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Recent Advances in Catalytic Enantioselective Rearrangement

Hua Wu,[a] Qian Wang,[a] and Jieping Zhu*[a]

Dedication ((optional))

Abstract: Among the fundamental chemical transformations in organic synthesis, rearrangement has been recognized as powerful and reliable reactions for the construction of carbon-carbon or carbon-heteroatom bonds. Benefiting from the advance of the novel catalytic system, catalyst design and activation mode, the chemistry of enantioselective rearrangements has experienced ever-growing development recently and has been successfully used in the synthesis of chiral non-racemic building blocks, natural products, and other valuable compounds. We present herein a survey of the recent development on the catalytic enantioselective rearrangement (from 2013 onward) organized according to the rearrangement type.

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1. Introduction

Rearrangement reaction is a broad class of organic transformations involving the migration of an atom or a group from one center (migration origin) to another (migration terminus) within the same molecule. Such bond reorganization process affords a structural isomer of the original substrate allowing, in many cases, the construction of molecular frameworks not easily accessible by other approaches. On the basis of the nature of the migrating group/atom, they can be classified into following categories: a) nucleophilic or anionotropic rearrangement in which the migrating group shifts with its electron pair. The pinacol and Wagner-Meerwein rearrangements for instance belong to this family (Figure 1a); b) electrophilic or cationotropic rearrangement, such as Stevens and Fries rearrangements, in which migrating group moves without its electron pair (Figure 1b); c) free radical rearrangement in which migrating group migrates with one single electron (Figure 1c); d) sigmatropic rearrangement in which a sigma bond and associated substituents interchanges termini on a conjugated π-system. It is a pericyclic reaction involving a cyclic transition state and proceeds in a concerted fashion with high levels of stereochemical fidelity. Cope, Claisen and [2,3]-Wittig rearrangements are typical examples (Figure 1d). With regard to asymmetric synthesis, the cationotropic and sigmatropic rearrangements have attracted more attention relative to two other types of bond reorganization processes.

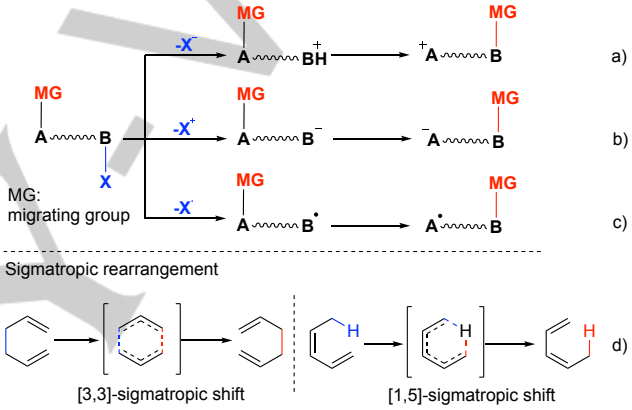

Figure 1. Generic presentation and classification of rearrangement reactions.

Over the past decade, the development of catalytic asymmetric rearrangements has attracted increasing attention among synthetic chemists and enantioselective versions have been developed for some of the most important rearrangement reactions. The achievement has provided intriguing and non-conventional retro-synthetic logics for the synthesis of chiral non-racemic molecules. While catalytic enantioselective semipinacol rearrangement has been extensively surveyed,[1] a general review documenting a broad range of asymmetric rearrangement reactions is, to the best of our knowledge, unavailable. This minireview, covering the current literature from 2013 to the end of 2018, aimed at filling this gap.

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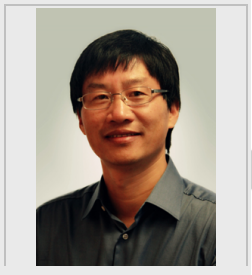
Hua Wu was born in 1986 and studied chemistry at Soochow University, obtaining his B.S. degree in 2009. Then he began his graduate studies at the University of Science and Technology of China under the supervision of Prof. Liu-Zhu Gong. In 2014, he received his Ph.D. and worked at Shandong University of Technology for one year. He joined Prof. Jieping Zhu's group as a postdoctoral associate in September, 2015. His has been focusing on enantioselective rearrangement reactions.

Qian Wang received her BSc and MSc degrees from Lanzhou University under the guidance of Professor Yulin Li. She got her PhD degree from the Chinese University of Hong Kong under the supervision of Professor Henry N. C. Wong. After several postdoctoral stays in Switzerland and in France, she joined CNRS (France) as a research engineer. In 2010, she moved to EPFL as a senior research scientist.



Jieping Zhu received his BSc from Hangzhou Normal University and his MSc from Lanzhou University (P. R. China) under the guidance of Professor Yulin Li. He obtained his PhD degree from University Paris XI (France) under the supervision of Professor H.-P. Husson and Professor J.-C. Quirion. After a postdoctoral stay with Professor Sir D. H. R. Barton at Texas A & M University in USA, he was nominated as the Chargé de Recherche in the "Institut de Chimie des Substances Naturelles", CNRS (France), and was promoted to Director of Research in 2000. He moved to EPFL (Switzerland) in September 2010 as a Professor of Chemistry.

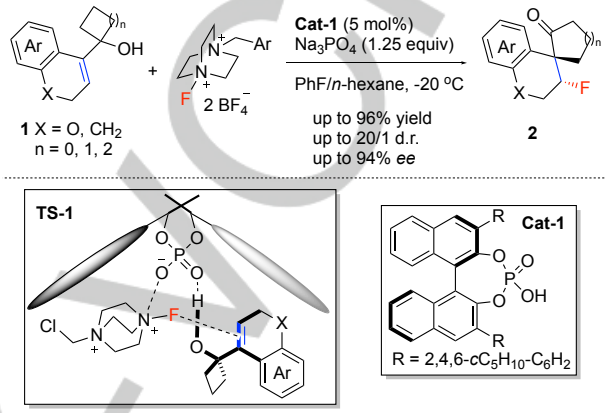
2. Enantioselective Pinacol-type Rearrangements

2.1. Enantioselective Semipinacol Rearrangement

2.1.1. Semipinacol Rearrangement of Allylic Alcohols

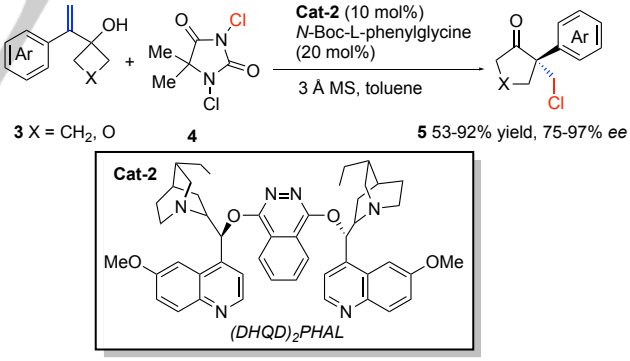
The semipinacol rearrangement has been identified as a powerful and versatile tool for the construction of all-carbon and heteroatom-containing quaternary stereocenters, which are present in various natural products and bioactive molecules.[1] In most cases, structurally diverse allylic alcohols were employed as starting materials and the reactions were usually triggered by halogenation or epoxidation of the double bond. The overall transformation represented therefore an unconventional methodology for the difunctionalization of alkenes. Tu and co-workers have made important contributions to the development of this field.[2]

In 2013, Alexakis and coworkers developed an enantioselective organocatalytic semipinacol rearrangement triggered by an electrophilic fluorination.[3a] In the presence of a chiral phosphoric acid[4a-4m] and Selectfluor®,[4n,4o] allylic alcohols **1** were converted to spirocycloalkanones **2** in excellent yields with high stereoselectivities. However, the allylic alcohols **1** lacking the aromatic ring or simple cyclohexene derivatives were not good substrates. As described in transition state **TS-1**, the catalyst structure **Cat-1** not only controlled the initial formation of the fluorinated stereocenter, but also assisted the alkyl migration process (Scheme 1). Subsequently, chiral phosphoric acid catalyzed enantioselective brominative and iodinative semipinacol rearrangements were realized and the related mechanistic studies were conducted by the same group.[3b,3c]



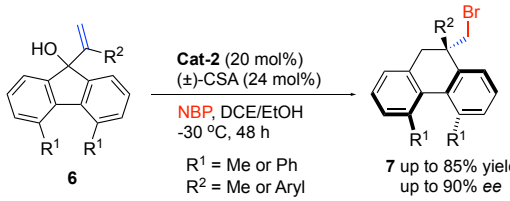
Scheme 1. Chiral phosphoric acid catalyzed enantioselective fluorination/semipinacol rearrangement.

In 2014, You and coworkers reported a highly enantioselective chlorination/ring expansion cascade of allylic alcohols **3** for the construction of cycloalkanones using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **4**) as chlorine source and $(DHQD)_2PHAL$ **Cat-2** as catalyst.[5] A series of functionalized dihydrofuranones **5** bearing an all-carbon quaternary center were obtained with excellent enantioselectivities (Scheme 2).



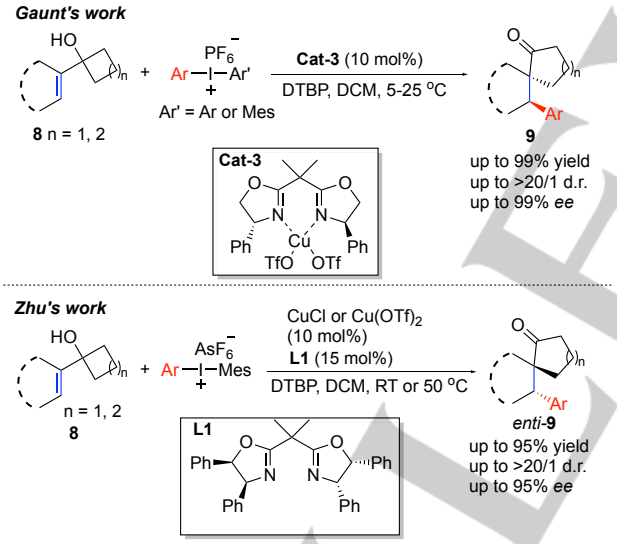
Scheme 2. Organocatalyzed enantioselective chlorination/ring expansion reaction.

Axially chiral biaryl system is widely present in bioactive natural products and is a privileged structural unit in ligand/catalyst design.[6] Very recently, Yeung and coworkers developed an organocatalytic enantioselective dynamic-kinetic resolution-semipinacol rearrangement of allylic alcohols **6** for the synthesis of compounds **7** containing both an axial and a central chirality (Scheme 3).[7] The *N*-bromophthalimide (NBP) was used as an electrophilic bromine source and $(DHQD)_2PHAL$ (**Cat-2**) turned out to be the catalyst of choice for this process.



