Review

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ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.5b02070 • Publication Date (Web): 29 Oct 2015

Downloaded from http://pubs.acs.org on November 3, 2015

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Catalytic Stereoselective [2,3]-Rearrangement Reactions

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ABSTRACT

[2,3]-Sigmatropic rearrangement processes of allylic ylides or their equivalents can be applied to a variety of different substrates and generate products of wide interest / applicability to organic synthesis. This review describes the development and applications of stereoselective [2,3]-rearrangement reactions in which a sub-stoichiometric amount of a catalyst is used in either the formation of the reactive intermediate or the [2,3]-rearrangement step itself.

Examples include [2,3]-rearrangement of:
- Onium ylides
- O-Propargylic oximes
- Sulfides, selenoxides, sulfimides, and N-oxides
- [2,3]-Wittig rearrangements

[2,3]-Sigmatropic rearrangement processes of allylic ylides or their equivalents can be applied to a variety of different substrates and generate products of wide interest / applicability to organic synthesis. This review describes the development and applications of stereoselective [2,3]-rearrangement reactions in which a sub-stoichiometric amount of a catalyst is used in either the formation of the reactive intermediate or the [2,3]-rearrangement step itself.

Keywords: Stereoselective catalysis, [2,3]-rearrangement, allylic oxonium ylides, allylic ammonium ylides, allylic sulfonium ylides, O-propargylic oximes, allylic sulfoxides, allylic N-oxides
1. INTRODUCTION

Stereoselective [2,3]-sigmatropic rearrangements have great utility in organic synthesis.\(^1\,\,2\) In particular, the ability to form carbon-carbon bonds with high diastereo- and enantioselectivity through well-defined and predictable transition states under often mild reaction conditions makes [2,3]-sigmatropic rearrangements attractive for the synthesis of complex targets.\(^2\) Sigmatropic processes can be broadly categorized into two main types: a) neutral rearrangements involving ylides and b) anionic rearrangements (Scheme 1). These reactions almost always involve at least one heteroatom and allow a number of different products containing various functional groups to be accessed.

![Scheme 1. General classifications of [2,3]-sigmatropic rearrangements](image)

Many stereoselective [2,3]-rearrangements developed for organic synthesis utilize either existing stereocenters within the starting materials, chiral auxiliaries, or stoichiometric chiral ligands to control the configuration of the newly formed \(\sigma\)-bond. Advances in the development and applications of catalytic, stereoselective [2,3]-rearrangement reactions are less prevalent. This review surveys stereoselective [2,3]-rearrangement processes where a sub-stoichiometric amount of a catalyst is used in either the formation of the reactive ylide / anion or to promote the [2,3]-rearrangement itself (Scheme 2). The most widely explored processes within this remit are transition-metal catalyzed formations of allylic onium ylides from diazo compounds, followed by a facile in situ [2,3]-rearrangement (Section 2). More recently, alternative methods for the catalytic [2,3]-rearrangement of allylic ammonium ylides derived from quaternary ammonium salts have been developed (Section 3). The transition-metal promoted rearrangement of \(O\)-propargylic oximes generates highly reactive
Allenyl nitrone intermediates that can participate in a number of different reaction cascades (Scheme 4). Catalytic variants of commonly used [2,3]-rearrangements of allylic sulfoxides (Mislow-Evans), selenoxides (Riley oxidation), sulfimides, and N-oxides (Meisenheimer) have also been explored (Section 5). Finally, a limited number of catalytic, stereoselective anionic [2,3]-Wittig rearrangements have been reported (Section 6).

2. Onium ylides from metal carbenoids

\[ \text{R}_2\text{N} + \text{X}=\text{R}_2\text{N} \rightarrow \text{X}\text{=R}_2\text{N} + \text{R}_2\text{N} \]

X = R₂N, RO, RS, halogen

3. Ammonium ylides from quaternary ammonium salts

\[ \text{R}_2\text{N} + \text{X}=\text{R}_2\text{N} \rightarrow \text{X}\text{=R}_2\text{N} + \text{R}_2\text{N} \]

4. O-Propargylic oximes

\[ \text{N} + \text{X}=\text{R}_2\text{N} \rightarrow \text{X}\text{=R}_2\text{N} + \text{R}_2\text{N} \]

5. Sulfoxides, selenoxides, sulfimides, and N-oxides

\[ \text{Z}-\text{Y} + \text{X}=\text{R}_2\text{N} \rightarrow \text{X}\text{=R}_2\text{N} + \text{R}_2\text{N} \]

X = RS, RSe, R₂N
Y = O, RN

6. [2,3]-Wittig rearrangements

\[ \text{R}_2\text{N} \rightarrow \text{R}_2\text{N} \rightarrow \text{R}_2\text{N} \]

Scheme 2. Overview of catalytic [2,3]-rearrangements discussed
1.1 General mechanism and stereochemical control

[2,3]-Sigmatropic rearrangements are symmetry allowed concerted processes that proceed through a five-membered, six-electron transition state with an envelope conformation. The presence of a heteroatom within the reaction framework lowers the energy of these processes and can provide additional stabilization of the transition state through resonance contributions. Generally, [2,3]-rearrangements of allylic ammonium ylides are favorable processes, but competing [1,2]- or [1,4]-rearrangements (where possible) are observed in some cases.

Stereocontrolled [2,3]-rearrangement processes can generate up to two new stereogenic centers around the newly formed σ-bond and allow (E)- or (Z)-selectivity within the new π-bond. The greater conformational flexibility of five-membered transition states compared with six-membered transition states of [3,3]-sigmatropic rearrangements make them more susceptible to substituent effects and complete stereocontrol can be difficult to attain. The observed diastereoselectivity of [2,3]-rearrangement of generic substrates such as (E)-1 is dependent on the relative energies of the exo-2 and endo-3 transition states as outlined by Houk and Marshall for the [2,3]-Wittig rearrangement (Scheme 3a). The stereochemical preference for a given process is dependent on both steric and stereoelectronic properties of the two-substituents (R¹ and R²) as well as the heteroatom present. [2,3]-Sigmatropic rearrangements are often stereospecific, with (E)-1 and (Z)-6 isomers leading to the formation of the opposite product diastereoisomers (Scheme 3b). For example, rearrangement of (E)-1 through exo-type transition state 2 leads to the formation of (±)-anti-4, whereas rearrangement of the corresponding (Z)-6 through exo-type transition 7 state gives (±)-syn-5.
Scheme 3. Generic pre-transition state assemblies for diastereoselective [2,3]-rearrangements

The geometry of the newly formed π-bond after [2,3]-rearrangement is also subject to stereocontrol by the substituents. As a result, the (E)-alkene geometry is often favored over the corresponding (Z)-alkene due to minimization of allylic 1,3-strain in transition state 10 compared with 11 (Scheme 4).[^3][^5]

Scheme 4. Control of (E)/(Z)-alkene geometry in [2,3]-rearrangements
While these general stereochemical considerations can often be used to account for the observed diastereoselectivity, the precise origin of any enantioselectivity is poorly understood in many cases. There are relatively few detailed mechanistic studies regarding catalytic stereoselective [2,3]-rearrangements as these processes are often highly complex and difficult to probe experimentally and computationally.

2. METAL-CATALYZED ONIUM YLIDE FORMATION AND [2,3]-REARRANGEMENTS VIA METAL CARBENOIDS

The use of diazo compounds as allylic onium ylide precursors in [2,3]-rearrangements has been widely studied. The metal-catalyzed decomposition of diazo compounds proceeds readily to form metal carbenoids with concomitant loss of nitrogen. A wide range of transition-metal complexes can be used for this purpose with catalysts based upon rhodium and copper by far the most common, although iron, cobalt, ruthenium, silver, platinum, and gold-based complexes have been used. The metal carbenoid species can react in situ with allylic ethers, amines, sulfides, and allyl halides to form the corresponding allylic onium ylides that can undergo the desired [2,3]-rearrangement. (Scheme 5) However, metal carbenoids are often highly reactive intermediates that can participate in a variety of competing processes including cyclopropanation reactions alongside C-H, O-H and Si-H insertions. It is therefore often necessary to tune the metal-ligand combination used in order to bias the desired chemoselectivity for [2,3]-rearrangement over any competing processes.
Scheme 5. Onium ylides generated from metal carbenoids 15 and subsequent [2,3]-rearrangement. X = R₂N, RO, RS, RSe, Br, or I

There has been extensive work on developing diastereo- and/or enantioselective onium ylide [2,3]-rearrangements originating from the catalytic decomposition of diazo compounds. A successful strategy in diastereoselective processes makes use of achiral transition-metal complexes reacting with diazo compounds bearing chiral auxiliaries and/or existing stereogenic centers. The development of [2,3]-rearrangements via metal carbenoids in which control of the product configuration is derived catalytically from a chiral metal complex has been more challenging. One of the key factors in determining the success of an enantioselective variant is the degree of association between the chiral metal complex and the ylide during the [2,3]-rearrangement step. If the metal complex dissociates prior to rearrangement then any enantiocontrol must arise from a configurationally restricted ylide, otherwise a racemic product will be observed. The number of potential reaction pathways and complexity of these processes makes detailed elucidation of the reaction mechanism challenging. As a result, many catalytic asymmetric [2,3]-rearrangements from metal carbenoid species are optimized through traditional ligand-screening approaches.
2.1 Oxonium ylides.

2.1.1 Intermolecular oxonium ylide formation and [2,3]-rearrangement. The [2,3]-rearrangement of allylic oxonium ylides generated from the intermolecular reaction between metal carbenoids and allyl ethers is challenging, with side reactions including cyclopropanation and [1,2]-insertion reactions potentially problematic. Doyle and co-workers were the first to report the diastereoselective [2,3]-rearrangement of oxonium ylides from the reaction of catalytically generated rhodium carbenoids and allylic ethers.7 For example, the dropwise addition of ethyl diazoacetate 20 to a solution of Rh2(OAc)4 (1 mol%) and allylic ether 21 led to the selective formation of [2,3]-rearrangement product 22 in 92% yield and 83:17 dr (syn:anti), although competitive cyclopropanation to generate 23 was also observed (Scheme 6a). The reaction was applicable to both diazoacetates and diazoacetophenones, alongside a small range of substituted allylic ethers, with [2,3]-rearrangement favored over cyclopropanation in all cases. Doyle subsequently reported a highly enantioselective version of this process utilizing a rhodium complex bearing enantiomerically pure oxazolidin-2-one ligand 24 (Scheme 6b).8 Under these conditions [2,3]-rearrangement is again favored over cyclopropanation, with the major product 25 isolated in 36% yield, 85:15 dr (anti:syn), and an impressive 98% ee. In this case the major diastereoisomer formed is opposite to that preferentially formed using the achiral rhodium catalyst. The catalyst-dependent diastereoselectivity observed suggests a metal-associated ylide is involved in the product forming step of these reactions.
Quinn and co-workers reported the copper-catalyzed reaction of diazoacetate 26 with C₂-symmetric vinyl epoxide 27 to give the ring-expanded cis-dihydropyran 28 in good yield as a single diastereoisomer (Scheme 7). However, the process was limited to symmetric epoxide 27, with other substituted vinyl epoxides giving low yields and poor selectivity towards the desired [2,3]-rearrangement pathway.

Njardarson and co-workers showed that copper carbenoids generated from the decomposition of diazoacetophenone 29 undergo oxonium ylide formation and [2,3]-rearrangement with a variety of substituted allylic ethers. For example, reaction with symmetrical allylic ether 30 forms product 31 in good yield and high diastereoselectivity, with subsequent ring-closing metathesis of 31 using Grubbs II catalyst giving pyran 32 in high yield (Scheme 8a).
reaction of 29 with unsymmetrical allylic ether (E)-33 followed by deprotection of the [2,3]-rearrangement product 34 with BF$_3$·Et$_2$O gave α-hydroxy ketone 35 with high levels of diastereoselectivity (Scheme 8b). This process is stereospecific, with (Z)-allylic ether 36 reacting to give the corresponding syn-product 37 with reasonable levels of diastereoselectivity (Scheme 8c).

