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Catalytic Asymmetric Intermolecular Allylic Functionalization of Unactivated Internal Alkenes

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Abstract

The asymmetric allylic functionalization of unactivated internal alkenes is an emerging strategy for the conversion of simple unsaturated starting materials into a diverse range of enantioenriched products. This Perspective summarizes the development of reactions wherein a chiral catalyst facilitates the intermolecular stereoselective reaction between an achiral unactivated internal alkene and a reagent.

Keywords

allylic oxidation; allylic esterification; allylic amination; allylic alkylation; internal alkenes; enantioselective catalysis; enantioselective heteroene

1. INTRODUCTION

The stereo- and regioselective transformation of simple unsaturated hydrocarbons through allylic functionalization provides a direct path to enantioenriched building blocks from abundant and inexpensive petrochemical feedstocks. Another advantage to this method lies in its ability to generate these chiral synthons with preservation of the alkene as a handle for further elaboration. As a result, catalytic enantioselective allylic functionalization has

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Notes

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emerged as a useful synthetic tool, streamlining the production of pharmaceuticals, natural products, fine chemicals, and other functional materials.^{1–5}

The most developed and widely used approaches for catalytic asymmetric allylic functionalization fall within three distinct categories, which have been reviewed elsewhere: (1) intramolecular allylic rearrangement,^{6–8} (2) transition metalmediated allylic substitution/coupling,^{9–13} and (3) allylic C–H functionalization^{14–28} (Scheme 1). The first two categories rely on the presence of activating or directing groups embedded within the starting material. Often in these cases, the necessary insertion and deletion of these additional functional groups limits the economy and generality of the transformation.

The third method of allylic functionalization relies solely on the presence of an alkene moiety that lacks any activation at the allylic position. The vast majority of these reactions require the use of tethered substrates for intramolecular reactions or terminal alkene starting materials for intermolecular reactions.^{14–28} A general catalytic intermolecular enantioselective allylic C–H functionalization of unactivated internal alkenes remains a longstanding challenge. Recent advances in the development of this type of transformation are the subject of this Perspective.

The utility of allylic C–H functionalization for the synthesis of valuable commodities and materials relies heavily on the ability to access products with significant chemo-, regio-, and stereo-control. Selective reactions with terminal alkenes have been studied most extensively, presumably because this class of substrates contains only one set of enantiotopic allylic protons (H_a and H_b , Scheme 2A). Internal alkenes, on the other hand, possess two sets of protons on either side of the alkene functional group, which leads to the additional challenge of regioselectivity (H_a and H_b , H_c and H_d , Scheme 2B). In addition, since the product that results from allylic C–H functionalization of an internal alkene is often an internal alkene itself, the issue of *E/Z* selectivity in product formation must be addressed, along with over-reaction of the product. For this more challenging class of substrates, C–H functionalization in a substrate with many electronically and sterically similar allylic protons often leads to a mixture of constitutional isomers, *E/Z* olefin isomers, and enantiomers.

The first examples of intermolecular asymmetric allylic C–H functionalization utilizing unfunctionalized internal alkenes began to appear nearly three decades ago. However, these transformations have been largely limited to symmetrical cycloalkenes. Nonetheless, these studies provided the first insights into the difficulty of tackling stereoselective allylic C–H activation without the challenges of *E/Z*- and regioselectivity.

2. ASYMMETRIC KHARASCH–SOSNOVSKY REACTION WITH UNACTIVATED CYCLOALKENES

One of the most notable advances in allylic C–H functionalization is the copper-catalyzed enantioselective Kharasch–Sosnovsky allylic oxidation.^{29,30} The initial discovery that copper(I) species catalyze the oxidation of alkenes with *tert*-butyl peroxybenzoate to yield allylic benzoates (e.g., **1** to **2**, Scheme 3) laid the groundwork for one of the most common catalytic asymmetric allylic oxidations of unactivated alkenes.^{31,32}

Following two seminal attempts at rendering this radical process enantioselective (up to 16% ee),^{33,34} several groups reported enantioselective variants of this oxidation with unfunctionalized cycloalkenes.^{35–48} Enantioselectivity, yield, and reaction time varied substantially throughout these reports and are largely dependent on ligand identity.

