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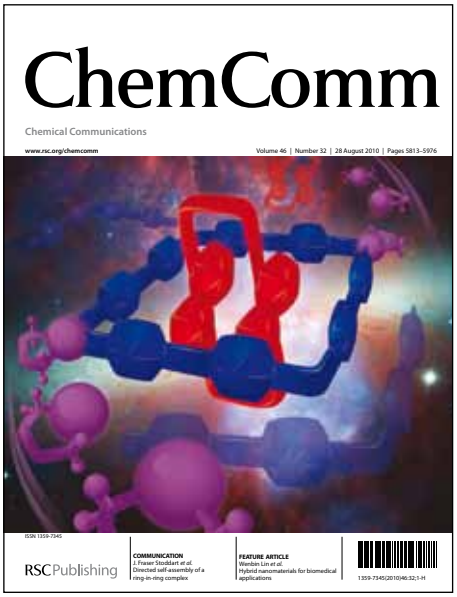

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FEATURE ARTICLE

Catalytic Asymmetric Semipinacol Rearrangements

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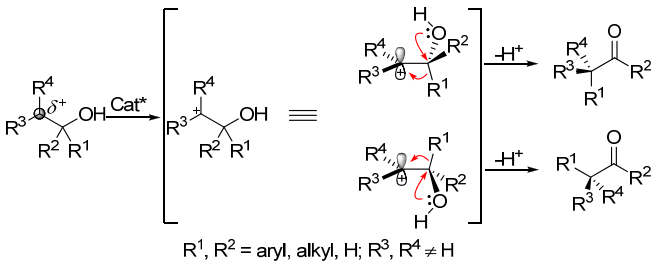
Over the past decades, semipinacol rearrangement has been widely applied in the field of Organic Synthesis. However, its catalytic asymmetric version did not catch much attention until the beginning of 21th century. Significant breakthrough has been made under the efforts of organic chemists. These important progressions are summarized in this paper.

Introduction

The all-carbon and heteroatom-containing quaternary stereocenters are a sort of valuable structural motifs in organic synthesis as they exist extensively in numerous important natural and non-natural organic molecules. Among various approaches for constructing these units, the semipinacol rearrangement is identified as one of the powerful and versatile methods. In addition, the semipinacol rearrangement also features the convenient and stereoselective construction of some other important functional groups, such as ketones, aldehydes, ethers and amines.[1] Since its emerging, however, semipinacol rearrangement is applicable mainly for the racemic transformations or substrate-induced asymmetric syntheses. One major reason for this is that the sterically hindered quaternary stereocenter is difficult to access and its catalytic asymmetric construction is much more challenging. In this regard, we have made longstanding efforts toward this topic, and recently we have made important breakthrough in the aspect of catalytic asymmetric semipinacol reangement.[2] This feature article will summarize the progress of the related reactions achieved by our group together with other chemists.

Generally, the stereoselective semipinacol rearrangement involves the formation of an α-hydroxy carbocation intermediate, and then a selective carbon-to-carbon 1,2-shift of R^1 (or R^2 depending upon their relative migrating aptitude) along one of the two possible ways under stereo-controlling to form the stereospecified α-quaternary (R^3 and $R^4 \neq H$) carbonyl products (Scheme 1). Selection of the migration pathway of R^1 is based on the interaction between chiral catalyst and the substrate. This interaction process normally involves the hydrogen bonding, imidization / enamination, Lewis acid / base interaction and transition metal-π-bond coordination, and so on, based on which this article describes six types of reactions: 1) organocatalytic halogenations / rearrangement of allylic alcohols; 2) organocatalytic or metal-catalyzed rearrangement of allylic alcohol; 3) organocatalytic rearrangement of vinylogous α-ketol; 4) transition metal complex catalyzed rearrangement of alkynyl and allenyl cycloalkanol; 5) Lewis acid catalyzed semipinacol rearrangement of α-hydroxy and α-amino aldehydes; 6) transition metal complex catalyzed rearrangement of α-diazo alcohols.