Scheme 8. Diastereoselective reaction of diazoacetophenone 29 with functionalized allylic ethers

In 2009, Davies and co-workers reported a highly enantioselective oxonium ylide generation-[2,3]-rearrangement of racemic allylic alcohols with donor-acceptor diazo compounds using a chiral rhodium catalyst. The substitution pattern of the allylic alcohol is key to determining the chemoselectivity of the reaction. For example, reacting diazo compound 38 with primary allylic alcohol 39 exclusively formed O-H insertion product 43, whereas the reaction with secondary allylic alcohol 40 selectively gave [2,3]-rearrangement product 42 in good yield and excellent enantioselectivity (Scheme 9a). This trend was general for a range of substrates,
with various substituted secondary and tertiary allylic alcohols reacting to give [2,3]-rearrangement products with high levels of chemo- and enantioselectivity. The enantioselectivity of the process is derived purely from the chiral ligand \(41\) as racemic, \((R)\)- and \((S)\)-allylic alcohol \(40\) all react with methyl 2-diazo-2-phenyl acetate \(44\) to give the same absolute configuration of the corresponding [2,3]-rearrangement product \(45\) (Scheme 9b).

\[
\begin{align*}
&\text{a)} \\
&\text{MeO}_2C\text{Ph} + \text{OH} \quad \text{Rh}_2(\text{S-DOSP})_4 (1 \text{ mol}\%) \\
&\text{pentane, 0 °C} \\
&\text{MeO}_2C\text{OH} \quad \text{MeO}_2C\text{OH} \\
&\text{R} \\
&\text{Yield (\%)} \\
&\text{42:43 ee (\%)}^a \\
&\text{H} \quad 74 \quad >5:95 \quad <5 \\
&\text{Me} \quad 66 \quad 94:6 \quad 98 \\
&\text{(S)-DOSP (41)}
\end{align*}
\]

\[
\begin{align*}
&\text{b)} \\
&\text{MeO}_2C\text{Ph} + \text{OH} \quad \text{Rh}_2(\text{S-DOSP})_4 (1 \text{ mol}\%) \\
&\text{pentane, 0 °C} \\
&\text{MeO}_2C\text{OH} \\
&\text{Yield (\%)} \\
&\text{45} \\
&\text{ee (\%)}^a \\
&\text{(+)-40} \quad 69 \quad 88 \\
&\text{(S)-40 (84\% ee)} \quad 61 \quad 85 \\
&\text{(R)-40 (83\% ee)} \quad 59 \quad 94
\end{align*}
\]

Scheme 9. Enantioselective [2,3]-rearrangement reactions using racemic allylic alcohols. $^a$ee of major product

This methodology was extended to the enantioselective synthesis of products containing two vicinal stereocenters.\(^{12}\) The reaction is stereospecific with respect to the geometry of the allylic alcohol, with \((E)\)-46 reacting with diazo compound \(38\) to give product \(47\) and \((Z)\)-48 reacting under the same conditions to give the opposite diastereoisomer \(49\) (Scheme 10). The matched/mismatched effect between the allylic alcohol configuration and chiral catalyst was much more significant for \((Z)\)-allylic alcohol \(48\) with the reaction using \((S)\)-DOSP \(41\) as the ligand leading to reduced yields and diastereoselectivity. Through judicious choice of alcohol configuration, alkene geometry and chiral ligand used, all four possible stereoisomers of the
[2,3]-rearrangement products were accessible. The scope of the reaction has been fully explored, with a number of α-aryl and α-alkenyl diazoacetates reacting with a wide variety of substituted allylic alcohols to give the rearranged products in uniformly high yields and excellent diastereo- and enantioselectivity. The same catalytic system has been utilized in the reaction of α-aryl and α-alkenyl diazoacetates with tertiary propargylic alcohols to form substituted allenes in high enantioselectivity.\textsuperscript{13} When racemic tertiary propargylic alcohols were used, kinetic resolution was observed with the allene rearrangement products formed in good dr and high ee and the unreacted propargylic alcohols recovered enantioenriched. A silica-supported version of Rh\textsubscript{2}(S-DOSP)$_4$ can also be used for the catalytic oxonium ylide formation and [2,3]-rearrangement reactions using both allylic alcohols and propargylic alcohols, forming the corresponding products in good yields with enantioselectivity comparable with those obtained in the homogeneous reactions.\textsuperscript{14}

![Scheme 10](image)

**Scheme 10.** Stereospecific [2,3]-rearrangement of allylic alcohols

Davies and co-workers have applied their methodology to the synthesis of highly functionalized cyclopentanes through a complex domino reaction sequence.\textsuperscript{15} As previously, reacting α-alkenyl diazo compounds such as 38 with allylic alcohol 46 in the presence of a
chiral rhodium catalyst promotes oxonium ylide formation followed by enantioselective [2,3]-rearrangement. Heating product 47 in a sealed-tube promotes an oxy-Cope rearrangement followed by tautomerization, and an intramolecular ene cyclization to form substituted cyclopentane 51 containing four contiguous stereocenters in high diastereo- and enantioselectivity (Scheme 11a). Although racemic allylic alcohols can be utilized in this reaction, higher enantioselectivity was obtained using enantiomerically pure allylic alcohols and a matched chiral rhodium catalyst.15b The process was applicable to a variety of substituted allylic alcohols, forming functionalized cyclopentanes in high yields and excellent diastereo- and enantioselectivity in all cases. Introducing a C(3) methyl substituent onto the allylic alcohol alters the reaction pathway, with a type II-ene cyclization favored to form cyclohexane products containing an exocyclic alkene substituent and four stereogenic centres.16 For example, the rhodium catalyzed reaction of 38 with allylic alcohol 52 followed by heating in heptane results in the formation of substituted cyclohexane 53 in 67% yield as a single diastereoisomer in 99% ee (Scheme 11b). This domino reaction sequence was applicable to a range of α-alkenyl diazo compounds and substituted allylic alcohols, forming the products in excellent diastereo- and enantioselectivity. Cyclic allylic alcohols, including a monoterpenoid derived substrate, could also be utilized to generate a series of structurally complex fused-bicyclic products with high diastereoselectivity.
Scheme 11. Domino reaction sequence for the synthesis of a) cyclopentanes and b) cyclohexanes

2.1.2 Diastereoselective intramolecular oxonium ylide formation and [2,3]-rearrangement. The intramolecular generation and [2,3]-rearrangement of oxonium ylides from diazo compounds offers an efficient and potentially stereoselective route towards a variety of highly functionalized oxocyclic products. The synthetic utility of these [2,3]-rearrangement products has been widely demonstrated through the synthesis of a variety of complex natural products.

In 1986 Johnson and Pirrung independently reported the first examples of diastereoselective catalytic generation and [2,3]-rearrangement of oxonium ylides. For example, treating allyloxy-substituted diazoketone 54 with Rh₂(OAc)₄ (1 mol%) generates oxonium ylide 55 in situ, which undergoes intramolecular [2,3]-rearrangement to form
furanone 56 in 65% yield and excellent 93:7 dr (anti:syn) (Scheme 12). Importantly, this class of allyloxy diazoketones exhibited excellent chemoselectivity for [2,3]-rearrangement over potential [1,2]-rearrangement under the reaction conditions.

Scheme 12. Rearrangement of oxonium ylide 55 generated from alkoxy-substituted diazoketone 54

Pirrung and co-workers subsequently utilized the catalytic oxonium ylide generation and [2,3]-rearrangement methodology in the first enantioselective total synthesis of the antifungal agent (+)-griseofulvin 59.19 The key step within this sequence involves the diastereoselective [2,3]-rearrangement of the oxonium ylide generated from enantiomerically pure diazoketone 57 using Rh2(piv)4 (5 mol%) to form advanced intermediate 58 in 62% yield as a single stereoisomer (Scheme 13). The reaction is also completely chemoselective, with no products from potential competing o-methoxy ylide formation or [1,2]-rearrangement observed.

Scheme 13. Enantioselective synthesis of (+)-griseofulvin 59

The concept of catalytic oxonium-ylide formation and [2,3]-rearrangement was further explored by Clark in 1992 with the demonstration of an intramolecular Cu(acac)2 catalyzed tandem carbenoid insertion and [2,3]-rearrangement process to form anti-tetrahydrofuran-3-
ones in good yields with excellent levels of diastereoselectivity (Scheme 14). In this case catalytic Rh$_2$(OAc)$_4$ was ineffective, giving the products in modest yields with lower levels of diastereoselectivity.

Scheme 14. Copper-catalyzed generation and [2,3]-rearrangement of oxonium ylides

Clark and co-workers have subsequently used this synthetic procedure as a key step towards the total synthesis of a wide variety of natural products. For example, the divergent synthesis of three of the family of amphidinolide macrolide natural products utilizes the copper-catalyzed decomposition of diazoketone 63 and diastereoselective rearrangement of the resulting oxonium ylide as a key step. Commercially available alcohol 62 is readily converted in three steps into diazoketone 63, which upon treatment with Cu(acac)$_2$ (10 mol%) in THF at reflux undergoes a diastereoselective oxonium ylide formation and [2,3]-rearrangement to give dihydrofuranone 64 in 91% yield as a single diastereoisomer (Scheme 15a). Dihydrofuranone 64 serves as a common intermediate in the divergent total synthesis of amphidinolides T1, T3 and T4 (65-67) (Scheme 15b). Analogous methodology has also been used as the key step in the preparation of fragments of large natural products including the amphidinolides, gambieric acid A, and cinatrin C.
Mechanistically, Clark found that the equilibrium between metal-bound and free-ylides in a non-stereoselective intramolecular oxonium ylide [2,3]-rearrangement process is highly dependent on both the catalyst and substrate. For example, treating $^{13}$C labelled $\alpha$-diazo $\beta$-keto ester 68 with various transition-metal catalysts resulted in a variable mixture of [2,3]-rearrangement product 69 and formal [1,2]-rearrangement product 70 (Scheme 16). The catalyst-dependent reaction outcome suggests this reaction may proceed via either a metal-bound ylide species or alternative non-ylide pathways to give the formally rearranged products.
In 2008, Hodgson and co-workers reported a tandem cross-metathesis-oxonium ylide formation [2,3]-rearrangement protocol for the diastereoselective synthesis of dihydrofuranones, which was applied to the synthesis of anti-HIV agent hyperolactone C.\textsuperscript{26} Diazoketone 71 was treated with Grubbs II catalyst and methacrolein 72 to form 73 \textit{in situ}, catalytic Rh\textsubscript{2}(OAc)\textsubscript{4} (4 mol\%) was then added to promote diastereoselective oxonium ylide formation and [2,3]-rearrangement (Scheme 17). The resulting dihydrofuranone 74 was immediately reduced with NaBH\textsubscript{3}CN to form fused hemiketal 75 in 26\% yield over the three-steps with good diastereoccontrol. A further two steps finished the synthesis of the spirocyclic hyperolactone C 76. Hodgson subsequently reported an enantioselective synthesis of (−)-hyperolactone C 76 starting form enantiomerically pure diazoketone 71.\textsuperscript{27}

![Scheme 17. Diastereoselective synthesis of (±)-hyperolactone C 76](image)

In 2014 Hodgson reported a new route to a small number of hyperolactone C analogues through intramolecular oxonium ylide formation and [2,3]-rearrangement of diazoacetals. For example, treating diazoacetal 77 with Rh\textsubscript{2}(tfa)\textsubscript{4} (1 mol\%) forms bicyclic acetal 78 in 43\% yield as a single diastereoisomer (Scheme 18).\textsuperscript{28} Acid-catalyzed elimination of acetal 78 and subsequent lactonization led to the formation of spirofuranone 79 in high yield.
Clark and co-workers have extended this methodology to the synthesis of tetrahydropyran-3-
ones. Building on an earlier diastereoselective synthesis,29 the enantioselective synthesis of
the fungal metabolite (+)-decarestrictine L 83 was reported starting from ethyl (R)-3-
hydroxybutyrate 80.30 Treatment of enantiomerically pure diazoketone 81 with Cu(tfacac)2 (2
mol%) gave tetrahydropyran-3-one 82 in 60% yield and 91:9 dr (Scheme 19). Four further
steps converted 82 into (+)-decarestrictine L 83 in an overall 9% yield over ten steps.

A similar approach has been employed to synthesize a large number of structurally complex
diterpene marine natural products through formation of bicyclic allylic oxonium ylides
followed by diastereoselective [2,3]-rearrangement. For example, the first total synthesis of
(±)-vigulariol 87, a member of the Cladiellin family possessing in vitro cytotoxic activity
against human lung cancer cells, utilized the copper-catalyzed decomposition of diazo
intermediate 84 and [2,3]-rearrangement of the resulting oxonium ylide (Scheme 20).31 The
bicyclic products (Z)-85 and (E)-86 were formed in 96% yield as an 83:17 mixture, with the
undesired (E)-86 subsequently isomerized into (Z)-85 using AIBN and ethanethiol. Related
strategies using bicyclic oxonium ylides generated in the same way have been utilized in the synthesis of a number of other natural products including other members of the Cladiellin family of diterpenes,\textsuperscript{32} sclerophytin F,\textsuperscript{33} the tricyclic core of labiatin A and Australin A\textsuperscript{34}, and neoliacinic acid.