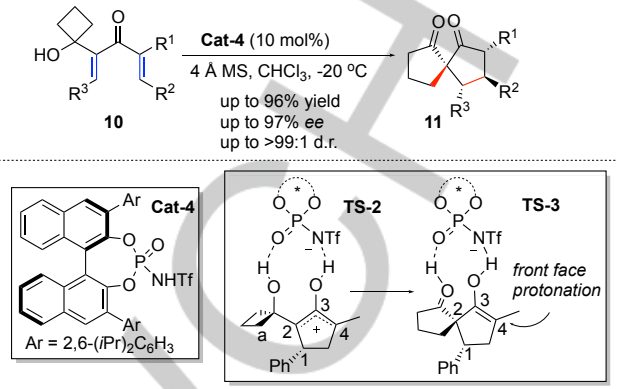
Scheme 3. Organocatalytic enantioselective dynamic-kinetic resolution-semipinacol rearrangement.

Most of the semipinacol rearrangements of allylic alcohols were initiated by protonation, halogenation or epoxidation leading to the concurrent formation of C-H or C-X bonds. On the contrary, examples of arylative or alkylative semipinacol rearrangements were scarce. Very recently, the group of Gaunt[8] and our group[9] reported independently an efficient copper-catalyzed enantioselective domino arylation/semipinacol rearrangement of allylic alcohols **8** using diaryliodonium salts as electrophilic aryl group donor (Scheme 4). While excellent enantioselectivity was observed in most cases, the diastereoselectivity of the reaction was found to be substrate depending. Generally, spiro[4,4]nonanes **9** were obtained in moderate selectivity, whereas excellent diastereoselectivity was observed for the spiro[4,5]decanes **9**. It was also observed that the counterion of the diaryliodonium salts impact significantly both the enantioselectivity and the reactivity of this rearrangement process.



Scheme 4. Copper catalyzed enantioselective arylative semi-pinacol rearrangement.

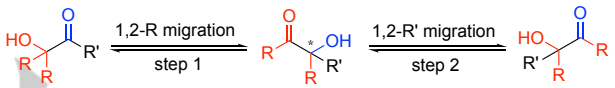
Tu and coworkers have developed a series of elegant enantioselective semipinacol rearrangements for the construction of enantioenriched spiroketones.[1,2] One of their recent achievements was a chiral phosphoric acid **Cat-4** catalyzed enantioselective Nazarov cyclization/semipinacol rearrangement cascade of allylic alcohols **10** (Scheme 5). A variety of chiral spiro[4.4]nonane-1,6-diones **11** with up to four consecutive stereocenters were obtained in excellent yields and enantiomeric excesses.[10] DFT calculations indicate that Nazarov cyclization is the most difficult step of the process and the stereochemistry of C-1 is controlled by the catalyst (**TS-2**). Furthermore, the chiral information at C-1 can influence the stereochemistry at C-2 via a [1,2]-C_a migration and the chiral catalyst directed the final protonation from the front face of the **TS-3** to create the C-4 chiral center.



Scheme 5. Chiral phosphoric acid catalyzed enantioselective tandem Nazarov cyclization/semipinacol rearrangement.

2.1.2. Enantioselective Acyloin Rearrangement

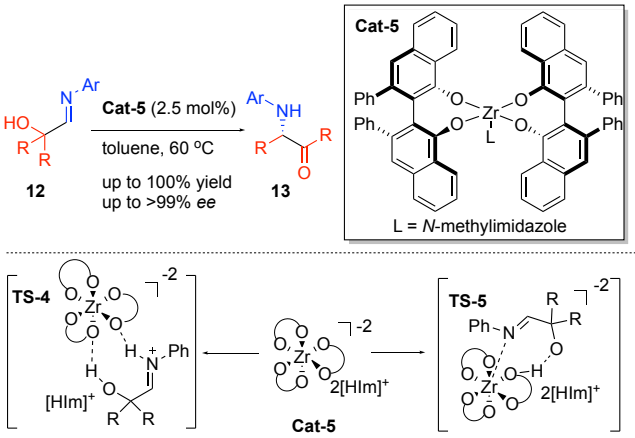
Acyloin (α-ketol) rearrangement, involving a 1,2-alkyl(aryl) migration that converts α-hydroxy ketone (aldehyde) to its isomer, has been recognized as a powerful tool in the synthesis of a variety of natural products and complex molecules. While a new stereocenter is produced during the process, the development of enantioselective catalytic version is very challenging owing to the inherent reversibility of this reaction (Scheme 6).[1, 11]



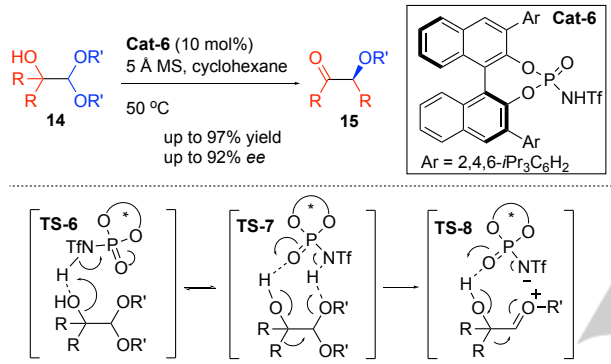
Scheme 6. Generic presentation of α-ketol rearrangement.

Rearrangement of α-hydroxy aldehydes generates the thermodynamically more stable compounds. Therefore, the development of enantioselective rearrangement of α-hydroxy aldehyde (R' = H) is, as expected, more successful compared to that of α-hydroxy ketones (R' ≠ H). The first example of chiral aluminium Lewis acid-catalyzed asymmetric rearrangement of α, α-disubstituted α-silyloxy aldehydes was developed by the group of Maruoka in 2007.[12]

In 2014, Wulff and coworkers reported an asymmetric α-iminol rearrangement of α-hydroxy imines **12** to α-amino ketones **13**. Various families of chiral catalysts were screened and the zirconium complex of VANOL **Cat-5** turned out to be the best.[13] A wide range of α-amino ketones **13** were synthesized in excellent yields and enantioselectivities under the catalysis of the novel chiral Zr complex **Cat-5**. Two possible transition states were proposed to be responsible for the high enantioselectivity: a) activation of both the imine and the alcohol by hydrogen bond interactions (**TS-4**); b) coordination of Zr to imine and a H-bond between an alkoxide ligand of the zirconium and the hydroxyl group of the substrate as shown in **TS-5** (Scheme 7).



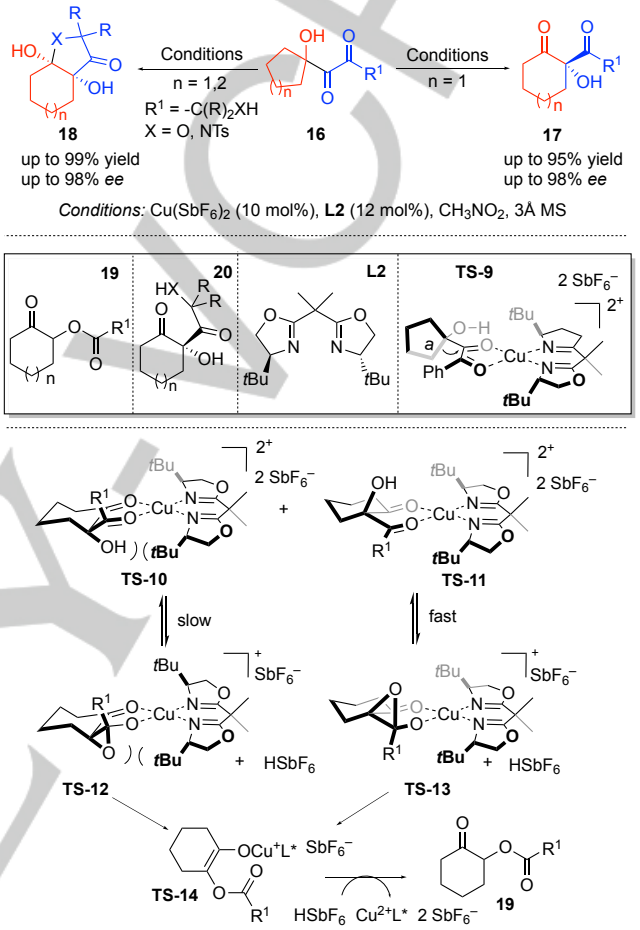
Scheme 7. Chiral Zr complex catalyzed enantioselective α-iminol rearrangement.



Scheme 8. Organocatalytic enantioselective acyloin rearrangement of α-hydroxy acetals.

In spite of the achievement of chiral Lewis acid catalyzed rearrangement of α-hydroxy aldehydes and α-iminols,[12,13] organocatalytic enantioselective acyloin rearrangement remained unknown until very recently. We developed a highly enantioselective acyloin rearrangement of α-hydroxy acetals to α-alkoxy ketones catalyzed by chiral binol derived *N*-triflyl phosphoramide.[14a] Mechanistically, hydrogen bonding between α-hydroxy acetal **14** and *N*-triflyl phosphoramide **Cat-6** could generate two possible intermediates **TS-6** and **TS-7**, which might be in equilibrium. A 9-membered double H-bonding system **TS-7** was assumed to be the predominant form. Subsequent elimination of R'OH from **TS-7** would generate the key oxonium intermediate which would form a chiral contact ion pair **TS-8** with **Cat-6**. Finally, enantioselective 1,2-carbon migration would provide product **15** with concurrent regeneration of the catalyst (Scheme 8). Formation of an ion pair between the in situ generated oxocarbenium ion and the chiral phosphoramide anion as well as H-bonding between the hydroxyl group and the phosphate oxygen might reduce significantly the conformational mobility of the oxonium intermediate and allowing a better stereochemical communication between substrate and **Cat-6** to afford the α-alkoxy ketones **15** in excellent enantioselectivity. However, concerted mechanism involving the generation of the phosphate acetal intermediate cannot be excluded.

Great effort has been made by Brunner, Kagan and coworkers in order to achieve the enantioselective rearrangement of α-hydroxy ketones (R' ≠ H, Scheme 6), but only moderate enantioselectivity (less than 48% *ee*) was obtained.[11] Recently, our group developed the first example of Cu(II)-**L2** catalyzed highly enantioselective α-ketol rearrangement (R' ≠ H, Scheme 6).[14b] A series of structurally diverse 2-acyl-2-hydroxy cyclohexan-1-ones **17**, dihydroxyhexahydrobenzofuranones and dihydroxyhexahydrocycloheptafuranones **18** were synthesized in high yields with excellent enantioselectivities (Scheme 9).



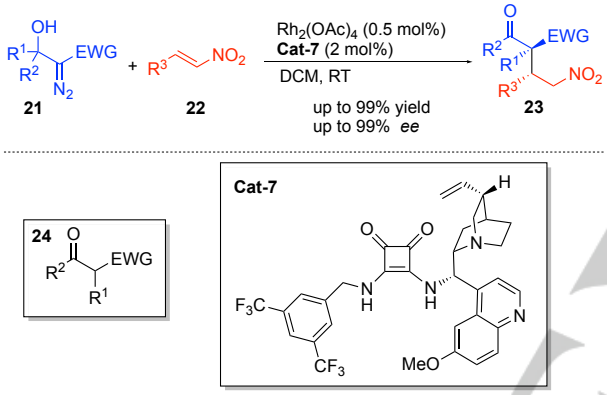
Scheme 9. Catalytic enantioselective α-ketol rearrangement.