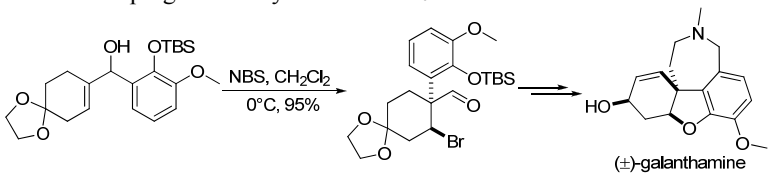


R^1, R^2 = aryl, alkyl, H; R^3, $R^4 \neq H$

Scheme 1 General Process of Enantioselective Semipinacol Rearrangement

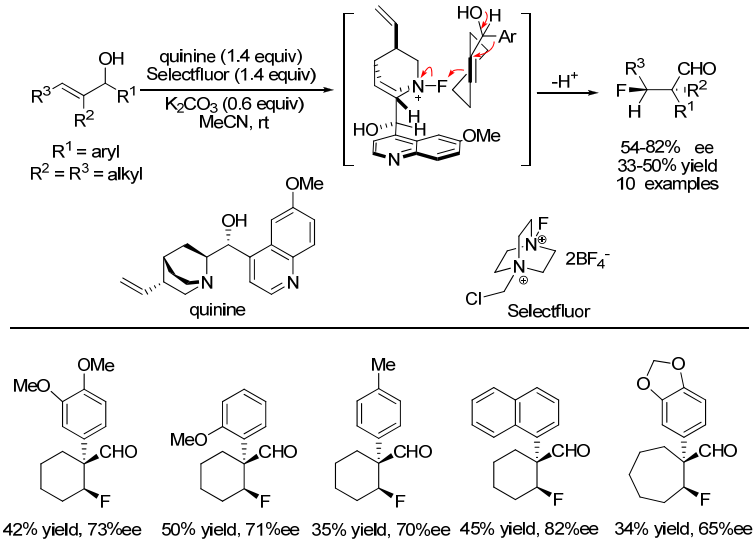
Organocatalytic Halogenation / Rearrangement of Allylic Alcohol

During the course of our synthesis of bioactive natural products at the beginning of this century, we noticed that the asymmetric halogenation / semipinacol rearrangement of allylic alcohols played a crucial role in developing some asymmetric synthetic strategies. For example, synthesis of galanthamine (Scheme 2), a drug for treating Alzheimer's disease, required such an asymmetric rearrangement to provide the key chiral α-quaternary β-bromo-ketone intermediate.[3] Despite our tremendous efforts, however, we were not able to carry out this asymmetric transformation, not to mention the catalytic version.



Scheme 2 Synthesis Example Using Bromination / Semipinacol Rearrangement

After extensive literature investigations about this type of reactions, we turned our focus on asymmetric fluorine-induced rearrangement reaction because the fluorine-containing compounds were also widely used in the chemistry of material, medicine as well as agriculture, and thus more asymmetric fluorination information was documented than other halogenations.[4,5] As indicated in Scheme 3,[6] through the screening of reaction reagents and conditions, the use of natural quinine as promoter and Selectfluor as F^+ reagent could effect the asymmetric fluorination / rearrangement of allylic alcohols in basic medium (K_2CO_3), generating a range of chiral α-all-carbon quaternary β-fluoro-aldehydes in up to 82% ee and 50% yield. However, the stoichiometric amount of quinine promoter must be used, and both reaction yields and enantioselectivities were not satisfactory.