![Scheme 20. Synthesis of (±)-vigulariol 87](image)

In 2001 West and co-workers reported a diastereoselective iterative synthesis of polypyran scaffolds, which are common cores in polyether marine natural products.\textsuperscript{35} Treatment of diazoketone 88 with Cu(tfacac)\textsubscript{2} (5 mol\%) induced a diastereoselective oxonium-ylide formation-[2,3]-rearrangement process to give bicyclic ether 89 in good yield and high diastereoselectivity (Scheme 21). Further manipulation of 89 into diazoketone 90 set up a second copper-catalyzed [2,3]-rearrangement step to form polypyran fragment 91 in 80% yield as a single diastereoisomer.
Scheme 21. Diastereoselective synthesis of polypyran motifs

Doyle and co-workers found that competing [1,2]- and [2,3]-rearrangements were observed when diazoacetate substituted tetrahydropyran-4-ones such as 92 undergo rhodium-catalyzed intramolecular oxonium ylide formation and rearrangement (Scheme 22). The poor selectivity observed for both rearrangement products 93 and 94 was independent of the catalyst structure, suggesting these reactions proceed through a metal-free ylide species. Moreover the modest diastereoselectivity observed in each case reflects the axial-equatorial conformational isomer distribution of the reacting diazoacetate.

Scheme 22. Competing [1,2]- and [2,3]-rearrangements

Tae and co-workers have reported the use of alkynes as gold-carbenoid precursors in intramolecular oxonium ylide formations. Treating propargylic ethers 95 with a gold (I) catalyst in the presence of stoichiometric oxidant 97 generates gold carbenoids 98, which can undergo intramolecular oxonium ylide formation and subsequent [2,3]-rearrangement into dihydrofuranone derivatives 99 in modest yields (Scheme 23). The diastereoselectivity of the process was dependent on the nature of the propargylic substituent. Electron-rich aryl (R = 4-MeOC₆H₄) or heteroaryl (R = 2-furyl) groups gave the anti-product exclusively, whereas various alkyl substituents gave lower levels of diastereoselectivity (61:39 to 80:20 dr). Tang and co-workers have reported a related gold-catalyzed rearrangement of benzannulated propargylic ethers to form dihydrobenzofuranones under similar oxidative conditions. Additionally, two diastereoselective examples utilizing carbocyclic aliphatic tethers were
investigated, with the resulting fused bicyclic tetrahydrofuranones formed in good yields as single diastereoisomers.

Scheme 23. Alkynes as gold carbenoid precursors

Boyer has utilized N-tosyl triazoles as alternatives to diazo compounds for the generation of rhodium carbenoids. For example, treating 100 with catalytic Rh$_2$(OAc)$_4$ results in decomposition of the triazole ring with release of nitrogen to form intermediate rhodium carbenoid 101. Subsequent in situ oxonium ylide formation and diastereoselective [2,3]-rearrangement followed by hydrolysis over basic alumina of the resultant N-tosyl dihydrofuran imine allowed isolation of dihydrofuranone ent-64 in 78% yield and >95:5 dr (Scheme 24a). A range of C(5) alkyl substituents was tolerated in this process giving dihydrofuranones in high yields and excellent dr, however incorporation of a C(5)-phenyl substituent gave the product in a reduced 83:17 dr. A small number of 2,2-disubstituted dihydrofuran-3-ones could also be synthesized using an increased catalyst loading of 15 mol% Rh$_2$(OAc)$_4$, with the products formed in reasonable yields with high levels of diastereoselectivity. This methodology was subsequently applied to the total synthesis of the acetogenin (+)-petromyroxol 104. Treatment of enantiomerically pure triazole 102 under the previously optimized conditions gave anti-tetrahydrofuranone 103 as a single
diastereoisomer, which was converted into (+)-petromyroxol 104 in four further steps (Scheme 24b).

Scheme 24. a) Diastereoselective synthesis of dihydrofuran-3-imines from N-tosyl 1,2,3-triazoles. b) Application in natural product synthesis

A series of C(2) tetrasubstituted tetrahydrofurans was accessible through the rhodium-catalyzed decomposition of triazoles such as 105 (Scheme 25). As previously, the intermediate N-tosyl imine 106 was unstable to purification but was readily hydrolyzed into aldehyde 107 in an overall 88% yield as a single diastereoisomer. The reaction tolerates a range of functionalized C(5) alkyl substituents, forming the synthetically useful products in high yields and excellent diastereoselectivity. The catalytic rearrangement of an O-propargylic triazole was also possible, with the corresponding allenyl tetrahydrofuran formed in excellent yield but with a slightly reduced dr (6:1).

Scheme 25. Diastereoselective synthesis of C(2)-tetrasubstituted saturated heterocycles
2.1.3 Enantioselective intramolecular oxonium ylide formation and [2,3]-rearrangement. In 1992 McKervey and McCann reported the first enantioselective intramolecular [2,3]-rearrangement of allylic oxonium ylides in which the stereochemistry is derived from the catalyst. The catalytic decomposition of diazo compound 108 (R = Me) using rhodium complexed with (S)-BNP 110 followed by oxonium ylide formation and [2,3]-rearrangement gave substituted benzofuranone 109 in 92% yield and 30% ee (Scheme 26). Hodgson subsequently showed that alkyl substituted phosphate ligand 111 gave higher levels of enantioselectivity, albeit in lower yield. Moody and co-workers tested a range of pyrrole 2-carboxylate ligands with chiral N-substituents in the same reaction, but only low levels of enantioselectivity were observed. An extensive study by McKervey and co-workers assessed a range of different chiral ligands in this process with (S)-PTTL 112, derived from (S)-tert-leucine, giving product 109 (R = H) in 96% yield and 60% ee. Hashimoto and co-workers found that the enantioselectivity of the reaction using 112 could be improved by performing the reaction in toluene at low temperature (–10 °C), although the product yield was reduced (Scheme 26).

Scheme 26. Enantioselective [2,3]-rearrangement of oxonium ylides using chiral rhodium complexes
Calter and Sugathapla reported that diazoacetal $113$ reacted with the rhodium complex of ligand $115$ to give bicyclic tetrahydrofuran derivative $114$ in 47% yield and 34% ee (Scheme 27). Hashimoto and co-workers later reported an improved variant of this reaction through screening of a wide range of chiral carboxylate Rh(II) complexes. The optimal catalytic system used fluorinated ligand $116$ to form rearranged product $114$ in 72% yield and an impressive 93% ee.

![Scheme 27. Enantioselective synthesis of bicyclic tetrahydrofuran derivatives](image)

Clark and co-workers screened a number of C$_2$-symmetric chiral diimines in the copper-catalyzed reaction of diazoketone $117$, with ligand $118$ giving dihydrofuranone product $119$ in 62% yield and reasonable 57% ee (Scheme 28). The substitution pattern around the diazoketone had a large impact on the enantioselectivity observed. For example, introduction of an $\alpha$-methyl substituent adjacent to the carbonyl had little effect, whereas placing a methyl group in either the $\beta$-position or the 2-position of the allyl group led to a dramatic drop in enantioselectivity. Benzannulation of the substrate also led to reduced levels of enantioselectivity in the resulting benzofuranone products.
Scheme 28. Copper-catalyzed enantioselective intramolecular [2,3]-rearrangement of 112

Doyle and co-workers reported the enantioselective [2,3]-rearrangement of a 13-membered ring oxonium ylide formed from decomposition of diazo compound 120 in the presence of a copper catalyst and BOX ligand 121 (Scheme 29). The reaction was selective for [2,3]-rearrangement over competing cyclopropanation (89:11), allowing macrocyclic ether 123 to be isolated as a single diastereoisomer in 35% yield and 65% ee. The relative stereochemistry was determined by analysis of γ-lactone 124, which was formed in excellent yield upon hydrogenation of macrocycle 123.

Scheme 29. Enantioselective macrocyclic ether synthesis
2.2 Ammonium ylides.

The [2,3]-rearrangement of allylic ammonium ylides leads to the formation of substituted α-amino acid derivatives. Despite the huge synthetic potential of this process, the development of a catalytic enantioselective variant using intermediate metal carbenoids has remained elusive, with only diastereoselective examples reported to date.

2.2.1 Intermolecular ammonium ylide formation and [2,3]-rearrangement. In 1981 Doyle and co-workers reported the first diastereoselective intermolecular ammonium ylide formation and [2,3]-rearrangement from the catalytic decomposition of a diazo compound.\(^{51}\) Reacting ethyl diazoacetate 20 with Rh\(_2\)(OAc)\(_4\) (0.5 mol%) and an excess of tertiary allylic amine 125 gave rearranged α-amino acid derivative 126 in 59% yield as a 75:25 mixture of anti:syn diastereoisomers (Scheme 30). Che and co-workers have performed a similar reaction using a ruthenium porphyrin based catalyst, with the rearranged product being obtained with same level of diastereoselectivity.\(^{52}\)

![Scheme 30](image)

Scheme 30. Intermolecular diastereoselective allylic ammonium ylide generation and [2,3]-rearrangement

In 2003 Sweeney and co-workers investigated the [2,3]-rearrangement of ammonium ylides 128 generated from the reaction of tetrahydropyridine 127 and ethyl diazoacetate 20 (Scheme 31a).\(^{53}\) In this case, using Rh\(_2\)(OAc)\(_4\) as the catalyst gave low yields and a complex mixture of products. Copper catalysts were more selective, with Cu(acac)\(_2\) (20 mol%) promoting ammonium ylide formation and subsequent endo-selective [2,3]-rearrangement to give syn-pyrrolidine 129 in 59% yield as a single diastereoisomer. The use of α-keto diazoacetates such as 130 was also investigated in this process, forming functionalized pyrrolidine 131.
containing a quaternary stereocenter in good yields with reasonable levels of diastereoselectivity (Scheme 31b). The use of a bicyclic tetrahydropyridine was also trialed, but the desired bicyclic rearrangement product was only formed in low yields and the stoichiometric base-mediated rearrangement of the pre-formed ammonium ylide was more efficient in this case.

\[
\begin{align*}
 \text{EtO} & \quad \text{N}_2 \\
20 & \quad + \quad \text{Cu(acac)}_2 (20 \text{ mol\%}) \quad \text{PhMe, } \Delta \\
& \quad \xrightarrow{\text{Cu(acac)}_2 (20 \text{ mol\%}) \text{PhMe, } \Delta} \quad \text{128} \\
& \quad \rightarrow \quad \text{129} \quad >95:5 \text{ dr}
\end{align*}
\]

\[
\begin{align*}
 \text{EtO} & \quad \text{N}_2 \\
130 & \quad + \quad \text{127} \quad \text{Cu(acac)}_2 (5 \text{ mol\%}) \quad \text{PhMe, } \Delta \\
& \quad \xrightarrow{\text{Cu(acac)}_2 (5 \text{ mol\%}) \text{PhMe, } \Delta} \quad \text{131} \\
& \quad \rightarrow \quad \text{131} \quad 56\% \quad 75:25 \text{ dr}
\end{align*}
\]

Scheme 31. Copper-catalyzed synthesis of substituted pyrrolidines

2.2.2. Intramolecular ammonium ylide formation and [2,3]-rearrangement. In 1994 Clark and co-workers reported the first diastereoselective [2,3]-rearrangement of an ammonium ylide generated from the intramolecular reaction of a metal carbenoid and an cyclic allylic amine. Treating diazoketone 132 with Cu(acac)\(_2\) (2 mol%) generated syn-ammonium ylide 133, which underwent [2,3]-rearrangement to give indolizidine 134 as a single diastereoisomer. Upon treatment with silica gel indolizidine 134 underwent complete epimerization into the opposite diastereoisomer 135, which was isolated in 72% yield (Scheme 32). This methodology was subsequently applied to the diastereoselective synthesis of a small range of pyrrolizidine, indolizidine and quinolizidine motifs. Acyclic substrates containing a stereogenic center on the tether connecting the allylic amine and diazoketone
also undergo metal-catalyzed ylide formation and [2,3]-rearrangement to form cyclic amine products in good yields but with little diastereoselectivity.\(^{58}\)

![Scheme 32. Diastereoselective synthesis of indolizidines via intramolecular ylide generation and [2,3]-rearrangement](image)

Clark and co-workers applied intramolecular ammonium ylide formation and [2,3]-rearrangement to the asymmetric synthesis of the CE ring system of the manzamine and ircinal families of marine alkaloids.\(^{57,59}\) Diazoketone \(136\), prepared in four steps from (S)-prolinol, was treated with Cu(acac)_2 (2 mol\%) to form the bicyclic rearrangement product \(137\) in 56% yield (Scheme 33). Diastereoselective reduction of ketone \(137\) with L-Selectride\(^\circledR\) gave alcohol \(138\) in 75% yield and >98% ee, confirming essentially complete transfer of stereochemistry during the [2,3]-rearrangement of the intermediate spiro-fused ammonium ylide.