It was shown that the presence of the α-dicarbonyl group is crucial to ensure the high enantioselectivity of this rearrangement. Mechanistically, formation of a square planar copper complex (**TS-9)** resulting from the coordination of the CuL2 to diketone **16** followed by selective 1,2-shift of the alkyl group to the *si* face of the neighboring carbonyl group accounted for the observed enantioselectivity. In addition, kinetic resolution of the rearranged product **17** via **TS-10** to **TS-14** converted the minor enantiomer (*S*)-**17** to **19**, amplifying therefore the enantiopurity of the product **17**. On the other hand, the chiral Cu-bisoxazoline complex catalyzed enantioselective α-ketol rearrangement of the substituted 1,4-dihydroxybutane-2,3-diones (X = O) or the tosylamide analogues (X = NHTs) provided the intermediate **20**, which then underwent a kinetically competent hemiacetalization or hemiaminalization to convert the intermediate **20** to the bicyclic products **18**.

2.1.3. Other Related Rearrangements

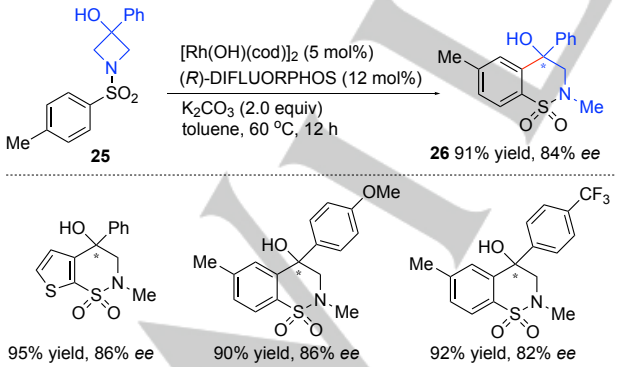
Apart from the enantioselective semipinacol rearrangements discussed above, where the enantioselectivity are determined by the migration step, there are examples in which a non-enantioselective semipinacol rearrangement was used for the in situ generation of a racemic intermediate that was subsequently engaged in an enantioselective process for the generation of chiral non racemic products.

Gong and coworkers have been very active in the field of enantioselective relay and cooperative catalysis.[15] In the presence of rhodium acetate and a chiral bifunctional urea **Cat-7**, the reaction of diazo compounds **21** with nitroalkenes **22** afforded δ-oxo nitroalkanes **23** in high yields with excellent enantioselectivities (Scheme 10).[16] In this relay catalytic process, $Rh_2(OAc)_4$ catalyzed initial semipinacol rearrangement to afford the racemic ketone **24**. Subsequent chiral amine catalyzed enantioselective Michael addition of **24** to nitroalkenes **22** afforded the functionalized nitro compounds **23** in excellent yields and *ees*.



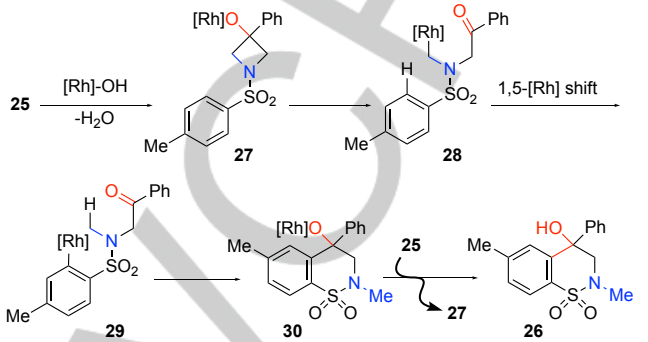
Scheme 10. Enantioselective semipinacol rearrangement/Michael addition cascade.

In 2013, Murakami and coworkers developed a rhodium-catalyzed enantioselective rearrangement of *N*-arenesulfonylazetidine-3-ols **25** to benzosultams **26**.[17] The reaction provided an unconventional way for the synthesis of biologically important benzosultams (Scheme 11).



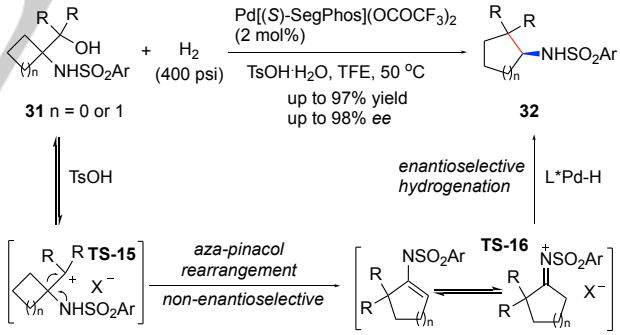
Scheme 11. Catalytic enantioselective rearrangement of *N*-arenesulfonylazetidine-3-ols.

A possible mechanism was proposed to explain the formation of **26** from **25** (Scheme 12). Rhodium alkoxide **27**, generated in situ from **25** and rhodium hydroxide, underwent strain-releasing β-carbon elimination to provide the alkylrhodium intermediate **28**. A 1,5-rhodium migration from $C(sp^3)$ to $C(sp^2)$ would produce the arylrhodium species **29**. An enantioselective intramolecular 6-*exo*-trig addition of the resulting arylrhodium intermediate to the carbonyl group would furnish the intermediate **30** which finally underwent the metathesis with the hydroxyl group of azetidinol **25** to release the benzosultam **26** with the concurrent regeneration of intermediate **27**.



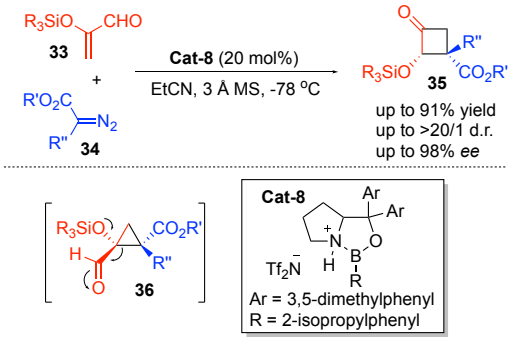
Scheme 12. Possible mechanism for the rearrangement of *N*-arenesulfonylazetidine-3-ols.

In 2014, Zhou and coworkers communicated an efficient palladium catalyzed enantioselective hydrogenation of enamide generated in situ by aza-pinacol rearrangement.[18] A Brønsted acid catalyzed dehydration of amino alcohol **31** would afford carbocation intermediate **TS-15** which underwent aza-pinacol rearrangement to provide the key iminium ion intermediate **TS-16**. Palladium catalyzed enantioselective hydrogenation of the latter furnished the desired chiral amine **32** in excellent enantiopurities (Scheme 13). It is noteworthy that, the high enantioselectivity resulted from the enantioselective hydrogenation process rather than the aza-pinacol rearrangement step.



Scheme 13. Palladium catalyzed enantioselective aza-pinacol rearrangement/hydrogenation cascade.

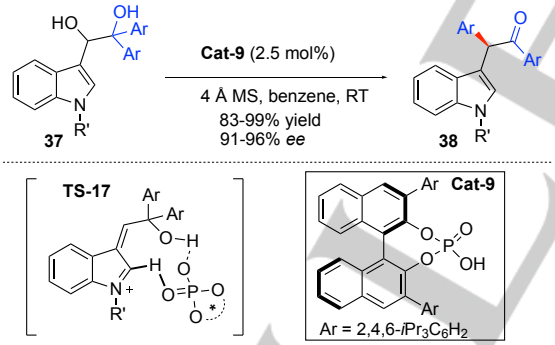
Chiral cyclobutane derivatives are valuable building blocks in medicinal chemistry and are present in a variety of natural products.[19] Very recently, Ryu and coworkers developed a chiral Lewis acid **Cat-8** catalyzed enantioselective annulation of α-silyloxyacroleins **33** with α-alkyl or α-aryl diazoesters **34** for the synthesis of highly functionalized cyclobutanones **35**.[20] Formation of 1-formyl-1-silyloxycyclopropane **36**, which was isolable and characterized, followed by Lewis acid catalyzed rearrangement of the α-silyloxy aldehyde afforded the substituted cyclobutanone in high yields with excellent diastereo- and enantioselectivity (Scheme 14).



Scheme 14. Lewis acid catalyzed tandem cyclopropanation/semipinacol rearrangement.

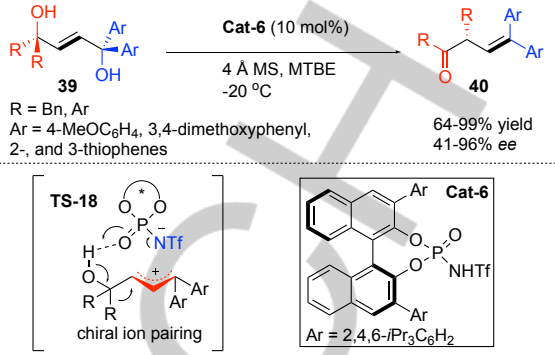
2.2. Enantioselective Vinylogous Pinacol Rearrangement

Compared with the enantioselective semipinacol rearrangement, the catalytic enantioselective pinacol rearrangement of 1,2-diols has been widely recognized to be much more challenging due to the likelihood involvement of the carbenium intermediate.[1] In 2010, Antilla and coworkers reported the first chiral phosphoric acid-catalyzed enantioselective pinacol rearrangement.[21a] In the presence of **Cat-9**, indolyl 1,2-diols **37** were converted to the 3-substituted indolyl ketones **38** with high yields and enantioselectivities. The reaction was proposed to go through the conjugated iminium species (Scheme 15). Very recently, a mechanistic study of this enantioselective pinacol rearrangement by DFT calculation was reported by Grayson and coworkers.[21b] A transition state (**TS-17**) involving one OH···O and one C_2H-O hydrogen bonds between the intermediate indolyl alcohol and the phosphate group was proposed to be responsible for the highly enantioselective 1,2-aryl group migration.



Scheme 15. Enantioselective pinacol rearrangement of indolyl 1,2-diols.

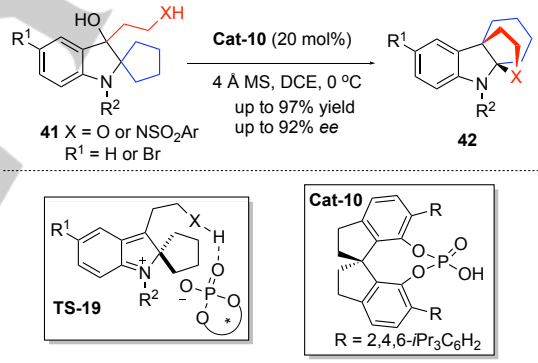
The first enantioselective vinylogous pinacol rearrangement has been developed in our group.[22] In the presence of a catalytic amount of chiral binol derived *N*-triflylphosphoramide **Cat-6**, various vinylogous pinacols **39** rearranged to the corresponding β,γ-unsaturated ketones **40** in excellent yields and enantioselectivities (up to 99% yield; up to 96% *ee*). Based on a series of control experiments, formation of chiral allylic contact ion pair **TS-18** between allyl cation and the conjugated base of chiral Brønsted acid was proposed to be responsible for the observed enantioselectivity (Scheme 16). It was found that strong electron-donating aryl groups, which were capable of stabilizing the in situ formed benzylic carbocation, were the key for the highly regio- and enantioselective process. The (*Z*)-vinylogous pinacol was converted to 2,5-dihydrofuran under the same conditions.