The Muzart, Andersson, and Feringa laboratories independently explored the use of proline-based ligands for the stereoselective oxidation of cyclohexene **1** with catalytic Cu(OAc)₂ (Scheme 4).^{37,39,44,46} Andersson's bicyclic amino acid **5** appeared to be superior to the conventional L-proline **4**, exhibiting the best enantioselectivity of the series (40% yield, 64% ee). Feringa and co-workers studied the effect of modifying **4**, but efforts to further increase the enantioselectivity of this process were unsuccessful.⁴⁸

Several examples of the asymmetric Kharasch–Sosnovsky reaction have also been reported utilizing bisoxazoline-based ligands.^{36,40,41,43,45,49–53} One of the earliest examples originated from Pfaltz and co-workers who utilized catalytic copper(I) triflate benzene complex and bisoxazoline ligand **8** in the presence of *tert*-butyl perbenzoate to access benzoate **7** from cyclopentene **6** in 61% yield and 84% ee (Scheme 5A).³⁶ Low temperatures were necessary to obtain higher selectivity but resulted in a slow reaction requiring 22 days to complete. Similar enantioselectivities were observed with a variety of C₂-symmetric bisoxazoline ligands in studies conducted by numerous research groups with wide-ranging reaction times and yields. Katsuki later discovered that cyclopentene could be converted to allylic ester **7** in 93% ee using a modified C₃-symmetric trisoxazoline ligand **9** (Scheme 5B).⁴¹ While various other ligand classes have been examined in the asymmetric Kharasch–Sosnovsky reaction, bisoxazoline ligands have shown the highest enantioselectivity to date.^{54–59} For example, Andrus utilized ligand **11** to form allylic ester **10** in 99% ee (Scheme 5C).⁵⁰

Trisubstituted alkenes **12** and **17** were also investigated under various reaction conditions (Scheme 6). In all cases, the secondary radical intermediate was preferentially formed over the tertiary, precluding any significant formation of **15** or **20**. Still, regioselectivity between isomeric products **13** and **14** or **18** and **19** was poor, and the enantiomeric excess varied significantly. Interestingly, the most substituted allylic esters **15** and **20** were generated with the highest enantioselectivity. Acyclic alkenes surveyed in this chemistry were limited to terminal alkenes that displayed diminished enantioselectivities.^{35,41}

Andrus and Singh have both offered stereoinduction models for the copper-catalyzed enantioselective allylic oxidation (Scheme 7).^{35,43} Both authors assumed that the final step of the Kharasch–Sosnovsky reaction proceeds via a rearrangement of a copper(III)-allyl intermediate. In the model proposed by Andrus, the minimization of steric interactions between the substrate, ester functional group, and chiral ligand dictates the substrate's approach (Scheme 7A). Singh's model, employing a tridentate pyridyl bisoxazoline ligand, invokes an additional stabilizing π – π interaction between one of the phenyl groups of the chiral ligand and the aromatic ring of the benzoate (Scheme 7B). In both cases, stereochemical models account for the lowered selectivity exhibited by acyclic alkenes lacking in conformational rigidity.

