanai reported an impressive enantio- and diastereoselective aldehyde-aldehyde cross aldol reaction, relying on Ir-catalyzed alkene isomerization to stereoselectively generate the nucleophilic *E*-boron enolates (Scheme 19).[62] Impressively, the authors found that by careful tuning of the reaction conditions, the formation of double- triple- and even quadruple aldol products could be achieved in a single step.

Scheme 19. Kanai (2015): Stereoselective enolate formation by alkene isomerization.

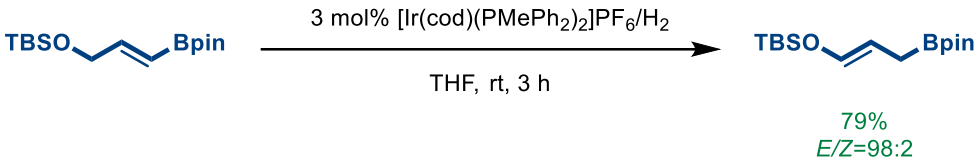


3.3.2. Isomerization-allylation

The reaction of allylboron reagents with carbonyl compounds is among the most reliable transformations in stereoselective synthesis. A major shortcoming of these reagents is that their preparation from the corresponding organometallic reagents often proceeds with

low yield and regioselectivity. In the late 1990's, Miyaura explored an alternative entry into γ-alkoxy allylboronate esters, by stereoselective isomerization of the isomeric vinylboronates, which are conveniently prepared by hydroboration of terminal propargyl ethers (Scheme 20).[63–65] Only γ-alkoxy allylboronate esters were explored, presumably since their isomerization is thermodynamically favored and can be carried out in a separate step from the reaction with electrophiles.

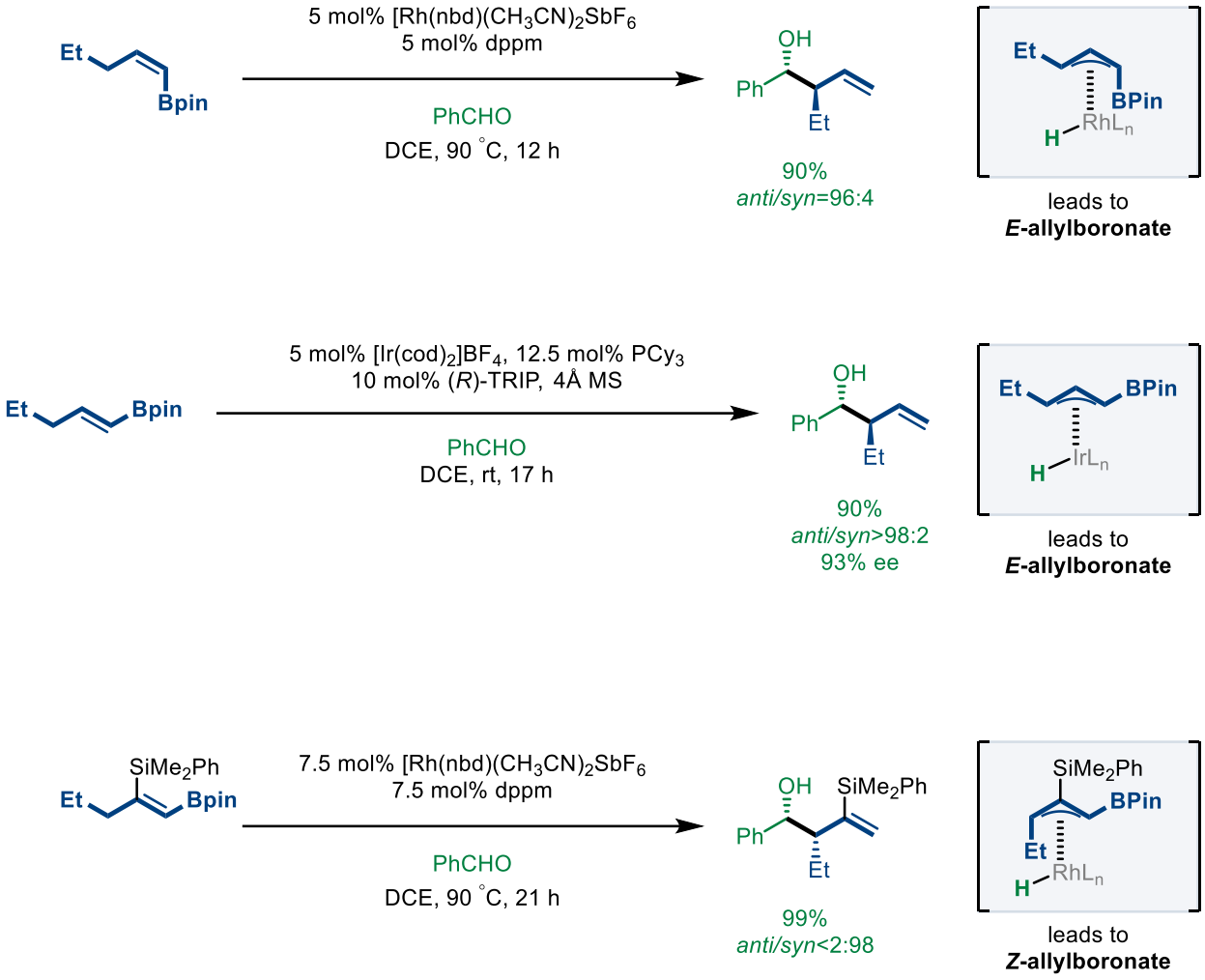
Scheme 20. Miyaura (1999): Stereoselective isomerization towards γ-alkoxy-allylboronate esters.