Scheme 16. Organocatalytic enantioselective vinylogous pinacol rearrangement.

2.3. Enantioselective aza-Pinacol Rearrangement

Very recently, Zhang, Zu and coworkers developed a truly enantioselective aza-pinacol rearrangement catalyzed by chiral phosphoric acid **Cat-10**.[23] A variety of tertiary alcohols **41** were converted to the indolines **42** via the formation of cyclic aza-*ortho*-xylylene intermediates **TS-19** (Scheme 17). The synthetic utility was demonstrated by the enantioselective synthesis of a key intermediate for the synthesis of minfiensine, a polycyclic indole alkaloid.



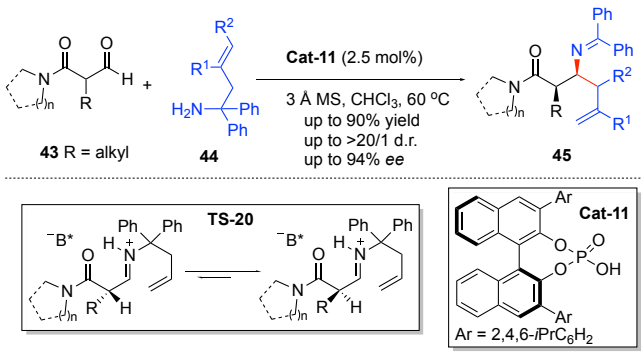
Scheme 17. Chiral phosphoric acid catalyzed aza-pinacol rearrangement.

3. Enantioselective [3,3]-Sigmatropic Rearrangements

3.1. Organocatalyzed Enantioselective [3,3]-Sigmatropic Rearrangements

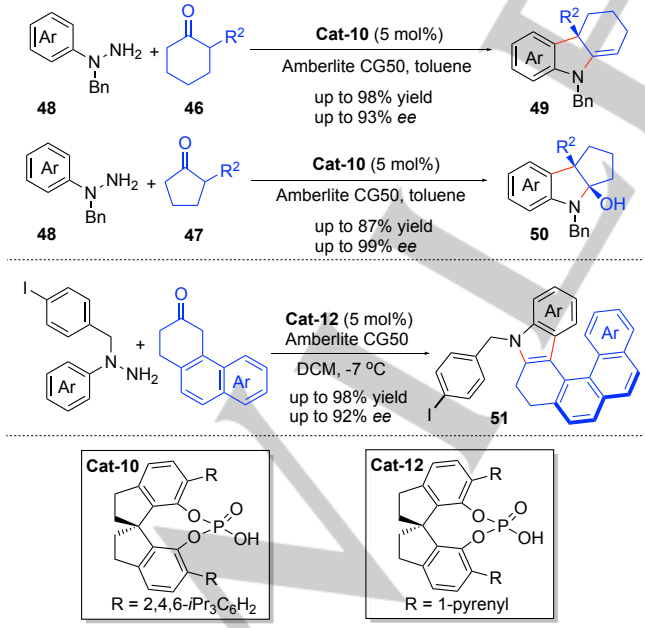
Although catalytic asymmetric sigmatropic rearrangements have been extensively investigated, examples of enantioselective 2-aza-Cope rearrangement are relatively rare. The group of Rueping[24a] and the group of Wulff[24b] reported the chiral Brønsted acid catalyzed aminoallylation of simple aldehydes via a sequence of condensation-enantioselective aza-Cope rearrangement. A dynamic kinetic resolution process utilizing stereochemically defined aminoallyl substrates via aza-Cope rearrangements was described by Overman and coworkers to access the angularly substituted 1-azabicyclic ring systems.[24c,d]

Johnson and coworkers communicated in 2015 a chiral phosphoric acid **Cat-11** catalyzed enantioconvergent 2-aza-Cope rearrangement starting from β-fomyl amides **43** and homoallylic amines **44**.[25] A series of β-amino amides **45** were obtained in high diastereo- and enantioselectivities through a DKR between homoallylic amines and α- stereogenic β-formyl amides as shown in **TS-20** (Scheme 18).



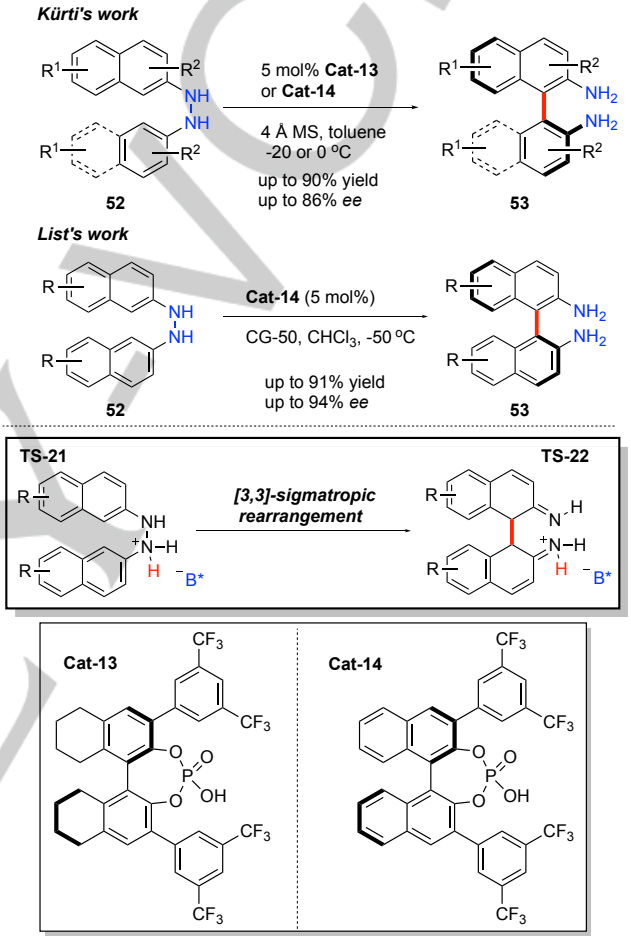
Scheme 18. Chiral phosphoric acid catalyzed enantioconvergent 2-aza-Cope rearrangement.

List and coworkers developed a chiral phosphoric acid **Cat-10** catalyzed enantioselective interrupted Fischer indolization of cyclohexanones **46** and monosubstituted cyclopentanones **47** with *N*-benzyl-protected hydrazones **48**. A series of enantiomerically enriched 3-substituted tetrahydrocarbazoles and fused indolines **49** and **50** bearing a quaternary stereocenter were obtained in high yields with excellent enantioselectivities.[26] Subsequently, the same group developed a SPINOL-derived phosphoric acid **Cat-12** catalyzed highly enantioselective Fischer indole reaction for the synthesis of chiral azahelicenes **51** (Scheme 19).[27]



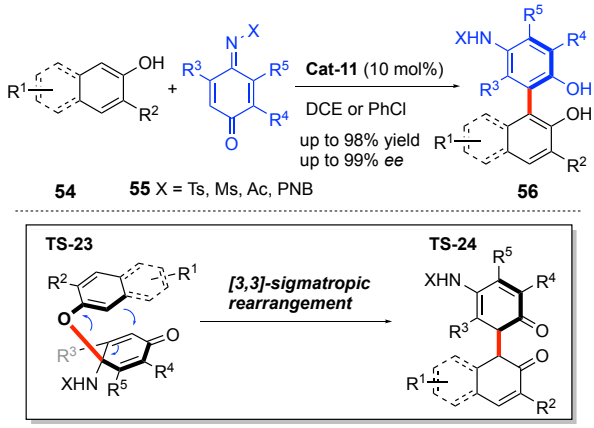
Scheme 19. Chiral phosphoric acid catalyzed enantioselective Fischer indolization.

Atropisomerism has enormous implications in the development of pharmaceuticals.[28] Recently, the group of Kürti[29a] and List's group[29b] reported independently a chiral phosphoric acid **Cat-13** or **Cat-14** catalyzed atroposelective [3,3]-sigmatropic rearrangement of 2,2'-hydrazonaphthalenes **52** for the regio- and atroposelective synthesis of enantioenriched 2,2'-diamino-1,1'-binaphthalenes **53**. Based on the DFT calculations, as shown in TS-21 and TS-22, the phosphoric acid proton of the catalyst was fully transferred to one of the *N*-atoms of the substrate, and the resulting phosphate acts as a chiral counterion for the subsequent enantioselective C-C bond formation (Scheme 20).



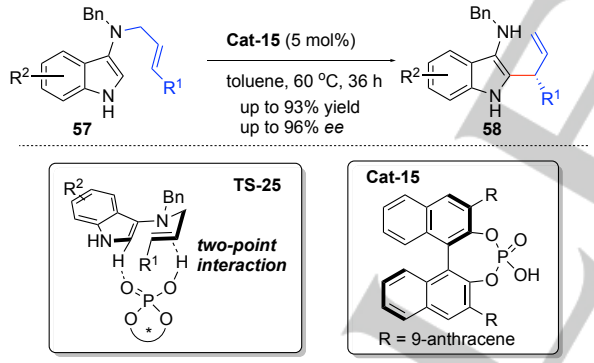
Scheme 20. Organocatalytic atroposelective [3,3]-rearrangement approach to BINAM derivatives.

More recently, Sun, Kürti and Xu[29c] developed an efficient strategy for the regio- and atroposelective construction of non-C_2-symmetric BINOLs from phenols or naphthols **54** and iminoquinones **55** by an organocatalytic direct arylation approach. A series of structurally diverse enantioenriched BINOL derivatives **56** were obtained in high yields with excellent enantioselectivities. Mechanistically, this reaction proceeded via a tandem process involving sequential aminal formation, [3,3]-sigmatropic rearrangement of **TS-23** and rearomatization of **TS-24**. Based on the results of the control experiments, the authors found that aminals with a plane of symmetry deliver BINOL derivatives with significantly lower enantioselectivities than unsymmetrical ones (Scheme 21).



Scheme 21. Organocatalyzed atroposelective direct arylation approach to BINOL derivatives.