3. ASYMMETRIC ALLYLIC AMINATION OF UNACTIVATED ALKENES

Despite the plethora of reports that began emerging in the 1990s for catalytic asymmetric allylic C–H esterification, the first enantioselective C–H amination utilizing unactivated cycloalkenes did not appear until 2001. In the course of examining the aziridination chemistry between [*N*-(*p*-toluenesulfonyl)imino]-phenyliodinane and cyclohexene, Katsuki discovered that various electron-deficient salen-manganese(III) complexes catalyzed the formation of C–H amination product **21** instead (Scheme 8).⁶⁰ While it is not uncommon for this reaction pathway to compete with aziridination, the electron-deficient cationic catalyst **22** was particularly well suited for asymmetric allylic amination, exclusively affording **21** in 44% yield and 67% ee (Scheme 8A). Additionally, cycloheptene **23** was assayed under the reaction conditions yielding **24** with lower enantioselectivity and as a mixture with the corresponding aziridine byproduct **25** (Scheme 8B). In 2003, Katsuki and co-workers reported a complementary enantioselective intermolecular benzylic and allylic C–H amination that is mediated by 2-(trimethylsilyl)ethanesulfonyl azide as an oxidant and a salen-based ruthenium complex.⁶¹

Four years later, the Clark lab reported a copper-catalyzed allylic C–H amination that proceeded with comparable levels of enantioselectivity.⁶² Inspired by a report on allylic C–H amination by Katsuki for the generation of racemic product, and their own work in the field of asymmetric allylic oxidation, Clark and co-workers were able to develop an enantioselective amination variant of the Kharasch–Sosnovsky reaction. Substoichiometric amounts of [Cu(CH₃CN)₄]PF₆ and bisoxazoline **11** facilitated the amination of cyclohexene **1** with peroxycarbamate **26** to furnish allylic amination product **21** in up to 70% ee (Scheme 9A).

Interestingly, the identity of the peroxycarbamate was critical for the formation of the amination product over that of the alternative oxidation product **27**. The authors noted that the aryl carbamates of allylic alcohols undergo stereospecific rearrangement to yield the desired allylic amines. In some cases, the introduction of certain ligands biased reactivity toward esterification (Scheme 9B).

Dauban developed an elegant strategy for asymmetric C–H amination in which chiral rhodium complex **30** catalyzed the coupling of chiral sulfonimidamide **31** and various alkenes (Scheme 10).^{63–66} This amination is postulated to occur by the C–H insertion of a chiral metallanitrene, resulting from the oxidation of rhodium catalyst **30** by an iminoiodane intermediate generated in situ. Both cyclic and acyclic alkenes were viable substrates for this method. Most notably, acyclic unsymmetrical alkenes such as **29c** and **29d** exhibited high regioselectivity in allylic amination, as methylene C–H bonds underwent amination preferentially to methyl C–H bonds.

4. ENANTIOSELECTIVE ALLYLIC ALKYLATION OF UNACTIVATED ALKENES

The asymmetric Mizoroki–Heck reaction has garnered considerable attention in recent years, due to the immense popularity of the robust and widely functional group tolerant

racemic version of this reaction. Several reviews have been written to summarize the most important advances in enantioselective Mizoroki–Heck reactions (Scheme 11A),^{67–74} oxidative Mizoroki–Heck reactions (Scheme 11B),⁷⁵ redox-relay Mizoroki–Heck reactions (Scheme 11C),⁷⁶ and other variants of this venerable transformation. Examples have been reported for the asymmetric allylic arylation or alkylation of cyclic and acyclic internal alkenes with organohalides, organotriflates, organoboronic acids, or organodiazonium salts.

Alternatively, site-selective carbenoid C–H functionalization has emerged as one of the most effective ways of accessing new C–C bonds in unactivated substrates with impressive regio- and stereoselectivity.^{77–79} Around the same time as Müller’s initial report of an acceptor/acceptor-substituted carbenoid for moderately enantioselective allylic C–H alkylations, Davies began to explore this mode of C–H functionalization with donor/acceptor stabilized carbenoids.^{80–85} These reports on the Rh₂(DOSP)₄-catalyzed decomposition of aryldiazoacetates have become one of the most selective methods for C(sp³)–H functionalization.