![Scheme 33. Asymmetric synthesis of the CE ring system of the manzamine and ircinal alkaloids](image)

McMills and co-workers reported an analogous method for the synthesis of medium-sized azacane rings.\(^{60}\) L-Proline derived diazoketone \(139\) also undergoes ylide formation and [2,3]-rearrangement with transfer of stereochemistry in the presence of Cu(hfacac)_2 (15 mol\%) to
form azacane 140 in 70% yield and 98% ee (Scheme 34). However, in this case competing [1,2]-Stevens rearrangement into bicycle 141 was also observed (70:30 140:141), which is attributed to the increased tether length of diazoketone 139 compared with 136.

Rowlands and Barnes have investigated the copper-catalyzed aziridinium ylide generation and [2,3]-rearrangement of diazo compound 142 (Scheme 35). Treating 142 with catalytic Cu(acac)₂ allowed indolizine 145 to be isolated in only 21% yield but as a single diastereoisomer. The low yield is proposed to be partially due to the slow rate of inversion of configuration at nitrogen in aziridines. Starting material 142 exists as a mixture of nitrogen invertomers (43:57) that react to give intermediate aziridinium ylides 143 and 144. In this case, only ylide 143 derived from the minor N-invertomer of 142 has the correct geometry to undergo [2,3]-rearrangement.

Scheme 35. Copper-catalyzed generation and rearrangement of aziridinium ylides
2.3 Sulfonium ylides

The [2,3]-rearrangement of sulfonium ylides, sometimes referred to as the Doyle-Kirmse reaction, generated from the reaction of a metal carbenoid with an allylic sulfide has been widely studied. While high diastere- and/or (E)/(Z)-selectivity is attainable, the development of catalytic enantioselective variants of this reaction is particularly challenging. This is due to the fact that the catalyst must first distinguish between the heterotopic lone pairs of the sulfur atom and then promote a selective [2,3]-rearrangement reaction in which the stereochemical information is efficiently transferred from sulfur to carbon.\(^{62}\)

2.3.1 Diastereoselective intermolecular sulfonium ylide formation and [2,3]-rearrangement. One of the early examples of a stereoselective [2,3]-rearrangement utilizing the catalytic in situ formation of sulfonium ylides was reported by Grieco et al. in 1973.\(^{63}\) Treating sulfide 147 with dimethyl diazomalonate 146 and catalytic CuSO\(_4\) gave product 148 in 70% yield and an 90:10 \(E:Z\) isomeric ratio (Scheme 36).

\[ \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \quad 146 (1.1 \text{ eq}) \quad \overset{\text{PhS} \quad r-\text{Bu}}{\text{CuSO}_4 \text{(cat.)}} \quad \rightarrow \quad \text{MeO}_2\text{C} \quad \text{Me} \quad \overset{\text{MeO}_2\text{C}}{\text{PhS} \quad r-\text{Bu}} \quad 148 \]

\(70\%\)

\(\text{90:10} \ E:Z\)

Scheme 36. Copper-catalyzed [2,3]-rearrangement using diazomalonate 146

Yoshimoto and co-workers demonstrated that cephalosporin derivatives such as 149 undergo completely diastereoselective ring-contraction into penicillin derivatives through the copper-catalyzed reaction with ethyl diazoacetate followed by [2,3]-rearrangement (Scheme 37a).\(^{64}\) Thomas and co-workers subsequently utilized the diastereoselective [2,3]-rearrangement of sulfonium ylides to form a series of functionalized penicillanates.\(^{65}\) For example, treating diazopenicillanate 151 with allylic sulfide 152 and Cu(acac)\(_2\) (11 mol%) resulted in formation of 6,6-disubstituted penicillanate 153 in 65% yield and 87:13 dr (Scheme 37b). However, the
reaction using the corresponding allylic selenide under the same conditions resulted in formation of the product with no diastereoselectivity.

Scheme 37. a) Ring-contraction of cephalosporin core into a penicillin derivative; b) Functionalization of diazopenicillanates 151

Early attempts to utilize [2,3]-rearrangements in ring-expansion reactions, for example copper bronze-promoted decomposition of diazomalonate 146 followed by reaction with cyclic sulfide 154 and subsequent [2,3]-rearrangement, gave ring-expanded product 155 in 53% yield (Scheme 38). However, subsequent attempts to explore the scope and utility of such ring-expansion processes have met with difficulties due to competing [1,2]-rearrangements and elimination reactions leading to mixtures of products.

Scheme 38. Ring-expansion of cyclic sulfide 154
Xu and co-workers demonstrated that sulfonium ylides derived from the rhodium-catalyzed reaction between ethyl 2-diazo-3,3,3-trifluoropropanoate 156 and a wide range of allylic sulfides undergo moderately diastereoselective [2,3]-rearrangements to form synthetically useful α-trifluoromethyl esters in high yields (Scheme 39a).\textsuperscript{72} The scope of this process was explored through the use of a wide range of functionalized allylic, propargyl, and allenyl sulfides, forming the corresponding products in high yields in all cases, although only modest levels of diastereoselectivity were obtained in most cases. The synthetic utility of the products was demonstrated through conversion into trifluoromethyl substituted conjugated dienes via oxidation of the sulfide with $m$-CPBA followed by thermal elimination of the resulting sulfoxide. This reaction sequence was successfully applied to a range of the rearranged sulfide products and was further utilized in the synthesis of trifluoromethyl epoxy-retinal derivative 162 (Scheme 39b). Subsequent attempts to render this process enantioselective by Müller and co-workers through use of a chiral rhodium catalyst were unsuccessful, with only low levels of enantioselectivity obtained for a range of catalysts.\textsuperscript{73}
In 2009, Davies and co-workers reported the first silver-catalyzed reaction between ethyl 2-diazo-2-phenylacetate and various allylic and propargylic sulfides. A wide range of rearranged products was obtained in good yields, although when a substituted cinnamyl phenyl sulfide was used only low levels of diastereoselectivity were observed.

In 1999, Aggarwal and Van Vranken independently investigated the use of trimethylsilyl diazomethane 163 as a sulfonium ylide precursor. Aggarwal and co-workers used Rh$_2$(OAc)$_4$ (1 mol%) to catalyze the reaction of trimethylsilyl diazomethane 163 with allylic sulfide 164 with [2,3]-rearrangement of the resulting sulfonium ylide forming syn-product 165 in 90% yield and 90:10 dr (Scheme 40). In this case an excess of 163 could be used and, unlike with alternative carbonyl-stabilized diazo compounds, slow addition was not
required. The scope of the process was examined using a small range of differentially substituted allylic sulfides, with the rearranged products formed in high yields with good levels of diastereoselectivity in each case. The use of a variety of chiral rhodium or copper catalysts in this process led to a decrease in diastereoselectivity and only low levels of enantioselectivity were obtained in all cases (up to 18% ee).

[Scheme 40. Use of trimethylsilyl diazomethane 163 as a sulfonium ylide precursor]

Van Vranken and co-workers also investigated the use of both Rh$_2$(OAc)$_4$ and CuOTf as catalysts for generation of sulfonium ylides through the decomposition of trimethylsilyl diazomethane 163. In 2000, dppeFeCl$_2$ (5 mol%) was reported to effectively catalyze the reaction between 163 and various allylic sulfides. For example, the reaction between 163 and cinnamyl phenyl sulfide 157 gave the rearranged product in 94% yield and 87:13 dr. This methodology has been applied to the synthesis of the meroterpene natural product (±)-3-hydroxybakuchiol 168 (Scheme 41). The iron-catalyzed reaction of 163 with allylic sulfide 166 was performed on a multi-gram scale to afford product 167 in 89% yield and 67:33, with subsequent manipulation of the α-silyl thioether functionality resulting in the first reported synthesis of 168. The use of various palladium catalysts has also been studied for the reaction between trimethylsilyl diazomethane 163 and allylic sulfides, however the yields and diastereoselectivity obtained are lower than those reported for the corresponding rhodium or iron-catalyzed processes.
A number of alternatives to highly reactive diazo compounds have been investigated as metal carbenoid precursors for the formation of allylic sulfonium ylides. For example, triazoles act as masked diazo compounds and react with allylic sulfides in the presence of a rhodium catalyst. The resulting sulfonium ylides undergo efficient [2,3]-rearrangement to form products in good yields, however the diastereoselectivity obtained with substituted allylic sulfides is low. In 2015, Wang and co-workers reported the use of highly strained cyclopropenes as rhodium carbenoid precursors that could be trapped with allylic sulfides, with [2,3]-rearrangement of the resulting sulfonium ylides leading to the isolated products. The reaction was demonstrated for a wide range of allyl sulfide substituents including S-aryl, heteroaryl, alkyl and allyl forming the rearranged products in excellent yields. Unfortunately, when substituted allylic sulfides such as were used, low levels of diastereoselectivity were obtained although the yields remained high (Scheme 42). A range of alternative substituted cyclopropenes was also explored as well as the use of propargylic sulfides, but only modest levels of $E:Z$ selectivity of the resulting allylic sulfides was obtained in either case. Furthermore, attempts to perform the reaction enantioselectively using a number of different chiral rhodium catalysts gave the rearranged products with only moderate levels of enantioselectivity (up to 53% ee).
Substituted alkynes have also been utilized as metal carbenoid precursors in catalytic [2,3]-rearrangements. Uemura and co-workers have developed the rhodium-catalyzed formation of sulfonium ylides and subsequent [2,3]-rearrangement starting from (2-furyl)-carbenoid precursors such as 171 and allylic sulfide 157 (Scheme 43). The resulting substituted furan 172 is obtained in excellent yield as a single diastereoisomer, although the scope of this process was only explored for two examples.

Davies and co-workers have reported the use of propargylic carboxylates as gold carbenoid precursors. Treating propargylic acetate 173 with AuCl (5 mol%) in the presence of allylic sulfide 152 led to the unexpected formation of (Z)-175 in 82% yield, with none of the expected [2,3]-rearrangement product 174 observed (Scheme 44). It is proposed that [2,3]-rearrangement product 174 undergoes a Cope rearrangement into 175, although an alternative mechanistic pathway involving an oxygen-assisted 1,4-shift followed by elimination of AuCl could not be ruled out. The process is general for a range of aryl substituted propargyl...
carbonates and aryl allylic sulfides, forming the (Z)-isomers of the rearranged products in high yields.

![Scheme 44](image)

**Scheme 44.** Gold-catalyzed rearrangement of propargylic carboxylates

Building upon the initial work of Davies and co-workers for a related intermolecular process (*vide infra*), Zhang and co-workers used a gold complex bearing sterically demanding ligand 177 to form [2,3]-rearrangement products such as 179 from the reaction of alkynes with allyl sulfides in the presence of stoichiometric oxidant 178 (Scheme 45a). The process works for a range of different substituted alkynes and allyl sulfides, forming the rearranged products in high yields albeit with moderate diastereoselectivity when substituted allylic sulfides were used. The proposed general mechanism for this process involves *in situ* oxidation of allylic sulfide 157 with 178 to form allylic sulfoxide 181, which can attack gold activated alkyne 180 (Scheme 45b). The resulting intermediate 182 can decompose into gold carbene 183, which can recombine with released allylic sulfide 157 to form sulfonium ylide 184 that readily undergoes [2,3]-rearrangement into the observed products.
At the same time, Davies and co-workers reported a similar process using substituted ynamides as gold carbene precursors. In this case pyridine N-oxide was utilized as the stoichiometric oxidant alongside gold complexed with ligand as the catalyst. The reaction proceeds under mild conditions to form the rearranged products in reasonable yields and importantly, unlike in many of the previously described cases, the reaction with substituted allylic sulfide was highly diastereoselective (Scheme 46).
Scheme 46. Diastereoselective [2,3]-rearrangement using ynamide 185 as a gold carbene precursor

2.3.2 Enantioselective intermolecular sulfonium ylide formation and [2,3]-rearrangement. The first attempted enantioselective [2,3]-rearrangement of a sulfonium ylide was reported in 1995 by Uemura and co-workers. The reaction between cinnamyl phenyl sulfide 157 and ethyl diazoacetate 20 was trialed using both CuBOX complexes and chiral rhodium catalysts, but in each case the rearranged product was formed with low levels of diastereo- and enantioselectivity. The effect of the sulfide substituent on the enantioselectivity of this process was subsequently investigated by McMillen and co-workers. The reaction between methyl diazoacetate 189 and various $S$-substituted allylic sulfides were studied using CuOTf (2 mol%) and BOX ligand 121 (2.1 mol%) as the catalytic system (Scheme 47a). Increasing the steric demand of the $S$-substituent increased the enantioselectivity of the process. For example, small sulfide substituents such as methyl gave no enantioselectivity whereas more sterically demanding 2,6-xylyl sulfide gave product 191 in 62% yield and 52% ee. The use of a (+)-menthy sulfide substituent as a chiral auxiliary in combination with the chiral catalyst only gave a marginal increase in the enantioselectivity of the process. Wang and co-workers have also investigated the influence of the allylic $S$-substituent alongside various aryl substituted diazoacetates using the same CuBOX complex as the catalyst (Scheme 47b). In this case the best enantioselectivities were obtained using 2-tolyl allyl sulfide 193, with the rearranged products formed in good yields and reasonable enantioselectivity for a range of $\alpha$-aryl diazoacetates 192. The highest enantioselectivity was
obtained using methyl 1-naphthyl diazoacetate, forming the corresponding product in 66% yield and 78% ee.