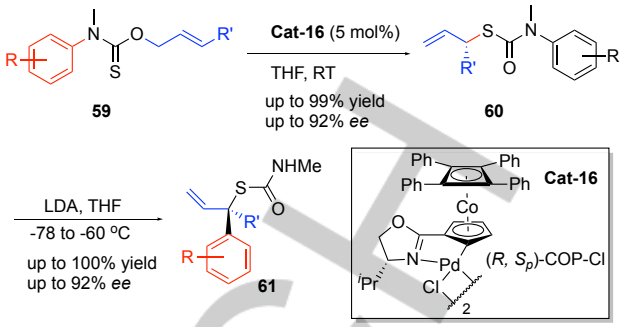
Aromatic aza-Claisen rearrangement is a powerful tool for the synthesis of substituted aromatic amines. However, the enantioselective versions are still in great demand and no highly enantioselective examples of this process have been reported.[30] Tantillo, Tambar and coworkers realized in 2013 a chiral phosphoric acid catalyzed enantioselective indole aza-Claisen rearrangement of *N*-allyl-3-aminoindoles **57**.[31] A series of 3-amino-2-substituted indoles **58** were obtained in high yields with excellent enantioselectivities (Scheme 22). An arene CH-O interaction between the C_2-proton and the phosphate counterion of the chiral phosphoric acid, as shown in **TS-25**, was proposed to accelerate this rearrangement and to be responsible for the high enantioselectivity.



Scheme 22. Chiral phosphoric acid catalyzed aza-Claisen rearrangement.

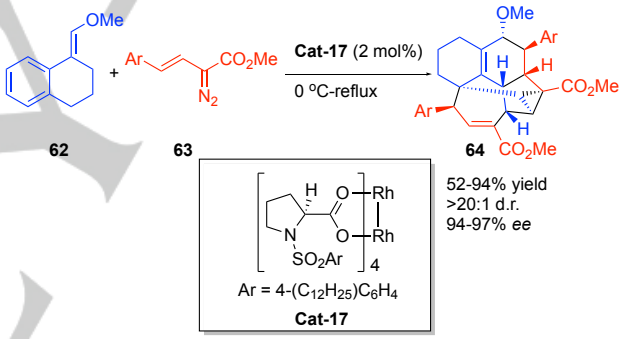
3.2. Transition Metal Catalyzed Enantioselective [3,3]-Sigmatropic Rearrangements

Thiols are widespread in natural products and synthesis of enantioenriched thiols is very challenging.[32] In 2014, Clayden and coworkers developed a chiral palladium complex **Cat-16** catalyzed enantioselective [3,3]-sigmatropic rearrangement of substrate **59** for the synthesis of *N*-aryl allylic thiocarbamates **60**. Under strong basic conditions, compound **60** underwent a second rearrangement to provide tertiary thiol carbamate **61** in excellent yields and *ee*s (Scheme 23).[33]



Scheme 23. Palladium catalyzed enantioselective [3,3]-sigmatropic rearrangement for the synthesis of enantioenriched tertiary thiols.

In 2014, Davies and coworkers developed an enantioselective synthesis of hexacyclic compound **64** bearing ten stereocenters by a dirhodium complex **Cat-17** catalyzed reaction of the α-tetralone-derived enol ether **62** with styryl diazoacetates **63.** A domino process involving enantioselective double cyclopropanation of the benzene ring/Cope rearrangement of a divinylcyclopropane/intramolecular Diels-Alder reaction was proposed to account for the outcome of this complexity-generating reaction (Scheme 24).[34]

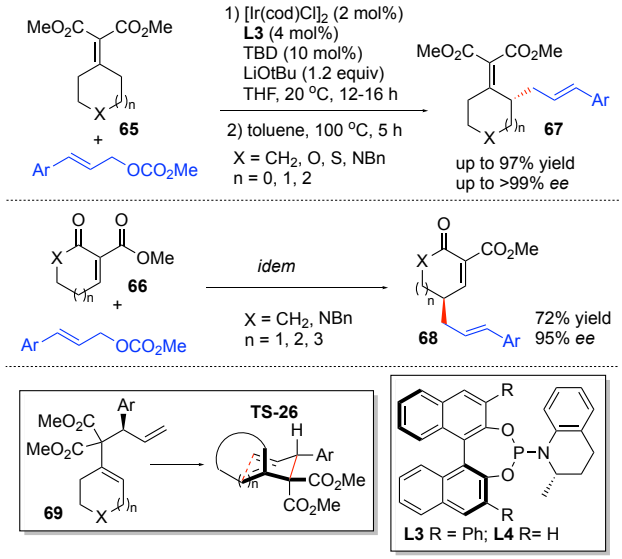


Scheme 24. Tandem Rh(II)-catalyzed double-cyclopropanation/Cope rearrangement/Diels-Alder reaction.

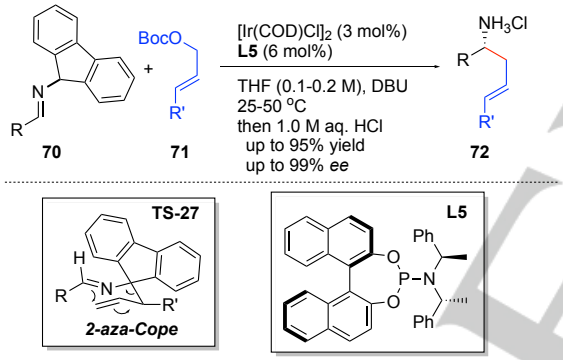
Recently, a catalytic enantioselective γ-alkylation of α,β-unsaturated malonates **65** and ketoesters **66** was developed by Stoltz and coworkers.[35] An enantioselective iridium-catalyzed α-alkylation of an extended enolate provided the intermediate **69**, which underwent a subsequent Cope rearrangement resulting in the translocation of chirality to the γ-position. The preferential rearrangement of the diene **69** through a chairlike transition state **TS-26** over the boatlike transition state was proposed to be responsible for the high degree of chirality transfer (Scheme 25). Various structurally diverse enantioenriched γ-substituted α,β-unsaturated malonates **67** and β-ketoesters **68** were synthesized by this enantioselective domino process.

In 2016, Niu and coworkers developed an iridium catalyzed enantioselective umpolung allylation of imines for the synthesis of 1,4-disubstituted homoallylic amines **72**, which are not easily accessible by literature methods.[36] Mechanistically, a regioselective allylation of N-fluorenyl imine **70** with *tert*-butyl cinnamyl carbonates **71** in the presence of Ir catalysis led to the formation of intermediate **TS-27** which underwent a facile 2-aza-Cope rearrangement to afford the homoallylamine **72**. The chiral ligand **L5** was found to be optimal for this transformation. A broad

range of 1,4-disubstituted homoallylic amines **72** were obtained in high yields with excellent enantioselectivities (Scheme 26).

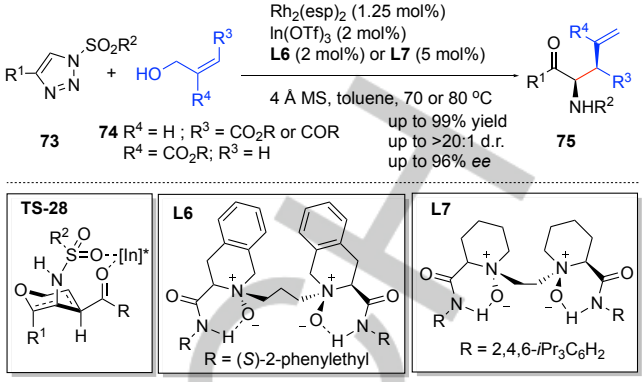


Scheme 25. Catalytic enantioselective sequential allylic alkylation/Cope rearrangement.



Scheme 26. Ir-catalyzed enantioselective allylation/2-aza-Cope rearrangement to chiral homoallylic amines.

Very recently, Feng group reported an example of domino achiral rhodium(II) catalyzed insertion/chiral indium(III) complex catalyzed enantioselective Claisen rearrangement of *N*-sulfonyl-1,2,3-triazoles **73** with allylic alcohol esters **74**.[37] Mechanistically, an allyl vinyl ether intermediate was presumably formed from the insertion of allylic alcohol to the in situ formed rhodium carbene species. Subsequent chiral indium catalyzed enantioselective Claisen rearrangement via six-membered transition state **TS-28** afforded the γ,δ-unsaturated α-amino ketones **75** in high yields with good to excellent diastereo- and enantioselectivities (Scheme 27). **L6** and **L7** were found to be the most efficient chiral ligands for indium(III) in this transformation.

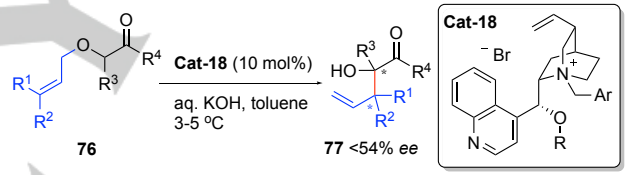


Scheme 27. Tandem insertion/enantioselective Claisen rearrangement by bimetallic rhodium(II)/indium(III) relay catalysis.

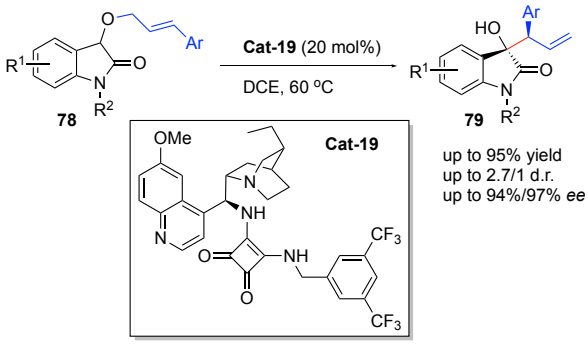
4. Enantioselective [2,3]-Sigmatropic Rearrangement

4.1. Enantioselective [2,3]-Wittig Rearrangement

The [2,3]-Wittig rearrangement is a [2,3]-sigmatropic rearrangement reaction converting an allylic ether into a homoallylic alcohol. The [2,3]-Wittig rearrangement has been widely used in organic synthesis.[38]



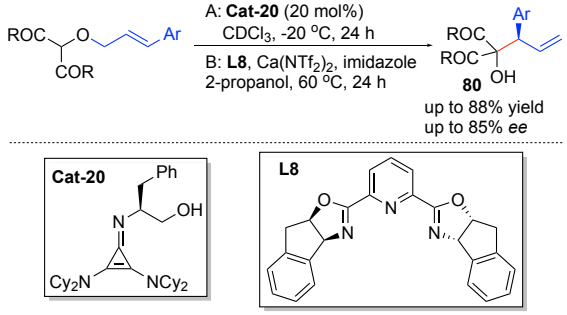
Scheme 28. Chiral ammonium salt catalyzed [2,3]-Wittig rearrangement developed by Denmark.



Scheme 29. Asymmetric organocatalytic [2,3]-Wittig rearrangement of oxindoles.

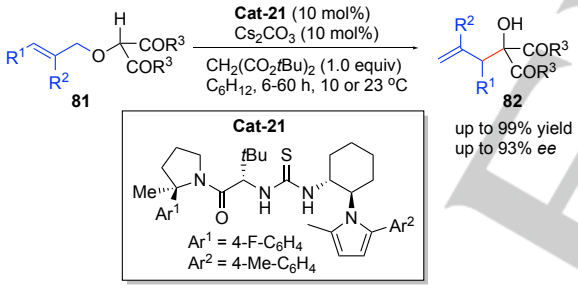
The group of Denmark reported in 2015 a phase-transfer catalyst for an anionic [2,3]-sigmatropic rearrangement of allyloxy carbonyl compounds **76**.[39] Various chiral quaternary ammonium salts as well as several other catalysts were examined for this enantioselective transformation and *Cinchona* alkaloid-derived ammonium salt **Cat-18** stood out from this screening (Scheme 28). While the *ee* of product **77** remained moderate, this work represented a rare example of phase transfer catalysis in enantioselective intramolecular transformation.