In 2011, Murakami and coworkers dramatically expanded the scope of this approach, by isomerizing the starting alkenylboronate ester already in the presence of an electrophilic aldehyde, thereby driving the equilibrium to the formation of the reactive allylboron species.[66] This procedure provides *anti*-configured homoallylic alcohols in impressive yield and diastereoselectivity for this one-pot procedure (Scheme 21). Unfortunately, the cationic Rh-based catalytic system employed required high temperatures and performed optimally using *Z*-alkenylboronates, which are harder to access compared to the corresponding *E*-stereoisomers. These shortcomings were soon overcome by switching to an Ir-based isomerization catalyst, which operated at room temperature with *E*-alkenylboronate esters, prepared by hydroboration of the corresponding terminal alkynes.[67] Even more impressively, the Ir catalyst was compatible with the chiral

phosphoric acid catalyst (*R*)-TRIP, affording the allylation products with high diastereo- and enantiocontrol. Finally, the authors demonstrated a one-pot hydroboration-alkene isomerization-allylation procedure which furnished the homoallylic alcohol products with respectable yield and stereoselectivity in a single step, starting from simple terminal alkynes. This remarkable result paved the way to further developments. For example, the use of 2-silyl-1-alkenyl boronates derived from silaboration of terminal alkynes led to homoallylic alcohols featuring *anti*-stereochemistry (resulting from the *Z*-stereochemistry of the key allylboronate), complementary to that of previously explored products.[68] The silyl group can be removed by fluoride or oxidized *in-situ*, generating simple *syn*-allylation products[69] or aldol-derived scaffolds.