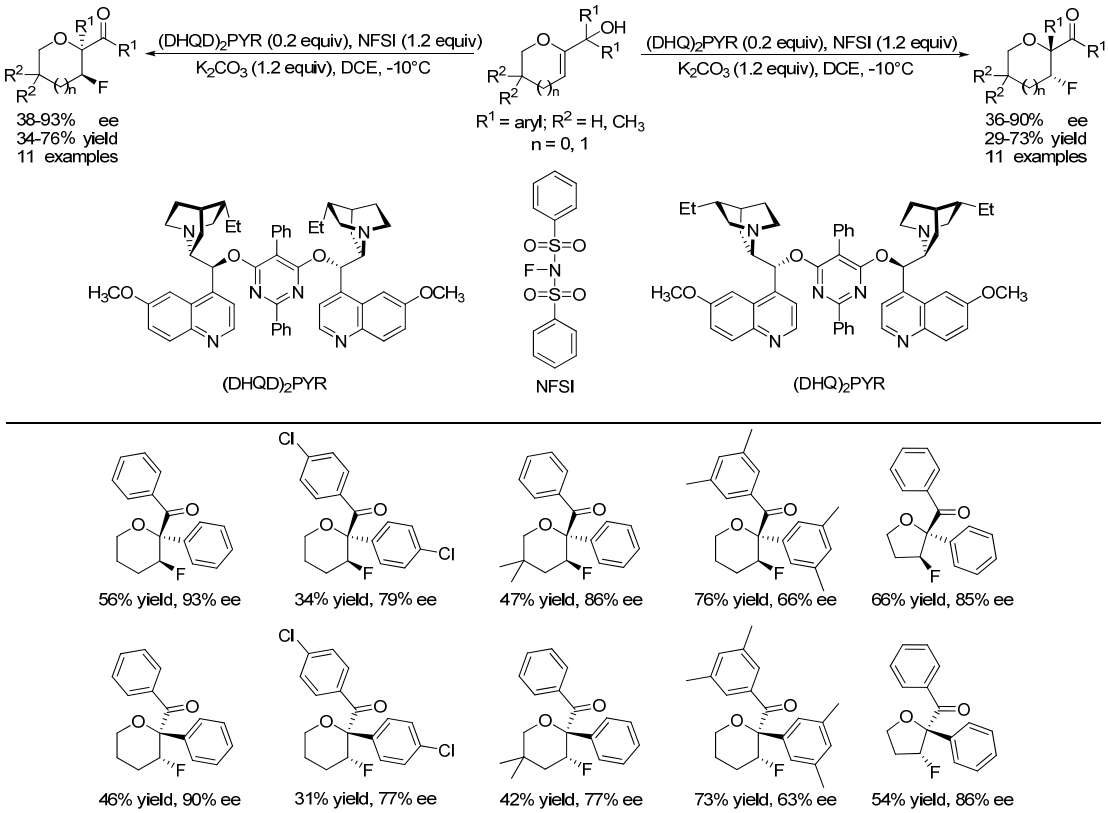


Scheme 3 Quinine-Promoted Fluorination / Rearrangement

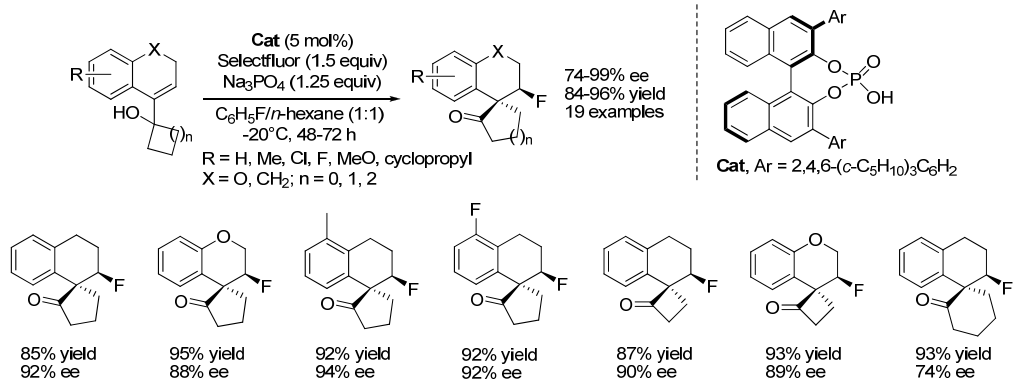
By further inspecting the reactivity of above reaction (lasting 6 days at room temperature), we postulated that the substrate with tri-carbon-substituted C=C bond and secondary hydroxy might not be reactive enough to initiate an efficient neucleophilic reaction with F^+. Therefore, the more reactive allylic alcohol substrate with enolate-type C=C bond and tertiary hydroxyl was subjected to this reaction (Scheme 4).[7] As expected, using the bis-quinine derivative $(DHQ)_2PYR$ as catalyst (10-20 mol%)[8] and NSFI as F^+ reagent could effect smoothly the fluorination / semipinacol rearrangement at lower temperature (-10°C), providing the chiral α-oxaquaternary β-fluoro- ketones in much better enantioselectivities (36-90% ee) in most cases and higher isolated yields (29-73%) than the protocol in Scheme 3. This is the first successful example of organocatalytic enantioselective fluorination / semipinacol rearrangements explored in our group. It was notable that the absolute configuration of the newly formed stereogenic center could be tuned with the catalysts. Catalysis carried out with $(DHQD)_2PYR$ generated (α*S*, *β*S)-stereochemistry of the products. While catalysis carried out with $(DHQ)_2PYR$ gave the inverse (α*R*, *β*R)-stereochemistry with the same good ee values but a little lower yields.