In 2016, Kanger and coworkers developed a highly enantioselective *Cinchona* alkaloid derived squaramide **Cat-19** catalyzed [2,3]-sigmatropic rearrangement of oxindole derivatives **78**.[40] Various enantioenriched 3-hydroxy 3-substituted oxindoles **79** were synthesized in high enantiomeric purities and moderate diastereoselectivities (Scheme 29).



Scheme 30. Chiral organic base and chiral Ca-complex catalyzed [2,3]-Wittig rearrangement.

Soon after, the same group developed two different approaches for enantioselective [2,3]-Wittig rearrangement by small molecule and transition metal catalysis.[41] Both the highly basic cyclopropenimine **Cat-20** and the Ca^{2+}/bisoxazoline complex **L8** were employed, respectively, to catalyze the [2,3]-Wittig rearrangement of allyloxymalonates to provide the corresponding homoallylic alcohols **80** in generally moderate to good enantioselectivities (Scheme 30).

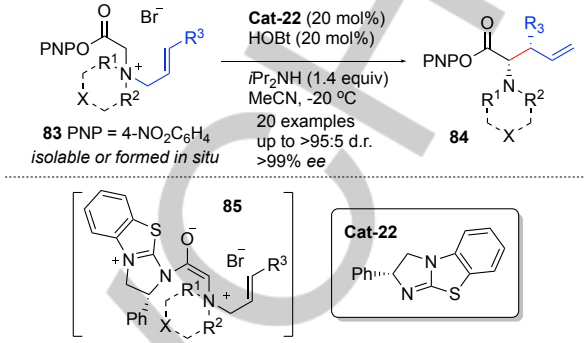


Scheme 31. Enantioselective [2,3]-Wittig rearrangement enabled by synergistic ion-binding catalysis.

In 2016, Jacobsen and coworkers found that dual catalysis combining chiral thiourea **Cat-21** and Brønsted base is highly efficient in catalyzing the enantioselective [2,3]-Wittig rearrangement of α-allyloxy carbonyl compounds **81** to afford homoallylic alcohols **82** in high yields and *ee*s (Scheme 31).[42] Based on the results of DFT calculation and control experiments, it was proposed that chiral thiourea is capable of stabilizing the transition state through the synergistic action of anion-binding and cation-binding motifs, rendering therefore the rearrangement highly enantioselective.

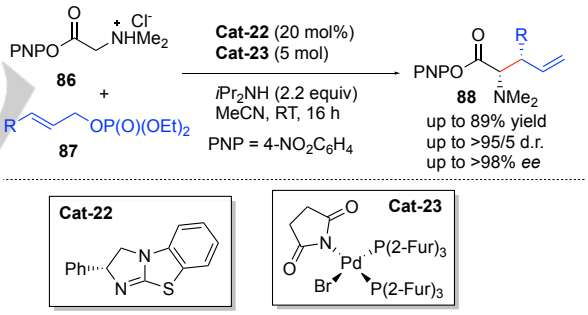
4.2. Enantioselective aza-[2,3]-Wittig Rearrangement

In 2014, Smith and coworkers reported a chiral isothiourea **Cat-22** catalyzed enantioselective [2,3]-sigmatropic rearrangement of allylic ammonium ylides, providing the corresponding *syn*-configured α-amino acid derivatives **84** with excellent stereocontrol (up to >95:5 d.r. and >99% *ee*).[43] The allylic quaternary ammonium salts **83** employed in this reaction can be either isolated or prepared in situ from *p*-nitrophenyl bromoacetate and the corresponding allylic amine (Scheme 32). The key dicationic intermediate **85** resulting from the acylation of the chiral isothiourea **Cat-22** with the ammonium salts **80** was proposed to be responsible for the efficient chirality transfer.



Scheme 32. Chiral isothiourea catalyzed enantioselective [2,3]-sigmatropic rearrangement of allylic ammonium ylides.

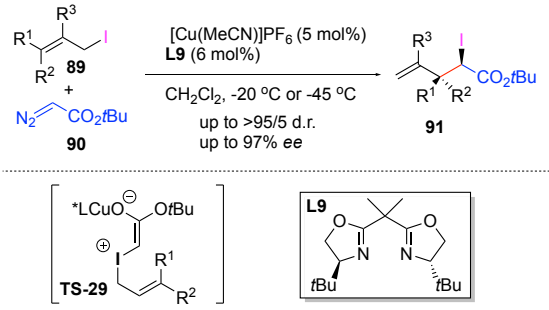
Very recently, the same group developed a relay catalysis combining achiral palladium catalyst and chiral isothiourea for the synthesis of chiral α-amino acid derivatives **88**. Under their optimized conditions, reaction of *N,N*-disubstituted glycine aryl esters **86** with an allylic phosphate **87** afforded the chiral α-amino esters **88** bearing two vicinal stereocenters in high yields with excellent diastereo- and enantioselectivities. Palladium-catalyzed allylic amination followed by enantioselective aza-[2,3]-Wittig rearrangement accounted for the reaction outcome (Scheme 33).[44]



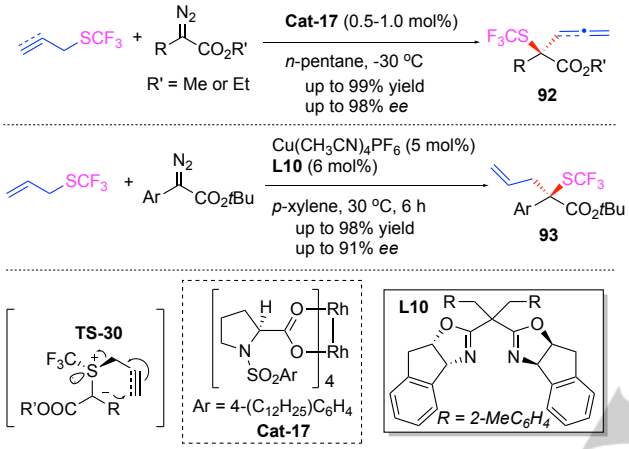
Scheme 33. Enantioselective [2,3]-rearrangement enabled by tandem palladium and isothiourea relay catalysis.

4.3. Enantioselective Doyle–Kirmse Reaction

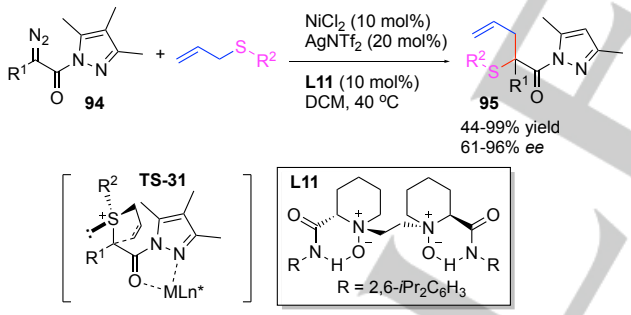
Tambar group has developed a series of elegant asymmetric [2,3]-sigmatropic rearrangement reactions.[45] Recently, this group reported a highly enantio-, diastereo-, and regioselective copper catalyzed [2,3]-rearrangement of iodonium ylides with a broad substrate scope of substituted allylic iodides.[46] Under the catalysis of chiral copper complex **L9**, substituted allylic iodides **89** coupled with α-diazoesters **90** to generate iodonium ylides **TS-29**, which underwent a [2,3]-sigmatropic rearrangement to afford the α-iodo ester **91** with high selectivities (Scheme 34). The resulting enantioenriched α-iodo esters **91** are synthetically useful building blocks.



Scheme 34. Copper catalyzed enantioselective [2,3]-rearrangement of iodonium ylides.



Scheme 35. Catalytic asymmetric trifluoromethylthiolation via enantioselective [2,3]-sigmatropic rearrangement of sulfonium ylides.



Scheme 36. Chiral Ni(II) catalyzed enantioselective Doyle-Kirmse reaction of α-diazo pyrazoleamides.

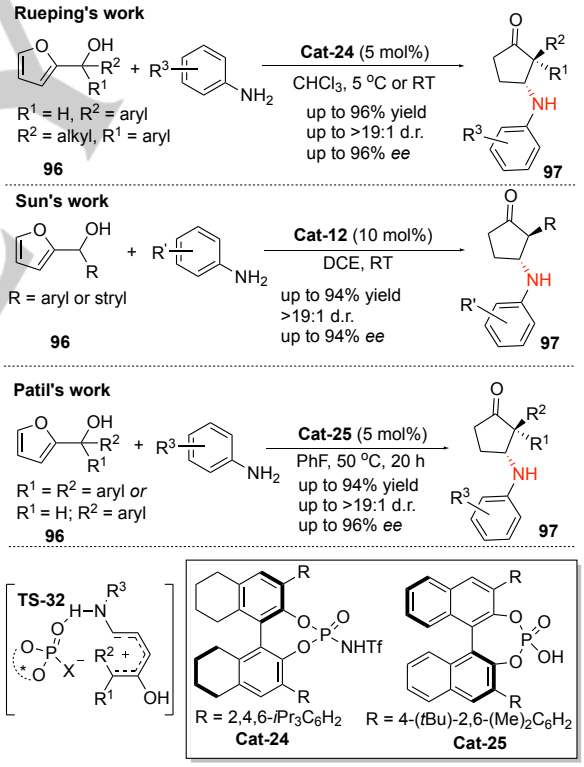
The trifluoromethylthio (SCF_3) functional group has recently attracted considerable attention in the fields of pharmaceuticals, agrochemicals and materials science. Very recently, Wang and coworkers reported an approach toward the enantioselective construction of chiral C(sp^3)-SCF_3 bond through Rh(II)- and Cu(I)-catalyzed [2,3]-sigmatropic rearrangement of sulfonium ylides **TS-30** generated from metal carbenes and sulfides.[47] This reaction was conducted under mild reaction conditions providing the desired products **92** and **93** in high yields with excellent enantioselectivities (Scheme 35). Successful chirality transfer from sulfur of the chiral ylide to the carbon of the product was proposed to be responsible for the high level of enantioselectivity. This transformation represented the first successful example of highly enantioselective catalytic Doyle-Kirmse reaction.

Subsequently, Liu, Feng and coworkers showed that the synergistic merger of new α-diazo pyrazoleamides **94** and a chiral *N,N'*-dioxide-nickel(II) complex enabled a highly enantioselective Doyle−Kirmse reaction (Scheme 36).[48] Under their optimized conditions, reaction of a series of aryl- or vinyl-substituted α-diazo pyrazoleamides **94** with allyl sulfides proceeded rapidly to provide, via intermediate **TS-31**, the products **95** in excellent yields (up to 99%) and enantioselectivities (up to 96% *ee*).