![Scheme 47](image)

The scope of the reaction has been further extended to the rearrangement of sulfonium ylides generated in situ from propargyl sulfides and α-aryl diazoacetates, with the products formed with levels of selectivity comparable with the allylic substrates. The rearrangement of allenyl sulfides with a range of chiral rhodium and copper catalysts has also been studied, with the products formed in generally good yields but with moderate levels of enantioselectivity. These reactions have also been performed using water as the solvent using chiral rhodium catalysts, although the enantioselectivities obtained were lower.

Rhodium and cobalt-based catalysts have also been utilized in the enantioselective [2,3]-rearrangement of sulfonium ylides. Hashimoto and co-workers used rhodium complexed with ligand 196 as a catalyst for the rearrangement of sulfonium ylides generated from the reaction of diazoacetates with allyl sulfides. Increasing the steric demand of the diazoester led to
higher levels of diastereo- and enantioselectivity, for example reaction of 195 with cinnamyl phenyl sulfide 157 gave product 197 in excellent 94:6 dr and 53% ee (Scheme 48a). Katsuki and co-workers used cobalt and salen ligand 198 to catalyze the reaction between t-butyl diazoacetate 26 and allylic sulfide 157, forming product 199 in 85:15 dr and 64% ee for the major anti-diastereoisomer (Scheme 48b).\textsuperscript{91} Comparable levels of diastereo- and enantioselectivity were obtained in the reaction with a small range of substituted allylic sulfides. The use of (−)-menthyl diazoacetate to act as a chiral auxiliary alongside the cobalt salen catalyst gave the rearranged products with increased diastereo- and enantioselectivity.

Scheme 48. a) rhodium and b) cobalt catalysts for the enantioselective rearrangement of sulfonium ylides

Wang and co-workers have reported the most enantioselective variant of this reaction to date using a series of diazo compounds bearing Oppolzer’s camphor sultam chiral auxiliary.\textsuperscript{92} The reaction between the diazo compounds and an allylic sulfide is efficiently catalyzed by copper bearing salen ligand 202, with the resulting chiral sulfonium ylides undergoing highly
stereoselective [2,3]-rearrangements. For example, reaction of diazo compound \textbf{200} with allylic sulfide \textbf{201} followed by reduction of rearranged product \textbf{203} with LiAlH\(_4\) to remove the chiral auxiliary gave alcohol \textbf{204} in 72\% yield and 92\% ee (Scheme 49a). The reaction was applicable to \(\alpha\)-alkyl, alkenyl and aryl substituted diazo compounds with the corresponding alcohol products formed in high yields with good levels of enantioselectivity. Attempts to improve the process through double-asymmetric induction using a chiral salen ligand in conjunction with the auxiliary did not offer any appreciable advantages in terms of either yield or enantioselectivity. Moreover, using either enantiomer of a chiral salen ligand in the reaction between \textbf{200} and \textbf{201} gave the same major enantiomer of alcohol \textbf{204} in 80\% ee in both cases, suggesting that the asymmetry of the process is induced solely by the chiral auxiliary and that a ligand-bound catalyst is not involved in the rearrangement step. The scope of this process was further extended to the reaction of a range of chiral sultam containing diazo compounds with propargyl sulfides, forming allenyl alcohols such as \textbf{206} in good yields with high levels of enantioselectivity (Scheme 49b).
Wee and co-workers investigated the ability of remote stereocenters within the allylic sulfide to influence the stereoselectivity in the rhodium-catalyzed reaction with diazoacetates. However, this approach proved to be challenging and only modest levels of enantioselectivity were achieved.\(^\text{93}\)

### 2.3.3 Diastereoselective intramolecular sulfonium ylide formation and [2,3]-rearrangement

Kido and co-workers have extensively studied the intramolecular reaction of allylic sulfides containing tethered stabilized diazo functionality for the diastereoselective synthesis of substituted cyclic systems. Early examples made use of allylic sulfides such as \(\textbf{207}\), which was synthesized by acylation of the corresponding alcohol with mono-ethyl...
malonate followed by diazotization.\textsuperscript{94} Treating allylic sulfide 207 with \( \text{Rh}_2(\text{OAc})_4 \) (1 mol\%) resulted in the intramolecular formation of eight-membered cyclic sulfonium ylide 208, which then undergoes [2,3]-rearrangement to form \( \gamma \)-butyrolactone 209 in 70\% yield as a single diastereoisomer (Scheme 50). The same methodology was also applied to the synthesis of related \( \delta \)-valerolactones, but the yields and diastereoselectivity were reduced.\textsuperscript{95,96} However, further investigation found that increasing the complexity and substitution of the substrates helped to improve the diastereoselectivity of \( \delta \)-lactone formation. For example, a series of structurally complex polycyclic bridged \( \delta \)-lactones such as steroid derivative 211 were synthesized in high yields as single diastereoisomers (Scheme 51).\textsuperscript{97} Altering the tether length in the system also allowed a small number of fused bicyclic seven-membered lactones to be synthesized with good levels of diastereoselectivity.\textsuperscript{98}

![Scheme 50. Intramolecular [2,3]-rearrangement to form \( \gamma \)-butyrolactones](image)

![Scheme 51. Synthesis of complex bicyclic \( \delta \)-lactones](image)
The intramolecular [2,3]-rearrangement of cyclic sulfonium ylides can also be used to synthesize substituted cyclohexanone rings with high levels of diastereoselectivity. The method has been demonstrated for the synthesis of functionalized cyclohexanones such as 215 that may be of use for the synthesis of sesquiterpene natural products. They key diazo-tethered allylic sulfide 213 was synthesized through a multi-step linear sequence starting from (R)-(+)limonene 212. Catalytic sulfonium ylide formation and [2,3]-rearrangement gave product 214 in 61% yield as a single diastereoisomer (Scheme 52). The phenyl sulfide substituent within 214 could be removed using zinc powder in acetic acid and subsequent decarboxylation gave substituted cyclohexanone 215 in 54% over the two steps. Incorporation of a ring system within the tethered diazoallyl sulfide allows synthetically useful cis-fused bicyclic systems such as 217 to be synthesized in high yields with excellent levels of diastereoselectivity (Scheme 52).

![Scheme 52](image)

Scheme 52. a) Synthesis of substituted cyclohexanone 215 staring from (R)-(+)limonene 212. b) Synthesis of cis-fused bicyclic ring systems
McMills and co-workers have studied the intramolecular [2,3]-rearrangements of sulfonium ylides to form substituted pyrrolizine cores.\textsuperscript{101} The reaction of (Z)-allylic sulfide 218 is sensitive to both catalyst and solvent, with the direct cyclopropanation of the allylic system to give 220 observed in many cases. However, treating (Z)-218 with catalytic rhodium caprolactamate in fluorobenzene resulted in the highly chemo- and diastereoselective formation of syn-pyrrolizine 219 in 60% yield (Scheme 53a). The reaction is stereospecific, with (E)-allylic sulfide 221 undergoing catalytic sulfonium ylide formation followed by rearrangement in benzene to give anti-pyrrolizine 222 in 71% yield as a single diastereoisomer (Scheme 53b).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme53.png}
\caption{Scheme 53. Stereoselective synthesis of substituted pyrrolizine cores. Cap = caprolactamate.}
\end{figure}

Kido and co-workers showed that by altering the position of the allylic sulfide a diastereoselective [2,3]-rearrangement to form spirocyclic products is possible.\textsuperscript{102} This method has been exemplified through the synthesis of the enantiomer of sesquiterpene natural product (–)-acorenone B (ent-227). Starting from commercially available (S)-(–)-perillaldehyde 224, key tethered diazoallylic sulfide 225 was synthesized over 15 steps. Catalytic cyclic sulfonium ylide formation using Rh$_2$(OAc)$_4$ (1 mol\%) and [2,3]-
rearrangement gave advanced intermediate 226 in 72% yield as a single diastereoisomer, with only four further steps required to convert 226 into (+)-acorenone B 227 (Scheme 54). \(^{102b}\)

![Scheme 54. Synthesis of spirocyclic sesquiterpene (+)-acorenone B 227](image)

Davies and co-workers have reported the use of tethered sulfoxides and alkynes as sulfonium ylide precursors in the presence of either gold or platinum catalysts.\(^1\) For example, allylic sulfoxide 228 undergoes an internal redox reaction in the presence of PtCl\(_2\) (10 mol%) to form a sulfonium ylide, with subsequent [2,3]-rearrangement forming product 229 in 60% yield and 83:17 dr (Scheme 55). The scope of the reaction was demonstrated for a range of substituted allylic sulfoxides, with the cyclic products generally formed in good yields under either gold or platinum catalysis. The diastereoselectivity of the reaction was better with terminal alkynes, with only moderate levels of diastereoselectivity obtained when substituted alkynes were used.

![Scheme 55. Tethered sulfoxides and alkynes as sulfonium ylide precursors. The relative configuration of the major diastereoisomer is unreported](image)
2.4 Halonium ylides

The reaction of metal carbenes with allyl halides and subsequent [2,3]-rearrangement of the resulting halonium ylides has been less widely studied and there are only a few reports of stereoselective variants of this reaction. An early diastereoselective example of such a process was reported in 1980 by Thomas and co-workers. Catalytic decomposition of diazopenicillanate 151 with Cu(acac)₂ (11 mol%) in the presence of excess allyl bromide 230 gave rearranged product 231 in 48% yield as a single diastereoisomer (Scheme 56), however product 231 was unstable and more readily characterized after dehalogenation using tributyl tin hydride.⁶⁵

![Scheme 56. Catalytic halonium ylide formation from diazopenicillanate 151](image)

Doyle and co-workers investigated the reaction of ethyl diazoacetate 20 with allyl halides using rhodium-based catalysts.⁵¹ The major reaction product obtained was dependent on the allyl halide used. For example both allyl chloride and allyl bromide predominantly gave cyclopropanation in the reaction with Rh₂(OAc)₄, whereas allyl iodide led to halonium ylide formation and [2,3]-rearrangement into 233 (Scheme 57). The reaction of ethyl diazoacetate 20 with crotyl bromide using either copper or rhodium catalysis led to a mixture of products from [2,3]-rearrangement, [1,2]-rearrangement, and cyclopropanation and in all cases essentially no diastereoselectivity was observed for the [2,3]-rearrangement product.
The reaction of ethyl diazoacetate 20 with substituted allyl bromide and chlorides has subsequently been investigated using catalytic silver (I) complexes\textsuperscript{103} and ruthenium porphyrin\textsuperscript{104} complexes. In these cases the desired [2,3]-rearranged products were obtained in high yields, but unfortunately the products were formed as a 50:50 mixture of diastereoisomers in all cases.

In 1998, Doyle and co-workers reported the first enantioselective halonium ylide rearrangement.\textsuperscript{8} The reaction of ethyl diazoacetate 20 with allyl iodide 235 catalyzed by a variety of chiral dirhodium carboxamides gave [2,3]-rearrangement product 236 in low yields and poor enantioselectivity, with products of carbene dimerization also observed in many cases. However, use of catalytic copper complexed with BOX ligand 121 led to selective [2,3]-rearrangement, forming product 236 in 62% yield and a promising 69% ee (Scheme 58).
The use of dirhodium complexes with fluorinated chiral carboxamide ligands has also been investigated in this process. In this case, competing cyclopropanation was observed and the [2,3]-rearrangement product 236 was only obtained in modest yields with low levels of enantioselectivity.