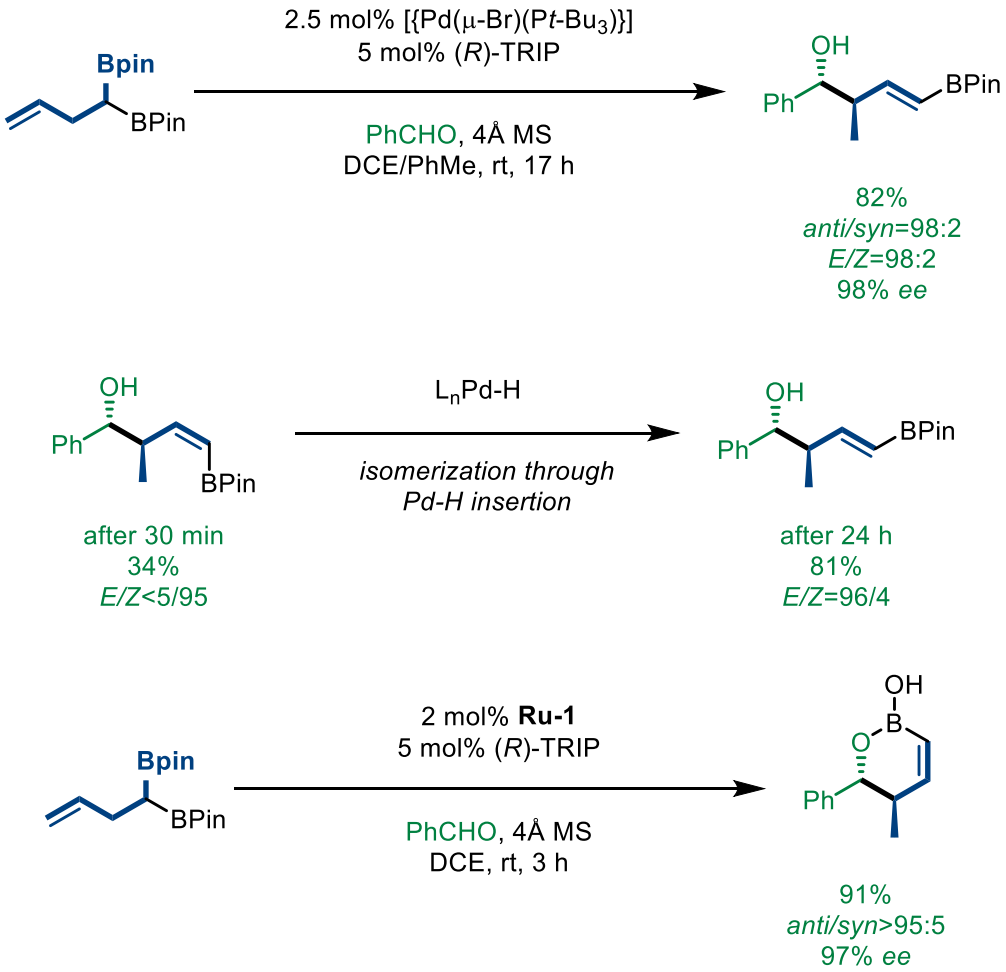
Scheme 21. Murakami (2011): Isomerization-carbonyl allylation.



Another example of stereodivergency in the isomerization-allylation strategy concerns the generation of 1,1-diboryl-2-alkenes by alkene isomerization (Scheme 22). Subjecting the known 1,1-diboryl-3-alkenes to alkene isomerization by a palladium hydride catalyst in the presence of an aldehyde and (*R*)-TRIP generates the allylation product with good yield and excellent stereocontrol both for the two chiral centers and the synthetically valuable *E*-alkenylboronate motif.[70] Interestingly, the kinetic product features an *Z*-alkenylboronate, which is generated with high stereoselectivity at early stages of the reaction. However, the Pd-H species which catalyzes the positional alkene isomerization also isomerizes the *Z*-alkenylboronate to the thermodynamic *E* form before the allylation

reaction is completed. Alternatively, using the Grotjahn catalyst, which does not promote such geometrical alkene isomerization, affords the *Z*-configured alkenylboronate motif exclusively. The alkenylboronate moiety serves as a useful handle for subsequent elaboration of the products, and complementary access to both stereoisomers increases the impact of the method even further.

Scheme 22. Murakami (2017): Diastereodivergent synthesis of alkenylboronate-containing homoallylic alcohols.



The development of this isomerization-allylation strategy by the Murakami group serves as a beautiful example of how alkene isomerization can be used to simplify the stereoselective synthesis of widely important compounds. It is also worth appreciating how different combinations of alkenylboronate substrates and alkene isomerization catalysts lead to widely different outcomes depending on the mechanistic subtleties in each case.[71]

4. Conclusion

The purpose of this Perspective was to illustrate the strategic power of alkene isomerization in stereoselective synthesis. We hope to have made two main points clear:

1. Alkene isomerization systems proceeding through 1,3-hydrogen shifts are capable of exerting exceptional control over alkene regio- and stereochemistry, which naturally follows from their mechanism of operation.

2. When employed in the appropriate synthetic context, alkene isomerization can dramatically simplify access to unstable or synthetically elusive alkenes in stereodefined form. Therefore, from a retrosynthetic perspective, selective alkene isomerization bridges between such target alkenes and their simpler regioisomeric counterparts.

Taken together, these arguments show that the strategic use of alkene isomerization can enable innovative solutions to difficult synthetic problems. Further development of selective alkene isomerization systems, as well as utilization of this concept in unexplored territories, will surely lead to exciting developments.

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Author Contributions

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