In 2013, Alexakis and co-workers also developed a organocatalytic fluorination-induced semipinacol rearrangement of allylic alcohols through an asymmetric-counterion-directed catalysis strategy.[9] Reaction optimization proved that the use of TRIP type of highly sterically congested

phosphoric acids was essential for the delivery of the expected enantioselectivity. And an anionic phase-transfer catalysis mechanism was confirmed by the requirement of such lipophilic chiral catalysts as well as the nonpolar solubilizing solvents. Moreover, it was also found that both the enantioselectivity and the diastereoselectivity were controlled by the catalyst. Therefore, reactions performed without chiral catalyst or with achiral catalyst gave the products as a mixture of diastereoisomers with close to 1:1 dr. This was different from what we observed for the halogenation reagents induced semipinacol rearrangements, which might be worth further study. Consequently, a variety of β–fluoro spiroketones were obtained from corresponding strained allylic alcohols with excellent ee (74-99%) and in excellent yield (84-96%) (Scheme 5). Especially, substrates with cyclopropanol or cyclobutanol moieties went through smoothly to give the desired products with different types of substituents on the phenyl ring. While the reaction including an expansion of five-membered ring only gave moderate result. Additionally, this transformation could be easily scaled up without affecting the corresponding selectivity.



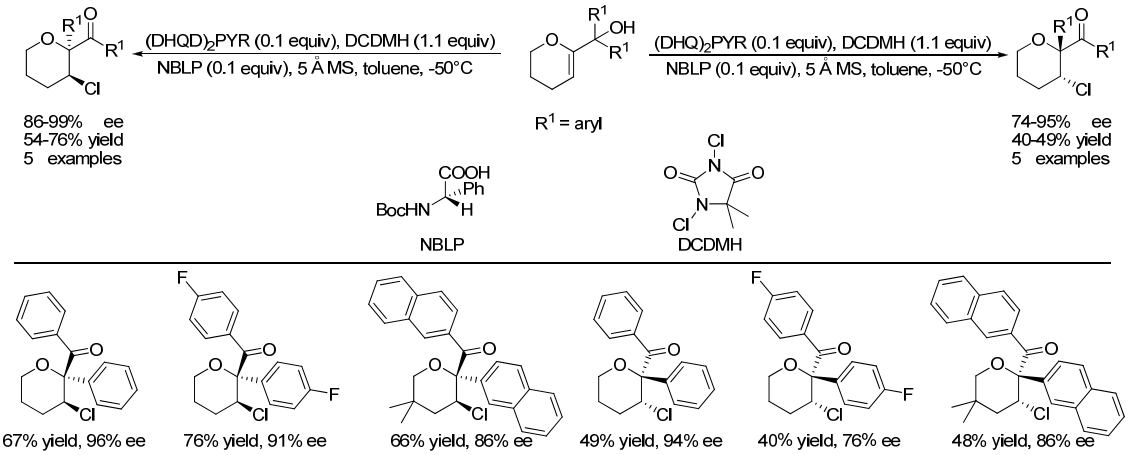
Scheme 4 $(DHQD)_2PYR$ and $(DHQ)_2PYR$-Catalyzed Fluorination / Rearrangement