3. [2,3]-REARRANGEMENTS OF AMMONIUM YLIDES FROM ALLYLIC QUATERNARY AMMONIUM SALTS

In 2011, Tambar and co-workers reported an alternative strategy to avoid the use of diazo compounds in catalytic [2,3]-rearrangements of allylic ammonium ylides. The methodology makes use of the palladium-catalyzed allylic substitution of allylic carbonates 237 with tertiary amino esters 239 (Scheme 59a). The resulting quaternary ammonium salt 240 undergoes rapid deprotonation into ammonium ylides 241 and subsequent [2,3]-rearrangement to generate α-amino ester products 242. Optimization of the catalyst system revealed that Pd$_2$dba$_3$·CHCl$_3$ in combination with electron-deficient P(2-furyl)$_3$ ligand gave the desired products in high yields with good levels of diastereoselectivity (Scheme 59b). The reaction was applicable to a range of aryl, heteroaryl and alkyl substituted allylic carbonates 244 alongside various substituted α-amino esters or α-amino ketones to form the corresponding anti-[2,3]-rearrangement products 245 in uniformly good yield and high diastereoselectivity in most cases. The observed anti-diastereoselectivity is proposed to be due to an exo-transition state during the [2,3]-rearrangement step. α-Amino sulfonimide 246 bearing Oppolzer’s camphor sultam auxiliary could also be utilized in this process, forming enantiomerically enriched α-amino acid derivatives such as 248 in excellent yield and high dr (Scheme 59c).
Scheme 59. Palladium-catalyzed allylic amination to form [2,3]-rearrangement precursors

This methodology was subsequently applied to the formal total synthesis of the marine alkaloid (±)-amathaspiramide F (253). Reacting proline derivative 249 under the previously optimized conditions with the allylic carbonate bearing the functionalized aryl ring found within amathaspiramide F (253) unexpectedly led to the preferential formation of undesired diastereoisomer 252 in 75% yield (Scheme 60). Further investigation on a simplified system revealed that the presence of an o-ortho-substituent within the aryl allylic carbonate led to a significant reduction in previously observed anti-diastereoselectivity. In light of this, the synthetic route was modified and the key ammonium salt formation-[2,3]-rearrangement step was performed using MOM-protected aryl carbonate, resulting in
preferential formation of the desired diastereoisomer 251 in 70% yield. Further manipulation of 251 gave an advanced intermediate in the formal total synthesis of (±)-amathaspiramide F (253). Although proline ester 249 was enantiomerically pure, the resulting [2,3]-rearrangement products 251 and 252 were racemic showing that the stereochemical information within 249 is lost during the allylic amination.

Scheme 60. Switch in diastereoselectivity observed en route to the formal synthesis of (±)-amathaspiramide F (253)

Tambar and co-workers reported the diastereoselective synthesis of cyclic α-amino acid derivatives through a tandem allylic amination-[2,3]-rearrangement followed by ring-closing metathesis. For example, reacting homoallyl amino ester 254 with allylic carbonate 255 under the previously optimized conditions followed by ring-closing metathesis of the intermediate [2,3]-rearrangement product using Hoveyda-Grubbs II gave cyclic α-amino acid 256 in 85% yield and 89:11 dr (Scheme 61). The methodology was applied to a range of aryl and alkyl substituted allylic carbonates, forming the cyclic products in generally good yields and high diastereoselectivity over the two steps. An enantiomerically pure cyclic α-amino acid was also accessible using a homoallyl α-amino acid derivative bearing Oppolzer’s camphorsultam auxiliary as the starting material.
In 2014, Smith and co-workers reported the first organocatalytic stereoselective [2,3]-rearrangement of allylic ammonium salts 259, which were either isolated or made in situ from p-nitrophenyl bromoacetate 257 and an allylic amine 258. Reacting allylic ammonium salts 259 with the isothiourea catalyst (R)-BTM 260 (20 mol%) and HOBt (20 mol%) as a co-catalyst in the presence of a mild base promoted a stereoselective [2,3]-rearrangement, with a nucleophilic quench giving syn-α-amino acid derivatives 261 in high yield and excellent stereocontrol (Scheme 62a). The reaction scope was demonstrated for a range of amine substituents and vinylic aryl groups alongside a number of different amine and alcohol nucleophiles for the quench, giving access to functionalized α-amino acid derivatives with excellent diastereo- and enantioselectivity. The proposed mechanism involves N-acylation of (R)-BTM 260 with allylic ammonium salt 259 to form dicationic species 262, with deprotonation forming ammonium ylide 263 (Scheme 62b). Stereoselective [2,3]-rearrangement of 263 generates acyl ammonium 264, which can be intercepted by either the HOBt 265 co-catalyst to form 266 or directly by p-nitrophenoxide to form ester 267. Nucleophilic quench of 267 displaces p-nitrophenol to give readily isolable α-amino acid derivatives 261. The high levels of stereocontrol observed can be rationalized by endo-type pre-transition state assembly TS-263 (Scheme 62c). Stabilizing interactions between the lone pair of the oxygen atom n_o and the σ^*_{CS} help to lock the conformation of N-acyl ammonium 263, while the stereodirecting phenyl substituent adopts a pseudoaxial position to minimize 1,2-steric interactions. Rearrangement occurs preferentially opposite to the stereodirecting...
group, with a favorable π-cation interaction been the allylic C(3)-aryl substituent and the acyl ammonium thought to be a requirement for high stereocontrol.

Scheme 62. Organocatalytic stereoselective [2,3]-rearrangement of allylic ammonium salts
4. [2,3]-REARRANGEMENT OF O-PROPARYLIC OXIMES

Nakamura and co-workers have extensively studied the transition metal-catalyzed [2,3]-rearrangement of O-propargylic oximes 268 (Scheme 63). The resulting N-allenyl nitrones 269 undergo a variety of further transformations into different products depending on the specific substrate utilized and the reaction conditions. N-Allenyl nitrones had received little attention previously due to their inherent instability, therefore in situ generation through [2,3]-rearrangement provides an effective method of investigating the reactivity of these intermediates in a variety of cascade processes. Although the N-allenyl nitrone intermediates are formal [2,3]-rearrangement products, it is possible that in many cases their formation proceeds through alternative metal-mediated pathways and therefore the reactions may not be true pericyclic processes.

![Scheme 63. [2,3]-Rearrangement of O-propargyl oximes](image)

4.1 Synthesis of pyridine N-oxides and four-membered cyclic nitrones

Nakamura and co-workers first reported the copper-catalyzed [2,3]-rearrangement of (E)-O-propargylic α,β-unsaturated aldoximes such as 270 for the synthesis of pyridine N-oxides (Scheme 64a).\(^{110}\) The initially formed [2,3]-rearrangement product 271 undergoes a 6π-electrocyclization followed by tautomerization to form pyridine N-oxide 272 in 70% yield. However, the reaction of (Z)-273 gave cyclic nitrone 275 in 84% yield and excellent E:Z selectivity, with intermediate 274 undergoing preferential 4π-electrocyclization followed by isomerization via an allyl cation into the observed product (Scheme 64b). Nitrone 275 could
also be thermally isomerized into a 2,3,6-trisubstituted pyridine N-oxide by heating in DMF at 180 °C.\textsuperscript{111}

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (a) at (0,0) {a) \hfill \includegraphics[width=0.5\textwidth]{scheme64.png} \hfill b)

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (E-270) at (-3,0) {\( (E)-270 \)};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (Z-273) at (3,0) {\( (Z)-273 \)};

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (CuBrPPPh3) at (0,-1) {CuBr(PPPh\textsubscript{3})(10 mol\%)};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (PPh3) at (0,-2) {PPPh\textsubscript{3}(10 mol\%)};

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (DMSO) at (0,-3) {DMSO, 120 °C, 2 h};

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (271) at (2,-1) {271};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (272) at (2,-2) {272};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (70\%) at (2,-3) {70\%};

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (CuBrPPPh3) at (3,-1) {CuBr(PPPh\textsubscript{3})(10 mol\%)};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (MeCN) at (3,-2) {MeCN, 100 °C, 7 h};

  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (274) at (5,-1) {274};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (275) at (5,-2) {275};
  \node[draw,shape=circle,minimum size=1cm,fill=red!20] (84\% \> >95:5 E:Z) at (5,-3) {84\% \> >95:5 E:Z};

  \draw[->] (E-270) -- (CuBrPPPh3);
  \draw[->] (CuBrPPPh3) -- (DMSO);
  \draw[->] (DMSO) -- (271);
  \draw[->] (271) -- (272);
  \draw[->] (272) -- (70\%);

  \draw[->] (Z-273) -- (CuBrPPPh3);
  \draw[->] (CuBrPPPh3) -- (MeCN);
  \draw[->] (MeCN) -- (274);
  \draw[->] (274) -- (275);
  \draw[->] (275) -- (84\% \> >95:5 E:Z);
\end{tikzpicture}
\end{center}

\textbf{Scheme 64.} Differential reactivity of \( (E)-270 \) and \( (Z)-273 \)

The stereoselective formation of cyclic nitrones was subsequently studied in more detail using aryl aldoximes.\textsuperscript{112} Reacting oxime 276 with [CuCl(cod)]\textsubscript{2} (5 mol\%) in MeCN at 70 °C led to the regioselective formation of nitrone 277 in 86% yield as a 73:27 \textit{E}:\textit{Z} mixture (Scheme 65). In this case the \textit{E}:\textit{Z} geometry of the aldoxime was not important, with both reacting to give nitrone 277 with similar levels of selectivity. The reaction was applicable to a range of propargylic aryl and alkyl substituents, forming the corresponding nitrones in high yields and with reasonable \textit{E}:\textit{Z} selectivity obtained in most cases. Mechanistically, the copper is thought to activate the alkyne towards [2,3]-rearrangement, with the resulting \textit{N}-allenyl nitrone undergoing a 4\(\pi\)-electrocyclization into the observed product. At high temperature, the minor \textit{(Z)}-isomer of 277 can undergo thermal isomerization into both \( (E)-277 \) and regioisomer 278 whereas \( (E)-277 \) is stable at high temperature.
Subsequently it was reported that the outcome of the reaction using alkyl propargylic substituents is highly dependent on the electronic nature of the aryl oxime substituent (Scheme 66). For example, reacting (E)-oxime 279 bearing an electron-deficient 3,5-Br<sub>2</sub>C<sub>6</sub>H<sub>3</sub> substituent with CuCl (10 mol%) led to exclusive formation of cyclic nitrone 280. However, 4-ClC<sub>6</sub>H<sub>3</sub> substituted oxime 279 gave a 60:30 mixture of nitrone 280 and amididiene 281 and introduction of a strongly electron-donating 4-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub> group led to selective formation of the corresponding amididiene 281 in 87% yield. This process was general for electron-rich aryl oxime substituents and could tolerate various propargylic alkyl groups, forming amididiene products with high levels of selectivity in good yield. It is postulated that the presence of an electron-rich aryl oxime substituent alters the mechanism of the reaction after the copper-catalyzed rearrangement of the O-propargylic oxime. In this case, the N-allenyl nitrone intermediate is thought to undergo selective oxaziridine formation instead of 4π-electrocyclization. A 1,2-hydrogen shift followed by copper-catalyzed isomerization of the allene leads to the observed amididiene products.

Scheme 65. Copper-catalyzed rearrangement of O-propargylic aryl aldoximes
4.2 Synthesis of seven- and eight-membered rings

Nakamura and co-workers further explored the utility of $O$-propargylic oximes in tandem rhodium-catalyzed [2,3]-rearrangement-heterocyclization processes to form azepine and azocine $N$-oxide derivatives. For example, treating ($Z$)-$O$-propargylic cyclopropylcarbaldoxime 282 with $[\text{RhCl(cod)}]_2$ (2.5 mol%) and sodium diphenylphosphinobenzene-3-sulfonate (tppms, 18 mol%) gave ($Z$)-azepine $N$-oxide 283 in 92% yield (Scheme 67a). Water soluble tppms was used as the ligand to avoid difficulties encountered in separating 283 from triphenylphosphine oxide. The reaction works well for a range of aryl substituents, but the presence of alkyl substituents on either the propargylic carbon or the alkyne led to longer reaction times and lower yields. The rhodium-catalyzed rearrangement of the corresponding ($E$)-$O$-propargylic cyclopropylcarbaldoximes exclusively gave the ($Z$)-azepine $N$-oxide products. However, the reactions using ($E$)-oximes were much more sensitive to the amount of ligand used and generally gave lower yields than the reaction using the corresponding ($Z$)-oxime.