In 2001, Davies reported a catalytic asymmetric allylic C–H activation to access γ,δ -unsaturated esters, providing an alternative route to Claisen rearrangement products (Scheme 12).⁸⁴ The donor/acceptor-stabilized carbenoids resulted in enhanced stability and chemoselectivity toward the C–H functionalization product over the alternative cyclopropanation pathway. A variety of substituted cyclohexenes were smoothly alkylated in the presence of catalytic D₂-symmetric Rh₂(*S*-DOSP)₄ and diazoester **32** revealing high levels of regioselectivity as a result of steric and electronic bias (**33a–d**). Enantioselectivity was generally high, even when acyclic internal alkenes were used (**33e–g**). However, the diastereomeric ratios varied substantially with some dropping as low as 1.3:1 in response to altered steric environments.

Recently, Davies reported a new method for accessing C–H functionalized products similar to **33e–g** with increased selectivity.⁸⁵ *N*-Sulfonyl-1,2,3-triazole **34** generates a donor/acceptor carbene with chiral rhodium(II) catalyst Rh₂(*S*-NTTL)₄ that exhibits increased regio-, diastereo-, and enantioselectivity for allylic alkylation (Scheme 13). Though only four examples are described, the conversion of acyclic alkenes to **35a,b** represents two of the most selective direct allylic alkylations of unactivated acyclic internal alkenes to date.

5. ENANTIOSELECTIVE HETERO-ENE REACTIONS

The Lewis acid-catalyzed enantioselective heteroene reaction between glyoxylate esters and unfunctionalized alkenes, first examined by the Evans group, represents one of the earliest advances in the asymmetric functionalization of internal unactivated alkenes.^{86–89} Various cationic copper(II)-bisoxazoline catalysts were investigated for their ability to catalyze the formation of α -hydroxy esters with both 1,1- and 1,2-disubstituted alkenes. Copper complex **38** reacted smoothly with ethyl glyoxylate **36** and cyclohexene (**1**), for example, to provide α -hydroxy ester **37a** in great yield and with exquisite enantioselectivity (Scheme 14).

X-ray crystallography and computational studies of [Cu((*S,S*)-*t*-Bu-BOX)(glyoxylate)]²⁺ indicate that the catalyst takes on a distorted square planar geometry with glyoxylate **36**

(Figure 1). This conformation provides insight into the factors that govern stereoselectivity, as the flanking *tert*-butyl groups of the ligand both block the *Re*-face approach of the enophile and sterically disfavor the *exo* transition state.

In noncoordinating solvents, various unfunctionalized internal alkenes furnished products in up to 98% ee and modest diastereoselectivity (**37a–d**). Even acyclic *cis*-2-butene produced α -hydroxy ester **37d** with comparable enantioselectivity to the structurally rigid cycloalkenes. Interestingly, this trend did not extend to cycloheptene, which failed to afford synthetically useful yield of **37b** under any of the conditions screened. Since this initial discovery by Evans, a palladium(II)-catalyzed version of this reaction has also been developed.⁹⁰

Recently Tambar and co-workers developed a catalytic asymmetric heteroene reaction utilizing enophilic sulfurimide reagent **41** to convert a wide range of *cis*-alkenes **39** to allylic sulfinamides **40** utilizing a catalytic combination of SbCl₅ and BINOL derivatives **42a** or **42b** (Scheme 15A).⁹¹ This chemistry, which accommodates a wide substrate scope including unactivated olefins, takes place with high enantioselectivity, diastereoselectivity, *E*-alkene selectivity, and regioselectivity. This reaction, thus, represents one of the earliest examples of asymmetric allylic C–S bond formation utilizing unactivated alkenes. A series of steric and electronic trends were identified to predict regio- and chemoselectivity in the enantioselective allylic oxidation of nonsymmetric internal alkenes (Scheme 15B).

Based on these reactivity trends, substrates accommodating multiple nonequivalent alkenes exhibited chemoselectivity, disfavoring the heteroene reaction with alkenes displaying diminished π -nucleophilicity (Scheme 16). It is important to note, however, that *trans*-alkenes and cycloalkenes provide the corresponding allylic sulfinamides with diminished enantioselectivities, presumably due to disfavored steric interactions.