5. Other Enantioselective Rearrangements

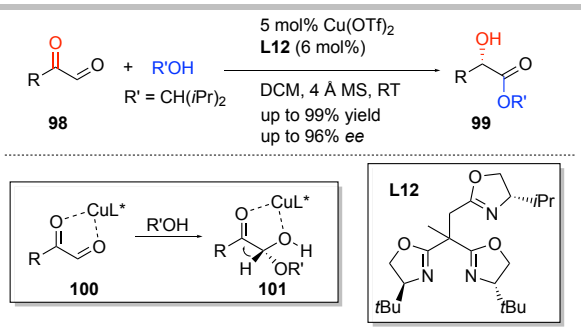
5.1. Enantioselective Piancatelli Rearrangements

Recently, chiral Brønsted acid catalyzed enantioselective aza-Piancatelli rearrangement was reported independently by the groups of Rueping,[49] Sun[50] and Patil.[51] Different chiral phosphoric acids, **Cat-24**, **Cat-12** and **Cat-25**, were employed as catalysts in these reactions. A series of structurally diverse aminocyclopentanones **97** were obtained starting from furylcarbinols **96** and anilines. Similar mechanism involving a chiral anion controlled enantioselective 4π electrocyclic ring closure via **TS-32** was proposed by these three groups to explain the high stereoselectivity of this transformation (Scheme 37).



Scheme 37. Chiral Brønsted acid catalyzed enantioselective aza-Piancatelli rearrangement.

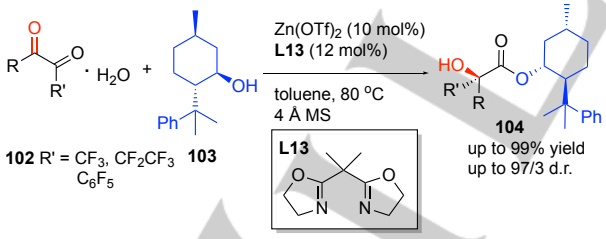
5.2. Enantioselective Intramolecular Cannizzaro Reaction



Scheme 38. TOX/copper catalyzed enantioselective intramolecular Cannizzaro reaction.

The first example of intramolecular Cannizzaro reaction converting α-keto aldehydes to α-hydroxy carboxylic acids was reported in 1887.[52] Since then, several groups, including Nishinaga, Morken, Ishihara and others, have made great efforts in rendering the reaction enantioselective.[53] However, only low to moderate enantioselectivities were obtained, implying the challenge associated with this endeavor. Indeed, the first highly enantioselective intramolecular Cannizzaro reaction was accomplished by the group of Tang only in 2013.[54] The reaction was enabled by TOX **L12**/copper complex. Both aryl and alkyl glyoxals **98** were well tolerated in this reaction giving the corresponding α-hydroxy esters **99** in excellent yields and enantioselectivities (Scheme 38). The catalyst-controlled face-selective addition of alcohols to the coordinated glyoxals **100** delivering an enantioenriched intermediates **101** which afforded, upon 1,2-suprafacial hydride shift, the observed product **99**.

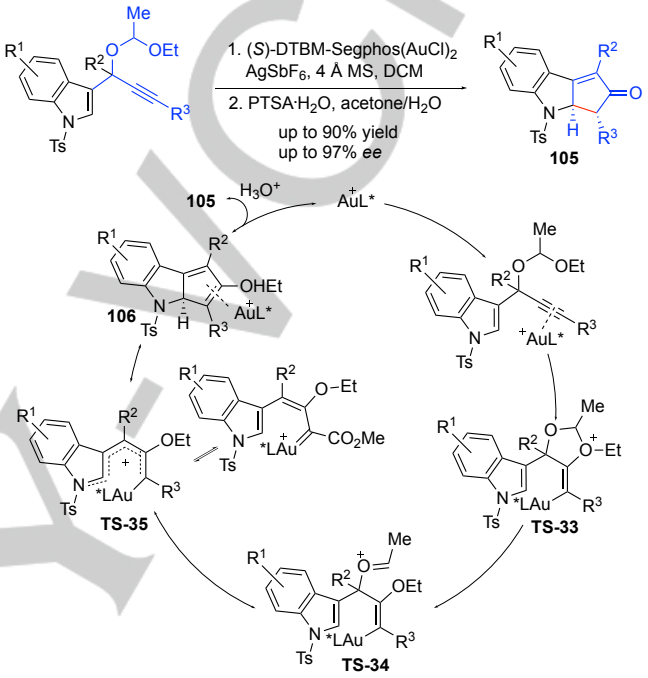
More recently, the same group reported a highly stereoselective Zn(II)/bisoxazoline **L13** catalyzed 1,2-perfluoroalkyl and perfluoroaryl migration reaction of 1,2-diketones **102** with (-)-8-phenylmenthol **103** (Scheme 39).[55] A wide range of enantioenriched α-hydroxy-α-perfluoroalkyl esters **104** were obtained in high yields with excellent diastereoselectivities. Unfortunately, catalytic enantioselective version of this 1,2-CF_3-migration reaction afforded the product with low *ee*.



Scheme 39. Zn(II)/bisoxazoline catalyzed stereoselective 1,2-perfluoroalkyl and perfluoroaryl migration.

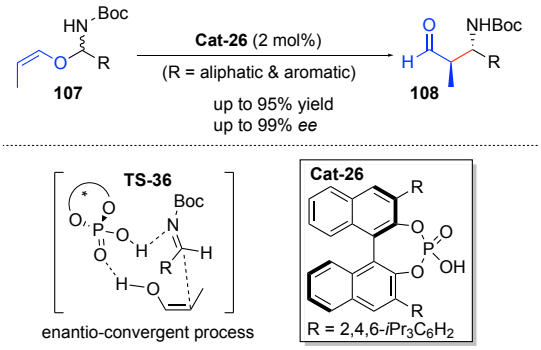
5.3. Enantioselective Rautenstrauch Rearrangement

Toste and coworkers[56] recently developed a cationic (*S*)-DTBM-Segphosgold(I) catalyzed enantioselective dearomative Rautenstrauch rearrangement for the synthesis of enantioenriched cyclopenta[*b*]indoles **105**. Mechanistically, initial *anti*-attack of the ethoxy ether of the acetal to the alkyne activated by the gold complex afforded the oxonium species **TS-33** which underwent fragmentation to the acyclic oxocarbenium intermediate **TS-34**. Extrusion of acetaldehyde provided the gold-substituted intermediate **TS-35**. The enantiodetermining C−C bond formation through chiral gold controlled imino-Nazarov cyclization afforded the intermediate **106**. Decomplexation of the cationic gold(I) followed by hydrolysis of intermediate **106** afforded the product **105** (Scheme 40). Employing the acetal-based substrates, a planar and achiral intermediate **TS-35** was generated rendering therefore the subsequent cyclization in a ligand controlled manner.



Scheme 40. Gold(I) catalyzed dearomative Rautenstrauch rearrangement for the synthesis of cyclopenta[*b*]indoles.

5.4. Enantioselective aza-Petasis-Ferrier Rearrangement



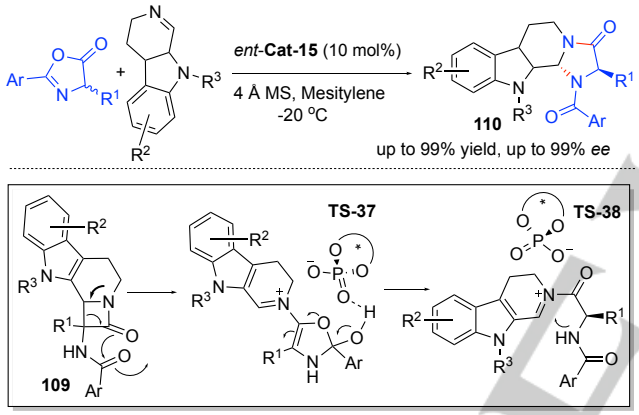
Scheme 41. Enantioselective aza-Petasis-Ferrier rearrangement catalyzed by chiral phosphoric acid.

Terada and coworkers reported in 2009 an *anti*- and enantioselective synthesis of β-amino aldehydes starting from allyl hemiaminal ethers.[57] The reaction proceeded through a sequence of a NiH-catalyzed isomerization of allyl ether to enol ether followed by a chiral phosphoric acid catalyzed aza-Petasis-Ferrier rearrangement. The reaction was proposed to proceed through the stereoablative loss of a vinyloxy group from the racemic mixture of hemiaminal **107** to generate in situ an imine

and enol. Chiral phosphoric acid catalyzed Mannich-type reaction via transition state **TS-36** produced the *anti*-adduct **108** with excellent diastereo- and enantioselectivity. A detailed experimental and theoretical studies on the enantioselective aza-Petasis-Ferrier rearrangement of hemiaminal vinyl ether **107** provided a clear mechanistic interpretation of this interesting enantioconvergent process (Scheme 41).[58]

5.5. Penicillin-penillonic Acid Rearrangement

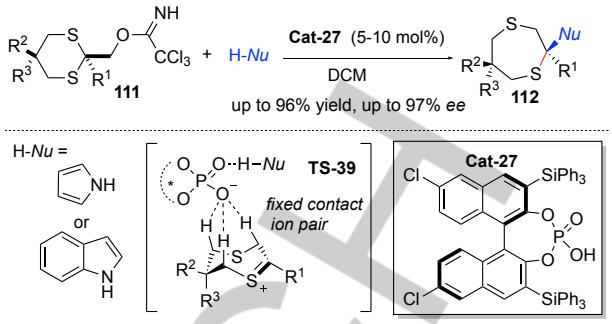
The penicillin-penillonic acid (PPA) rearrangement, which gives direct access to imidazolidin-5-ones, was first reported in 1964.[59] Very recently, Sun, Hong, Wang and coworkers[60] described a phosphoric acid catalyzed enantioselective synthesis of imidazolidin-5-ones starting from azlactones and N-substituted dihydrocarbolines. The reaction was proposed to proceed through an initial formal [2+2] cycloaddition leading to the formation of intermediate **109** followed by chiral phosphoric acid catalyzed asymmetric PPA rearrangement via **TS-37** and **TS-38**. A series of imidazolidin-5-ones **110** were synthesized in moderate to high yields with excellent enantioselectivities (Scheme 42).



Scheme 42. Phosphoric acid catalyzed enantioselective [2+2] cyclization/penicillin-penillonic acid rearrangement.