This methodology was extended to the synthesis of azocine $N$-oxides using ($E$)-$O$-propargylic cyclobutylcarbaldoxime as substrates. For example, the rhodium-catalyzed reaction of ($E$)-284 gave ($Z$)-azocine $N$-oxide 285 in 93% yield with complete control of the alkene geometry.
A number of aryl substituents was tolerated in this process, but propargylic alkyl substituents gave the products in lower yields and the use of a terminal alkyne gave a complex mixture. The tandem [2,3]-rearrangement-metallacyclization of enantiomerically pure (E)-oxime 286 gave (Z)-azocine N-oxide 287 in 87% yield and 74% ee, showing reasonably high levels of chirality transfer through the axially chiral N-allyl nitrene intermediate (Scheme 67c).

Scheme 67. [2,3]-Rearrangement of a) O-propargylic cyclopropyl- and b) cyclobutylcarbaldoximes. c) Chirality transfer in the [2,3]-rearrangement of cyclobutylcarbaldoximes. The absolute configuration of the major enantiomer of 287 was unreported. tppms = sodium diphenylphosphinobenzene-3-sulfonate

A simplified mechanistic proposal for the tandem [2,3]-rearrangement-heterocyclization reaction is shown in Scheme 68. Coordination of the rhodium catalyst to (Z)-O-propargylic oxime 282 promotes rearrangement into η^4-coordinated N-allyl nitrene 289.
While this step represents a formal [2,3]-rearrangement, it may proceed stepwise via a cyclic vinyl rhodium species. Metallacyclization of 289 gives aza-rhodacycle 290, which undergoes ring-expansion through cleavage of the least hindered cyclopropane bond to form eight-membered aza-rhodacyclic 291, with subsequent reductive elimination of the rhodium giving product 283.

Scheme 68. Proposed mechanism for the tandem [2,3]-rearrangement and heterocyclization of 282

Alternative cascade processes using the N-allenyl nitrone intermediates generated from [2,3]-rearrangement of O-propargylicaldoximes as 1,3-dipolar reagents have also been investigated.116 Treating (Z)-O-propargylicaldoxime 292 and N-phenylmaleimide 293 with [CuCl(cod)]₂ (5 mol%) promotes a cascade sequence involving [2,3]-rearrangement, [3+2] cycloaddition, and [1,3]-oxygen migration to form oxazepine derivative 294 in 71% yield as a single diastereoisomer (Scheme 69). The [3+2]-cycloaddition between the intermediate nitrone and N-phenylmaleimide 293 is thought to be highly exo-selective, accounting for the high levels of diastereoselectivity. The reaction scope was demonstrated for various aryl and alkyl substituted O-propargylic formaldoximes, giving the oxazepine products in good yields.
Alternative dipolarophiles including various N-substituted maleimides and fumaric acid esters were also tolerated.

\[
\text{PhO} \quad \text{N} \quad \text{Ph} \\
\text{F}_3\text{C} \quad (Z)292
\]

\[
+ \quad \text{293 (5 eq)} \quad \text{[CuCl(cod)]}_2 (5 \text{ mol%}) \quad \text{MeCN, 50 °C} \\
\text{PhN} \quad \text{O} \quad \text{H} \\
\text{F}_3\text{C} \quad (Z)292 (5 \text{ eq}) + \text{PhN} \quad \text{O} \quad \text{H} \\
\text{294} \quad 71\% \\
>95:5 \text{ dr}
\]

Scheme 69. Copper-catalyzed cascade to form substituted oxazepines

5. [2,3]-REARRANGEMENT OF ALLYLIC SULFOXIDES, SELENOXIDES, SULFIMIDES, AND N-OXIDES

5.1 Catalytic [2,3]-Rearrangement of Allylic Sulfoxides and Selenoxides

The [2,3]-rearrangement of allylic sulfoxides (Mislow-Evans rearrangement) into allylic alcohols has found a number of uses in organic synthesis. The reaction is stereospecific as any stereochemistry on sulfur can be transferred onto carbon during the rearrangement.\(^3\) Given the potential synthetic utility of this reaction, it is perhaps surprising that relatively few stereoselective catalytic procedures have been developed.

Hilvert and co-workers reported one of the first stereoselective catalytic [2,3]-rearrangements of a single allylic sulfoxide using catalytic antibodies. Although significant rate-enhancement over the background rearrangement was observed, the resulting allylic alcohol was only obtained in modest enantioselectivity (40% ee).\(^{117}\)

Hagiwara and co-workers reported a tandem Knovenagel condensation-[2,3]-rearrangement reaction catalyzed by silica-supported nitrogen base 297 (50 mol%).\(^{118}\) The catalytic Knovenagel reaction between a range of substituted aldehydes and aryl sulfinylacetonitrile
296 gave intermediate 298, which underwent isomerization into an allylic sulfoxide followed by [2,3]-rearrangement under the reaction conditions. Addition of diethylamine promoted hydrolysis of the resulting sulfinate ester into allylic alcohol 299 (Scheme 70). A range of substituted aldehydes could be used, selectively forming the (E)-allylic alcohol products in reasonable yields with excellent E:Z selectivity. When (R)-(+)citronellal was used the resulting allylic alcohol was formed in 50:50 dr, with the stereocenter within the aldehyde having no influence on the diastereoselectivity of the [2,3]-rearrangement.

Scheme 70. Tandem Knoevenagel condensation-[2,3]-rearrangement promoted by silica supported base 297

Miura and co-workers have reported a stereoselective organocatalytic [2,3]-rearrangement of α-sulfinyl enones.119 Treating enantiomerically pure enone 300 with catalytic DBU (10 mol%) in the presence of an excess of triphenyl phosphine promotes isomerization into an allylic sulfoxide, which spontaneously undergoes a stereoselective [2,3]-rearrangement. Quenching the reaction with aqueous hydrogen peroxide to hydrolyze the initially formed sulfinyl ester was optimal, forming allylic alcohol 301 in 77% yield and 99% ee (Scheme 71). The reaction was applicable to a range of alkyl and aryl substituted enones, with the allylic alcohol products formed in good yield. In the majority of cases the configuration of the enantiomerically enriched α-sulfinyl enone was efficiently transferred into the corresponding allylic alcohol.
Diastereoselective allylic oxidation reactions using selenium dioxide (Riley oxidation) have also been utilized in organic synthesis, for example in one of the final steps in Corey’s first total synthesis of Miroestrol. The oxidation can be rendered catalytic in SeO₂ by using an excess of a suitable oxidant, such as hydrogen peroxide. The reaction is thought to proceed through an ene reaction between the allylic system and SeO₂, followed by [2,3]-rearrangement of the intermediate seleninic acid 303 (Scheme 72).

Paquette and Lobben used a catalytic diastereoselective Riley oxidation in the synthesis of cyclohexanone 308, which was used as a substrate for investigating the facial selectivity of indium promoted allylations of various 2-hydroxycyclohexanone (Scheme 73). Treating exo-methylene cyclohexane 306 with catalytic SeO₂ (5 mol%) and an equivalent of t-butyl hydroperoxide gave allylic alcohol 307 in 75% yield as a single diastereoisomer.
Carter and co-workers reported the first catalytic oxidation of prochiral allylic selenides and tandem [2,3]-rearrangement.\textsuperscript{122} Vanadyl acetylacetonate (10 mol\%) in the presence of cumene hydroperoxide 310 promoted the tandem oxidation and [2,3]-rearrangement of a small range of allylic selenides. Addition of tributyl phosphine efficiently cleaved the initially formed selenate to give a range of allylic alcohols in good yield. However, initial attempts to perform the reaction stereoselectivity by introducing a remote stereocenter were unsuccessful, with allylic selenide 309 reacting to give allylic alcohol 311 as a mixture of diastereoisomers (Scheme 74a). Further attempts to induce stereochemical control over this tandem process using chiral ligands for the vanadium were also unsuccessful.\textsuperscript{123} However, introduction of an oxazole-based auxiliary onto allylic selenide 312 resulted in a more diastereoselective rearrangement, with allylic alcohol 313 obtained in good enantioselectivity after cleavage of the selenate (Scheme 74b).

\textbf{Scheme 73.} Catalytic diastereoselective Riley oxidation

\begin{align*}
\text{Catalyst: VO(acac)\textsubscript{2}} & \quad \text{BP3} \\
\text{Conditions: } & 4\text{Å MS, CH\textsubscript{2}Cl\textsubscript{2}, } -10{}^\circ\text{C} \\
\text{Product: } & \text{Diastereoisomers} \quad \text{52:48 dr}
\end{align*}

\textbf{Scheme 74.} Vanadium-catalyzed tandem oxidation and [2,3]-rearrangement

\begin{align*}
\text{Catalyst: VO(acac)\textsubscript{2}} & \quad \text{t-BuOOH} \\
\text{Conditions: } & 4\text{Å MS, CH\textsubscript{2}Cl\textsubscript{2}, } -50{}^\circ\text{C} \\
\text{Product: } & \text{Enantiomer} \quad \text{70\% ee}
\end{align*}
5.2 Catalytic [2,3]-Rearrangement of Allylic Sulfimides

Sharpless first reported that sulfur diimide species react with alkenes in a similar way to selenium dioxide, undergoing an ene reaction into an intermediate sulfimide (the nitrogen analogue of a sulfoxide) followed by [2,3]-rearrangement into an allylic amine. For many years this process was thought to be incompatible with enantioselective catalysis due to the facile nature of the thermal [2,3]-rearrangement of sulfimides without a catalyst.

However, in 1996 Uemura and co-workers reported the first enantioselective copper-catalyzed sulfimidation using N-tosyliminobenzyliodinane as a nitrene source. Applying these conditions to allylic sulfides resulted in sulfimidation followed by [2,3]-rearrangement to afford sulfonamides, with no competing aziridination observed. For example, treating allylic sulfide with in the presence of CuOTf (5 mol%) and BOX ligand (6 mol%) gave sulfonamide in 80% yield and 58% ee (Scheme 75). This methodology was applied to a small range of substituted allylic sulfides, with the corresponding sulfonamides formed in only moderate yields and low enantioselectivity. The same conditions were also applied to the catalytic [2,3]-rearrangement of allylic selenides, but lower levels of enantioselectivity were obtained.

![Scheme 75. Enantioselective sulfimidation followed by [2,3]-rearrangement. Configuration of the major enantiomer is unreported](image)

Bolm and co-workers subsequently reported an iron(III) PyBOX catalyst system for highly enantioselective sulfimidation reactions. A single example of enantioselective
sulfimidation and subsequent [2,3]-rearrangement was reported using allylic sulfide 318 (82:18 E:Z) and nitrene precursor 314, forming sulfonamide 320 in 73% yield and 80% ee (Scheme 76).

Katsuki and co-workers reported the ruthenium-catalyzed tandem sulfimidation and [2,3]-rearrangement of allylic sulfides with tosyl azide 321. The initially formed sulfonamides were conveniently hydrolyzed into N-Ts allyl amines using potassium hydroxide. For example, reacting allylic sulfide 318 with tosyl azide 321 in the presence of ruthenium salen complex 322 (2 mol%) gave sulfonamide 323, which was immediately hydrolyzed to give 324 in an overall 82% yield and 78% ee (Scheme 77). The reaction was applicable to a range of substituted S-aryl allylic sulfides to give the corresponding N-tosyl allylic amines in good yield with comparable enantioselectivity obtained in each case.
Tambar and co-workers have developed a two-step method for the conversion of unactivated terminal alkenes into sulfonamides though a sequential hetero-ene reaction and enantioselective palladium-catalyzed formal [2,3]-rearrangement protocol. Reactions of terminal alkenes 326 with benzenesulfonyl sulfurdiiimide 325 forms stable sulfimides 327 through a hetero-ene reaction. Sulfimides such as 327 could be purified by filtration and did not undergo un-catalyzed background [2,3]-rearrangement at low temperatures. Treating sulfimide 327 with Pd(TFA)2 (10 mol%) and BOX ligand 316 (12 mol%) promoted a highly enantioselective [2,3]-rearrangement to form allylic sulfonamides 328 (Scheme 78a). This reaction sequence was applicable to substrates possessing an impressive range of aliphatic substituents at the homoallylic position, including those containing benzyl ether, phthalimide, nitrile, aldehyde, or alkyl chloride functional groups. In all cases the corresponding sulfonamide products were obtained in high yields with excellent enantioselectivity. Interestingly, this catalytic system was not suitable for substrates containing aryl substituents in the homoallylic position, giving sulfonamide products 331 with essentially no enantioselectivity. However, using alternative BOX ligand 330 and 1,2-DCE as the reaction solvent a range of aryl substituents was tolerated, including those bearing both electron-withdrawing and electron-donating substituents, forming sulfonamides 331 in high
yields with excellent enantioselectivity (Scheme 78b). The synthetic utility of these methodologies was exemplified through the synthesis of the antiepileptic drug vigabatrin 332 and the enantiomer of peptidase inhibitor sitagliptin ent-333, approved for the treatment of Type II diabetes (Scheme 78c). Mechanistically, the palladium-BOX complex is proposed to bind to π-system of intermediate sulfimide 327 to promote aminopalladation, with subsequent fragmentation of the five-membered cyclic intermediate giving the formal [2,3]-rearranged sulfonamide 328.