The catalytic combination of Lewis acidic SbCl₅ and BINOL derivatives **42a** or **42b** proved imperative, with diminished yields when either catalytic component was excluded. This observation, in combination with pioneering studies by Corey and co-workers,^{92,93} led the authors to further investigate and propose a Lewis acid-assisted Brønsted acidity-based mechanism wherein SbCl₅ further acidifies a proton of BINOL to activate enophile **41**.^{94–98} The regio-, diastereo-, and enantioselectivity are rationalized through an organized 6-membered closed transition state **43** with oxidant **41** favoring an *exo*-selective approach (Scheme 17).

The utility of Tambar's stereoselective heteroene chemistry is showcased in the stereospecific elaboration of the allylic sulfinamide product **40a** to a variety of derivatives containing stereocenters with C–S, C–C, C–Cl, C–N, and C–O bonds (Scheme 18). Copper-mediated alkylation chemistry affords allylic alkylation product **44**.⁹⁹ Simple reduction conditions yield allylic thiol **45**. Rearrangements afford allylic alcohol **46**, allylic amine **47**, and allylic chloride **48**. Thus, this chemistry represents a general strategy toward enantioenriched products from both unactivated and activated *cis*-alkene starting materials.

6. CONCLUSIONS

Recent advances in catalytic enantioselective intermolecular allylic C–H oxidation, amination, and alkylation of unactivated internal alkenes have begun to address several selectivity issues encountered when utilizing unsaturated hydrocarbons. These powerful strategies have provided chemists with the ability to directly access value-added products from inexpensive and abundant starting materials. While relatively few examples of selective intermolecular allylic C–H functionalization utilizing *acyclic* systems have been demonstrated, several recent discoveries have established a foundation to address this need. Future advances in the asymmetric allylic functionalization of internal alkenes will undoubtedly focus on selective transformations that can be performed in molecular settings that are amenable to the synthesis of complex target molecules.

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Figure 1.
Model for stereinduction of copper-bisoxazoline-catalyzed asymmetric hetero-ene reaction.

Scheme 1.

Approaches to Catalytic Asymmetric Allylic Functionalization

Scheme 2.

Allylic C–H Functionalization of Terminal and Internal Alkenes

Scheme 3.
Early Kharasch-Sosnovsky Reaction with Cycloalkenes

Scheme 4.
Amino Acids as Chiral Ligands for the Asymmetric Kharasch–Sosnovsky Reaction

Scheme 5.
Oxazolines as Chiral Ligands for the Asymmetric Kharasch–Sosnovsky Reaction

Scheme 6.

Asymmetric Kharasch–Sosnovsky Reaction with Trisubstituted Alkenes

Scheme 7.

Model for Stereoinduction in the Copper-Bisoxazoline-Catalyzed Asymmetric Kharasch–Sosnovsky Reaction

Scheme 8.
Catalytic Asymmetric C–H Amination with Manganese-Salen Complex

Scheme 9.

Amination Variant of Asymmetric Kharasch–Sosnovsky Reaction

Scheme 10.
C–H Amination with a Chiral Rhodium Catalyst and Chiral Sulfonimidamide

Scheme 11.
Asymmetric Mizoroki-Heck Reactions

Scheme 12.
Rhodium-Catalyzed Asymmetric Allylic C–H Alkylation with Stabilized Carbenoids

Scheme 13.
Rhodium-Catalyzed Asymmetric Allylic C-H Alkylation with Triazoles

Scheme 14.

Copper-Bisoxazoline-Catalyzed Asymmetric Hetero-Ene Reaction

Scheme 15.
Catalytic Asymmetric Allylic Oxidation of Internal Alkenes via a Hetero-Ene Reaction

Scheme 16.

Regio-, Enantio-, and Chemoselective Allylic Oxidation of Dienes with Multiple Internal Alkenes

Scheme 17. Transition-State Model for SbCl_5 -BINOL-Catalyzed Allylic Oxidation of Internal Alkenes

Scheme 18.
Synthetic Derivatization Products from Catalytic Regio- and Enantioselective Allylic Oxidation of Internal Alkenes