5.6. Enantioselective 1,2-Sulfur Rearrangement

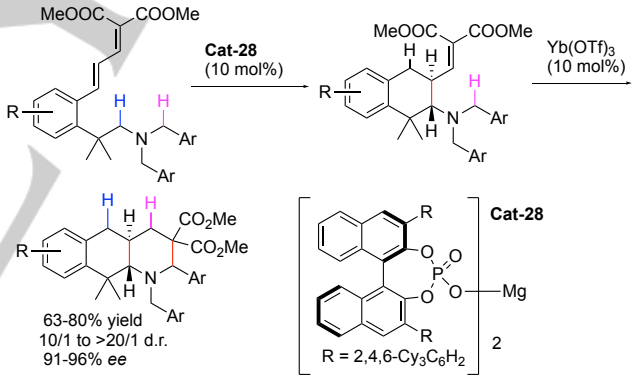
The thionium ion, the sulfur analog of oxocarbenium ion, has been widely used as a reactive intermediate in organic transformations, as exemplified by the Pummerer rearrangement.[61] The catalytic enantioselective reactions of thionium to provide enantioenriched sulfur-containing compounds remain rare. Very recently, Terada and coworkers reported a chiral phosphoric acid **Cat-27** catalyzed enantioselective ring expansion of 1,3-dithiane derivatives **111** (Scheme 43).[62] The products **112** were obtained in high yields and enantioselectivities. Experimental and theoretical studies revealed that the reaction proceeded through an enantioselective 1,2-sulfur rearrangement/stereoselective nucleophilic addition cascade. Based on the DFT calculation using a simplified model, the authors proposed that a nonclassical C-H···O hydrogen bond formed between the phosphoric acid and the substrate fixed the conformation of the ion pair as shown in **TS-39** and increased consequently the enantioselectivity.



Scheme 43. Phosphoric acid catalyzed enantioselective 1,2-sulfur rearrangement/stereospecific addition sequence.

5.7. Enantioselective [1,5]-H Shift/Cyclization

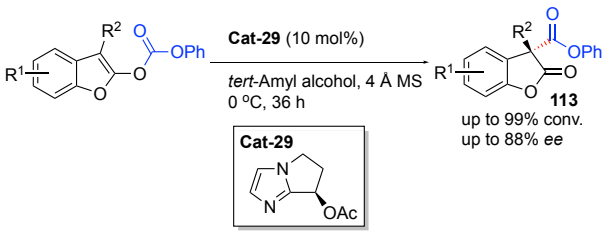
Direct functionalization of an unreactive C-H bond has been recognized as a powerful strategy for rapid construction of synthetically useful compounds. Mori, Akiyama and coworkers reported a chiral magnesium bisphosphate **Cat-28** catalyzed enantioselective double Csp^3-H bond functionalization enabled by sequential [1,5]-hydride shift/cyclization process (Scheme 44).[63,64] The second highly diastereoselective [1,5]-hydride shift and cyclization were catalyzed by an achiral Lewis acid $Yb(OTf)_3$. The authors highlighted that the employment of a benzyl group bearing an electron-withdrawing moiety was the key to achieve high enantioselectivity.



Scheme 44. Phosphoric acid catalyzed enantioselective double [1,5]-H shift/cyclization reaction.

5.8. Enantioselective Black Rearrangement

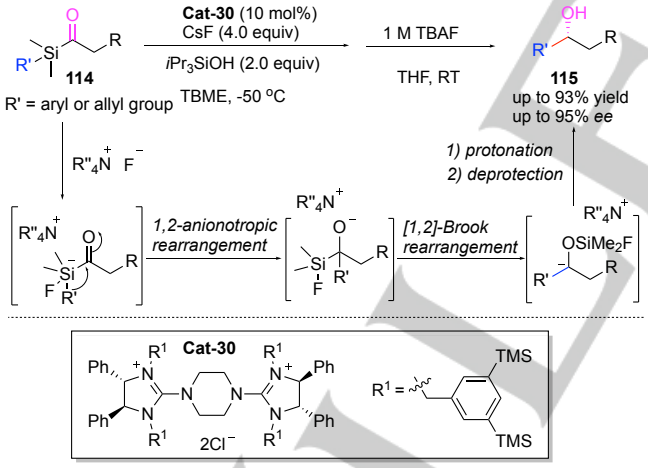
3,3-Disubstituted benzofuran-2(3*H*)-one, bearing a quaternary stereocenter at C-3, is an important structural motif present in a wide range of bioactive molecules. Black rearrangement through carboxyl migration is one of the most efficient strategies for the synthesis of such compounds. However, only few reports have appeared on the asymmetric version of this rearrangement utilizing mainly the chiral DMAP, chiral PPY (PPY = 4-(pyrrolidino)pyridine) and chiral isothioureas as catalysts.[65] In 2014, Zhang, Zhang and coworkers examined a series of chiral bicyclic nucleophilic imidazole to catalyze the enantioselective Black rearrangement.[66] They found that the readily available Acyloxy-DPI **Cat-29** catalyzed the Black rearrangement to afford compound **113** with up to 88% *ee* (Scheme 45).



Scheme 45. Enantioselective Black rearrangement catalyzed by chiral bicyclic imidazole.

5.9. 1,2-Anionotropic Rearrangement/Brook Rearrangement

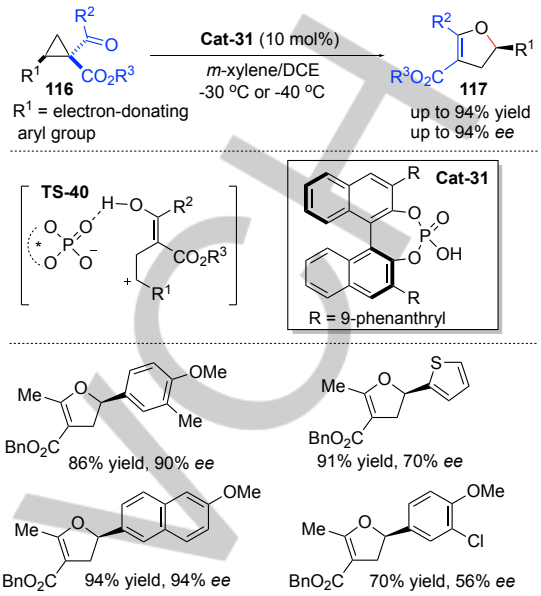
Acylsilanes are carbonyl derivatives behaving similarly to aldehydes or ketones and are susceptible to nucleophilic additions. Very recently, Lee, Tan and coworkers communicated a highly efficient enantioselective bisguanidinium-catalyzed tandem rearrangement of acylsilanes **114** (Scheme 46).[67] In this transformation, a key penta-coordinate anionic silicate intermediate was formed by the activation of acylsilanes by nucleophilic attack of the fluoride. Enantioselective aryl or allyl group migration took place to afford the alkoxide under the catalysis of chiral bisguanidinium **Cat-30**. [1,2]-Brook rearrangement followed by protonation afforded the corresponding secondary chiral alcohols **115** in excellent enantioselectivities. Both theoretical and experimental results suggested that the 1,2-anionotropic rearrangement via a bisguanidinium silicate ion pair was the stereodetermining step and the subsequent [1,2]-Brook rearrangement occurred with retention of configuration at carbon.



Scheme 46. Enantioselective 1,2-anionotropic rearrangement/[1,2]-Brook rearrangement of acylsilane.

5.10. Enantioselective Cloke-Wilson Rearrangement

Ring-enlargement of cyclopropanes constitutes a powerful tool for accessing structurally diverse carbo- and heterocycles. Analogous to the vinylcyclopropane-cyclopentene (VCP-CP) rearrangement, the isomerization of cyclopropyl imines, aldehydes and ketones, namely the Cloke-Wilson rearrangement, affords 2-pyrrolines and 2,3-dihydrofurans, respectively.[68]



Scheme 47. Enantioselective Cloke-Wilson rearrangement.

Very recently, Uria, Merino, Vicario and coworkers developed the first example of chiral phosphoric acid **Cat-31** catalyzed enantioselective Cloke-Wilson rearrangement (Scheme 47).[69] In this transformation, racemic cyclopropyl ketones **116** were converted to dihydrofurans **117** in high yields and enantioselectivity. The reaction proceeded via an initial strain-releasing ring opening of the push-pull cyclopropane followed by enantioselective cyclization of the resulting transient carbocationic intermediate **TS-40**, stabilized by both ion-pairing and H-bonding. Notably, the electron-rich aryl substituent in the racemic cyclopropyl ketones played an important role in the stabilization of the in situ formed carbocation which was crucial for the enantioselectivity of the reaction.

6. Conclusion and Perspective

Many well established catalytic enantioselective transformations involved the activation of the reactant, either electrophile or nucleophile or both, before the C-C/C-X bond forming event that create the stereocenter. The close association of catalyst with the substrate(s) via coordination (Lewis acid or Lewis base catalysts) or via covalent bond formation (Imine-enamine chemistry) facilitated stereoinduction, hence high enantioselectivity. However, most of the rearrangements discussed in this review generated a carbocation, and/or a carbanion intermediate before the stereocenter-generating C-C/C-X bond forming process. This rendered the stereoinduction much more difficult to realize and indeed in many cases, the traditional approach employing chiral Lewis acid catalysts failed. However, the advent of organocatalysts has provided a new perspective to meet this challenging task. Indeed, it has been demonstrated recently that attractive non-covalent interactions including H-bonding, electrostatic effects, hydrophobic, π-π, cation-π and Van der Waals forces are, akin to enzymatic processes, capable of preorganizing the substrate–catalyst

association to achieve high enantioselectivity. Since non-covalent interactions are weak and less-directional compared to covalent and dative bonds, multiple interactions are generally needed in order to impose certain geometrical and conformational constraints required for efficient stereochemical communication. As illustrated in this minireview, multiple H-bondings, the association of ion paring with H-bonding, and anion-binding with cation-binding are highly rewarding approaches in searching for asymmetric solutions to otherwise very challenging synthetic problems.[70]

In spite of the great achievement in asymmetric synthesis, it is fair to say that the development of catalytic asymmetric rearrangement is still in its infancy. Many important rearrangements such as [1,2]-Wittig rearrangement,[71] Pummerer rearrangement,[72] and even pinacol rearrangement,[1] have to date no truly efficient enantioselective versions. However, it is reasonable to expect that more and more efficient catalytic enantioselective rearrangements will be discovered in the near future. It is also anticipated that rearrangement reactions will continue to play a significant role as a test ground for the development of new catalysts and new catalysis concept in general.

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Keywords: pinacol rearrangement • enantioselectivity • sigmatropic rearrangement • transition metal catalysis • organocatalysis • carbon migration • hydride shift

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Recent Advances in Catalytic Enantioselective Rearrangement

*Hua Wu, Qian Wang, Jieping Zhu**

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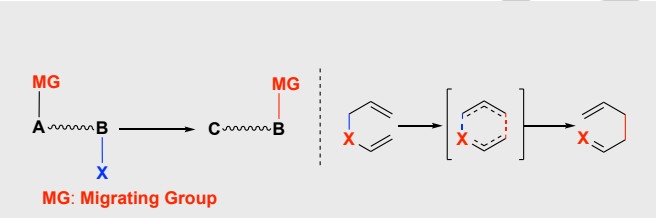

Multiple H-bondings, the association of ion pairing with H-bonding, and anion-binding with cation-binding are highly rewarding approaches in the development of catalytic enantioselective rearrangements.