Scheme 5 Chiral Phosphoric Acid-Catalyzed Fluorination / Rearrangement

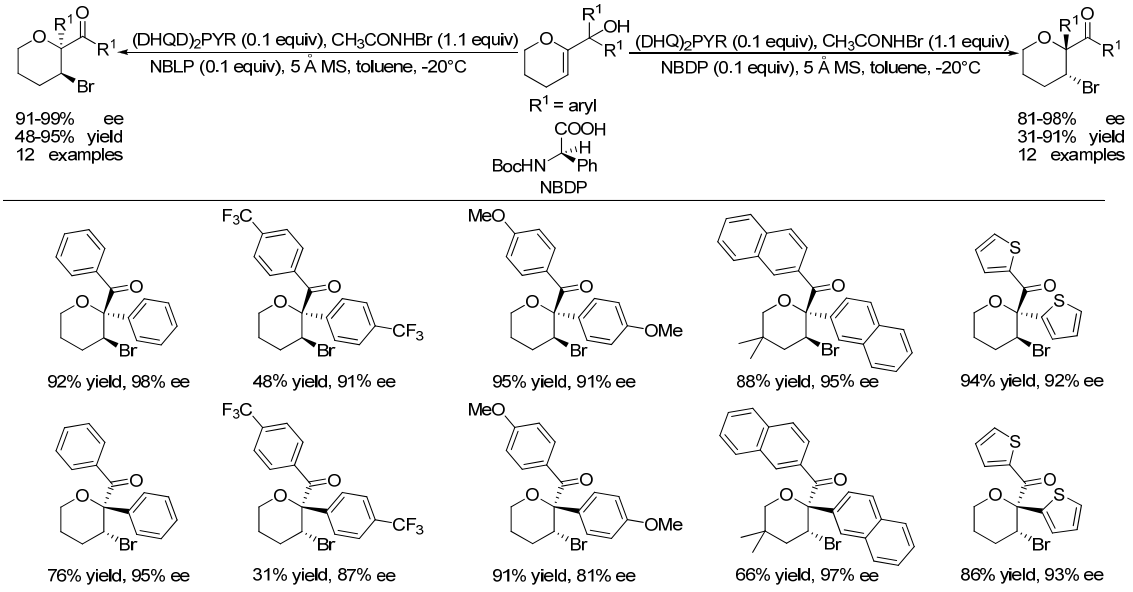
Following the above success, we continued to explore the catalytic asymmetric Cl^+-induced semipinacol rearrangement. A broad optimization of reaction conditions indicated that by using $(DHQ)_2PYR$ or $(DHQD)_2PYR$ as catalysts (10 mol%)

and DCDMH as Cl^+ agents, an asymmetric chlorination / semipinacol rearrangement of the above substrate could be obtained in acidic medium (NBLP, 10%) rather than the basic one in Scheme 4 at -50 or -70°C, generating the α-oxaquaternary β-chloro-ketones in good to high enantioselectivities (74-99% ee) and moderate yields (40-76%) (Scheme 6).[10] It was noteworthy that using $(DHQ)_2PYR$ gave lower yields and enantioselectivities than using $(DHQD)_2PYR$. In addition, the reaction speed could be largely accelerated by the use of acidic additive NBLP together with 5 Å MS, but the yield and enantioselectivity were just slightly improved.