Scheme 78. Tandem homo-en e reaction and palladium-catalyzed [2,3]-rearrangement of terminal alkenes bearing a) aliphatic homoallylic substituents and b) aryl homoallylic substituents. c) Pharmaceutically active compounds synthesized using this methodology.

5.3 Catalytic [2,3]-Rearrangement of Allylic N-Oxides

The [2,3]-rearrangement of allylic N-oxides into hydroxylamine derivatives was first reported by Meisenheimer in 1919 and the reaction often bears his name. Although there has been
some limited success in developing stoichiometric stereoselective versions of the Meisenheimer rearrangement, a catalytic version remained elusive for many years. In 2011, Tambar and co-workers reported the first such catalytic enantioselective [2,3]-rearrangement of amine N-oxides. Allylic amines 334 were first oxidized into isolable allylic N-oxides 335 using m-CPBA. Treating allylic N-oxides 335 with Pd(OAc)$_2$ (10 mol%) and phosphoramidite ligand 336 (24 mol%) promoted the highly enantioselective [2,3]-rearrangement into allylic hydroxylamines 337 (Scheme 79). The addition of catalytic amounts of MeOH and m-CPBA gave a slight increase in the enantioselectivity, although the exact role of these additives is currently unknown. The reaction was applicable to a variety of aliphatic allylic N-oxides 335 including those bearing pendent alcohol, ether, aldehyde, and phosphate ester functional groups, forming hydroxylamines 337 in good yields and excellent enantioselectivity. The palladium(II) phosphoramidite catalyst is proposed to activate the allylic N-oxide to enantioselective oxypalladation, with fragmentation of the resulting heterocyclic intermediate giving the formal [2,3]-rearranged products. This presence of a heterocyclic intermediate is supported by the fact that C2 substituted substrates do not undergo rearrangement, while crossover experiments suggest that an allylpalladium intermediate is unlikely.

Scheme 79. Palladium catalyzed [2,3]-rearrangement of allylic N-oxides to form hydroxylamines 337
6. CATALYTIC [2,3]-WITTIG REARRANGEMENTS

The base-promoted anionic [2,3]-Wittig rearrangement of allylic ethers into homoallylic alcohols has been widely used in organic synthesis.\(^1\) These reactions can be highly stereoselective depending upon the nature of any substituents, with the transition-state models calculated by Houk and Marshall often used to rationalize any diastereoselectivity observed.\(^4\) However, catalytic asymmetric [2,3]-Wittig rearrangements remain an underdeveloped area, probably due to the typical requirement for a strong base to promote anionic [2,3]-rearrangements.

6.1 Base-Catalyzed [2,3]-Wittig Rearrangements

One strategy for rendering base-mediated [2,3]-Wittig rearrangements asymmetric is the use of stoichiometric amounts of chiral ligands. Kimachi and co-workers first reported the use of a catalytic amount of chiral ligand for the [2,3]-rearrangement of allylic ether 338 (Scheme 80a).\(^{133}\) Treating 338 with an excess of \(n\)-BuLi and catalytic \((−)\)-sparteine 339 (20 mol\%) at low temperature gave homoallylic alcohol 340 in 44% yield and 48% ee, compared with 83% yield and 60% ee when an excess of \((−)\)-sparteine 339 (2.2 eq) was used. Building upon earlier reports of chiral BOX ligands in [2,3]-rearrangements,\(^{134}\) Maezaki and co-workers reported catalytic [2,3]-Wittig rearrangement of allylic ether using ligand 121 (50 mol\%) and a large excess of \(t\)-BuLi to form homoallylic alcohol 342 in 52% yield as a single diastereoisomer in excellent 98% ee (Scheme 80b). Lower amounts of ligand (10 mol\%) could be used, but although the high stereoselectivity was retained a decrease in yield (23%, >95:5 dr, 98% ee) was observed.\(^{135}\)
Scheme 80. Asymmetric base-mediated [2,3]-Wittig rearrangements using catalytic chiral ligands

Terada and Kondoh reported the first [2,3]-Wittig rearrangement that was catalytic in Brønsted base by utilizing a tandem phospha-Brook rearrangement.\textsuperscript{136} Treating allyloxyphosphonate 343 with catalytic KO\textsubscript{t}-Bu (10 mol%) resulted in deprotonation followed by [2,3]-rearrangement into alkoxide 344 (Scheme 81). Subsequent phospha-Brook rearrangement of 344 followed by protonation to regenerate the catalyst gave product 345 in 85% yield and 68:32 dr. The reaction was applicable to a range of substituted allyloxyphosphonates forming the products in generally high yield but modest diastereoselectivity. Cyclic allyloxyphosphonates underwent the tandem reaction sequence to form ring-contracted lactone products with slightly higher levels of diastereoselectivity.
Gaunt and co-workers reported a conceptually new method of performing stereoselective [2,3]-Wittig rearrangements using organocatalysts under mild conditions without the use of a strong base. Using pyrrolidine 347 as a catalyst, α-allyloxy ketone 346 reacts to form an enamine that can undergo highly diastereoselective [2,3]-rearrangement into homoallylic alcohol 348 in good yield (Scheme 82a). The syn-diastereoselectivity could be further improved to 91:9 dr by lowering the reaction temperature to –25 °C, although a significantly longer reaction time was needed to achieve complete conversion. The use of methanol as solvent was essential for obtaining diastereoselectivity, suggesting that the protic solvent is involved in hydrogen-bonding to the substrate during the rearrangement. The reaction of an enantiomerically enriched allylic ether resulted in complete chirality transfer into the product, suggesting a concerted mechanism is in operation. The reaction was applicable to a range of aliphatic ketones as well as allylic ethers bearing alkyl, aryl, alkynyl, and alkenyl functional groups, forming the homoallylic alcohol products in high yields with mostly good diastereoselectivity. In a single example, chiral proline derivative 350 was investigated as an enantioselective catalyst for this process, promoting the rearrangement of α-allyloxy ketone 349 into alcohol 351 in 75% yield with moderate diastereoselectivity but promising 60% ee (Scheme 82b).

Scheme 81. Catalytic tandem [2,3]-Wittig rearrangement and phospha-Brook rearrangement. Configuration of the major diastereoisomer is unreported.
6.2 Non-Base-Catalyzed [2,3]-Wittig Rearrangements

While [2,3]-Wittig rearrangements are traditionally performed using strong inorganic bases, a few examples of non-base catalyzed [2,3]-rearrangements of allyloxy ethers have been reported. In 1986, Nakai and co-workers found that silyl ketene acetals such as 352 undergo highly diastereoselective [2,3]-rearrangements in the presence of catalytic trimethylsilyl triflate (20 mol%) at low temperature.\textsuperscript{138} It is proposed that trimethylsilyl triflate reacts with the ether oxygen of 352 to form a silyloxonium salt, with subsequent reaction of the triflate anion with the silyl ketene acetal forming silyloxonium ylide 353 and regenerating the catalyst. Ylide 353 can then undergo a diastereoselective [2,3]-rearrangement via an endo-transition state to form α-hydroxy ester 354 in high yield and >95:5 dr (Scheme 83).
More recently, Porco and co-workers synthesized a range of enantiomerically enriched 3,4-chromanedione derivatives through the scandium-catalyzed rearrangement of 3-allyloxyflavones. For example, treating 355 with Sc(OTf)$_3$ (30 mol%) and PyBOX ligand 319 (30 mol%) gave rearranged 3,4-chromanedione 357, which was immediately reacted with 1,2-ethylenediamine to allow dihydropyrazine 358 to be isolated in 98% yield and 94% ee (Scheme 84). Various 2-aryl and benzenoid substituents were tolerated and a few different diamines were utilized to form substituted dihydropyrazines in excellent yield and enantioselectivity. Preliminary mechanistic studies using both fluorescence and $^{13}$C NMR spectroscopy favor an enantioselective scandium-catalyzed [2,3]-rearrangement into benzopyrylium 356 followed by a stereospecific [1,2]-allyl shift into 357 over a direct [3,3]-sigmatropic rearrangement of the allyl vinyl ether.

More complex cascade processes utilizing [2,3]-Wittig rearrangements for the synthesis of nitrogen heterocycles using metallonitrene intermediates have been investigated by Blakey and co-workers. For example, sulfamate ester 359 and enantiomerically pure allylic ether
360 react under oxidative rhodium catalysis to selectively give 361 in 64% yield as a 73:27 E:Z mixture in 80% ee (Scheme 85a). Product 361 was subsequently derivatized into the core AB-ring system of the Securinega alkaloid family of natural products. The cascade reaction was applicable to a range of terminal allylic ethers, but only modest diastereoselectivity was obtained with substituted allylic ethers. The proposed mechanism involves a metallonitrene-initiated alkyne oxidation, with nucleophilic attack of benzyl ether 360 onto intermediate 363 leading oxonium 364 (Scheme 85b). Stereospecific [2,3]-rearrangement of 364 forms product 361 and releases the catalyst.

![Scheme 85](image)

**Scheme 85.** Rhodium-catalyzed cascade process to form nitrogen heterocycles. tfacam = trifluoroacetamide

7. CONCLUSION AND OUTLOOK

Catalytic stereoselective [2,3]-rearrangements are powerful methods in asymmetric synthesis. Many efficient catalytic protocols have been developed for a diverse range of [2,3]-
rearrangements, allowing new carbon-carbon and/or carbon-heteroatom bonds to be formed with high levels of diastereo- and enantioselectivity. The synthetic utility of a number of these methodologies have also been demonstrated through the synthesis of target molecules.

The [2,3]-rearrangement of onium ylides generated catalytically through reaction of a metal carbenoid remains the most widely explored methodology in the area. However, there is an increasing number of alternative catalytic strategies available using different methods of accessing reactive intermediates capable of undergoing stereoselective [2,3]-rearrangements. The incorporation of stereoselective [2,3]-rearrangements within tandem catalytic processes is an expanding area of research that is likely to increase further in the future.

Although the number of catalytic asymmetric [2,3]-rearrangements has increased dramatically over the last 20 years, there is still room for improvement in many areas. While highly diastereoselective reactions are more readily attained, the development of highly enantioselective variants remains a significant challenge in many cases. The ability to rationally design effective enantioselective protocols is often hampered by the limited detailed mechanistic understanding of many of these processes. Therefore an increased understanding of how catalysts interact and participate in [2,3]-rearrangements is likely to be hugely beneficial for the further development of highly stereoselective reactions.

Given the demonstrated synthetic utility of [2,3]-rearrangements, the further development of highly stereoselective catalytic variants will remain an active and worthwhile area of research. The design of new substrates capable of undergoing [2,3]-rearrangement processes as well as incorporation of known [2,3]-rearrangements within complex cascade reactions are also likely to lead to further advances in this field.
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Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We thank the Royal Society for a University Research Fellowship (A.D.S.), the European
Research Council under the European Union’s Seventh Framework Programme (FP7/2007-
2013) ERC Grant Agreement No. 279850 (J.E.T., T.H.W., K.K.), and the European Union
(Marie Curie ITN ‘SuBiCat’ PITN-GA-2013-607044) (S.S.M.S.) for financial support.

REFERENCES

Stewart, C.; West, F. G. Tetrahedron 2013, 69, 2667-2686.

2556-2591.


(37) Han, M.; Bae, J.; Choi, J.; Tae, J. *Synlett* **2013**, *24*, 2077-2080.


(42) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. 


(55) Sançon, J.; Sweeney, J. B. *Synlett* **2008**, 2213-2214.


(89) Liao, M.; Wang, J. Green Chem. 2007, 9, 184-188.


(103) Krishnamoorthy, P.; Browning, R. G.; Singh, S.; Sivappa, R.; Lovely, C. J.; Dias, H. V. 

(104) Deng, Q.-H.; Chen, J.; Huang, J.-S.; Chui, S. S.-Y.; Zhu, N.; Li, G.-Y.; Che, C.-M. 


*136*, 4476-4479.


10816-10819.