Scheme 6 $(DHQD)_2PYR$ and $(DHQ)_2PYR$-Catalyzed Chlorination / Rearrangement

Having the efficient organocatalytic system above, we then continued to examine the Br^+-induced semipinacol rearrangement.[10] Fortunately, after the screening of different bromination reagent, the use of MeCONHBr could achieve the expected transformation under the catalysis of $(DHQD)_2PYR$ at -20°C, affording the chiral α-quaternary-β-bromo-ketones in both high enantioselectivities (91-99% ee) and yields (48-95%) (Scheme 7). Similarly, using $(DHQ)_2PYR$ reversed the absolute configuration of the newly formed stereogenic center and gave a little lower enantioselectivities (81-98% ee) and yields (31-91%) (Scheme 7).[10]

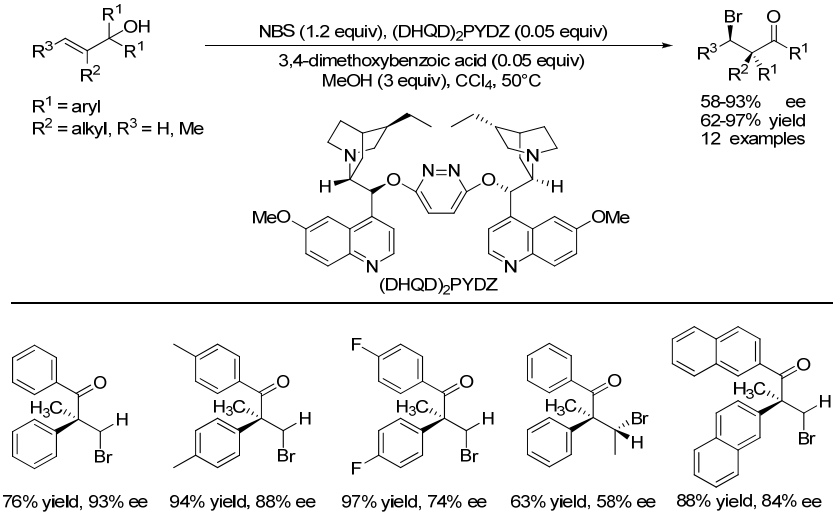


Scheme 7 $(DHQ)_2PYR$ and $(DHQD)_2PYR$-Catalyzed Bromination / Rearrangement

In comparison of Cl^+-induced reaction with the Br^+-induced one (Schemes 6 and 7), both reactions worked well under the catalysis of $(DHQ)_2PYR$ and $(DHQD)_2PYR$. As the chlorinating reagent used showed stronger electrophilicity than the brominating reagent, the former-induced rearrangement should be carried out at lower temperature (-50 to -70°C) so as to avoid the background reaction, but still gave a little lower selectivity and yield. While the latter could be set up at higher temperature (-20 °C) and provided higher selectivity. Overall,

the Br^+-induced asymmetric rearrangement was easier to handle than the Cl^+-induced one.

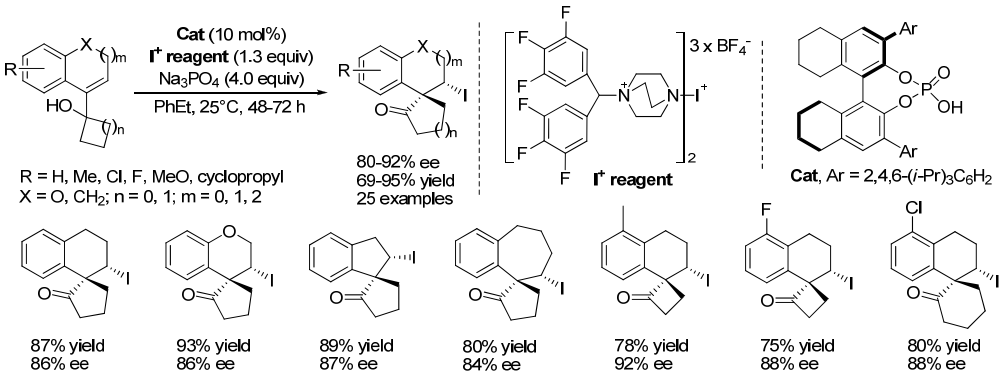
Based on the above analysis and successful experience, we went back to re-examine the more challenging reaction for constructing the β-bromo-ketones with all-carbon quaternary center using the less reactive allylic alcohol substrate bearing tri-carbon-substituted C=C bond as illustrated in Scheme 8. The optimization of reaction conditions demonstrated that using the bis-quinine derivative $(DHQD)_2PYDZ$ as catalyst, NBS as Br^+ reagent and 3,4-dimethoxybenzoic acid as additive could promote the asymmetric bromination/ rearrangement in good ee (58-93%) and yields (62-97%).[11] This protocol showed much better enantioselectivity than our previous one using stoichiometric quinine as promoter (Scheme 3), but still required much higher reaction temperature (50 °C) and longer time (72 h) than that one using the reactive enol ether-type allylic alcohol substrate (Scheme 7).



Scheme 8 Bromination / Rearrangement for Constructing All-Carbon-Quaternary Center

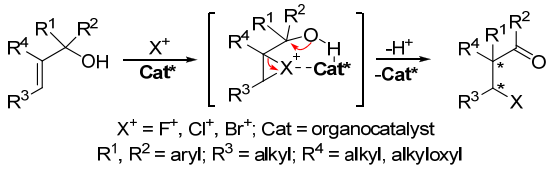
Nearly at the same time, Hennecke and co-workers also reported a similar asymmetric bromination/ rearrangement of cyclic allylic tertiary alcohols with inactivated C=C bonds,[12] which was feasible by using $(DHQD)_2Pyr$ (5 mol%) as catalyst and NBAc (1.2 equiv) as Br^+ source in basic medium (10% Na_2CO_3) at -15°C to room temperature, providing the desired products with up to 90% ee and 91% yield.

As for the iodination-induced semipinacol rearrangement, only one protocol has been reported to date. Based on their previous results in asymmetric fluorination / semipinacol rearrangement, Alexakis and co-workers further investigated an iodination reagent-induced variant (Scheme 9).[13] Interestingly, this reaction only afforded a single diastereomer regardless of the catalysts used, which was different from their previous results. Besides, proper structure modification of the DABCO-derived iodination reagent was crucial for its reactivity as well as the expected enantioselectivity. Further optimization revealed that the use of a H_8-BINOL derived phosphoric acid and Na_3PO_4 could give the best result in ethylbezene at 25 ºC. And the reaction conditions could be applied to broader substrate scope compared to the one in Scheme 5. And various three-membered and four-membered allylic alcohols with different substituents on the phenyl ring could be transformed to corresponding chiral β–iodo spiroketones in good to excellent ee (80-92%) and yield (69-95%) (Scheme 9).



Scheme 9 Chiral Phosphoric Acid-Catalyzed Iodonation / Rearrangement

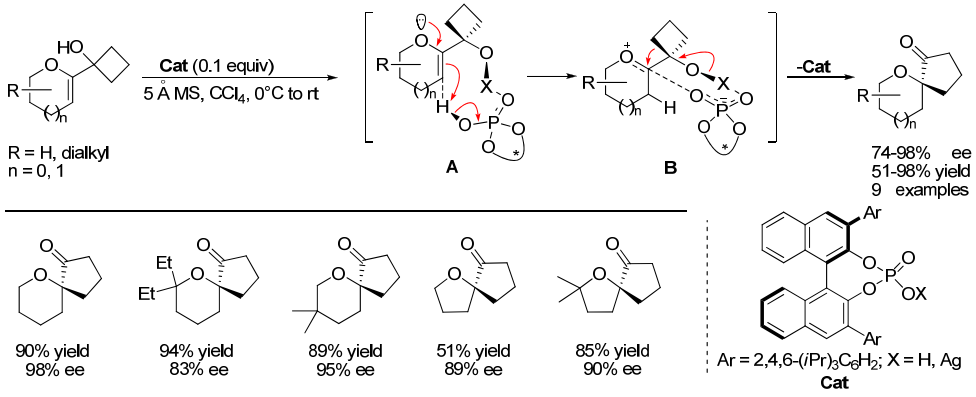
In summary, the organocatalytic asymmetric halogenations / semipinacol rearrangement of allylic alcohols has received much more attention in recent years. Among the F^+, Cl^+, Br^+ and I^+ sources, Br^+-induced rearrangement provided the best enantioselectivities and isolated yields, then the Cl^+-induced, F^+-induced and I^+-induced reactions in turn. The enol ether-type allylic alcohol substrates showed higher reactivity than those with non-activated C=C bonds. However, all reactions were limited to the substrates with high migration aptitude moieties or motifs that can better stabilize the carbenium ion intermediate. As for the exact stereo-controlling mechanism for reaction in Schemes 4, 6, 7 and 8, there was still no direct evidence to provide. A preliminary proposal was that the halogenium ion X^+ and OH of substrate were initially coordinated respectively with the N-atom(s) of chiral organocatalyst. Then the X^+ took a stereo-specified electrophilic addition to the C=C bond of allylic alcohol to form a chiral halonium ion intermediate (illustrated in Scheme 10), which further underwent the stereo-controlled 1,2-migration. During this process, a suitable basic or acidic additive, depending upon certain reaction system, played a role for improvement of selectivity, yield and / or reaction speed.[14] Currently, the catalytic asymmetric iodination / semipinacol rearrangement is undergoing in our group.



Scheme 10 Proposed Stereo-Controlling Process of Halogenation / Rearrangement

Organocatalytic or Metal-Catalyzed Rearrangement of Allylic Alcohol

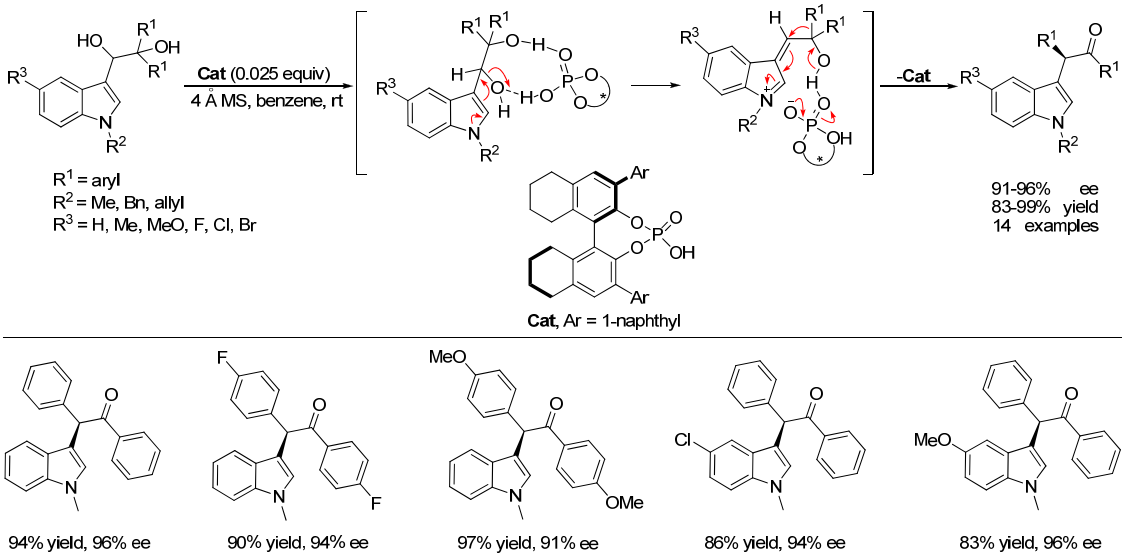
The proton of Brønsted acids has been used as one of the most suitable electrophiles for promoting semipinacol rearrangements over a hundred years ago.[15] However, the proton-catalyzed asymmetric version has not been accessible until the recent emerging of the chiral Brønsted acids.[16] One typical type of the chiral Brønsted acids widely used was the BINOL-derived phosphoric acid.[17] Our initial effort toward this asymmetric rearrangement focused on preparing and screening various 3,3′-disubstituted BINOL-phosphoric acids. Additionally, in light of the chiral counterion strategy proposed by Toste,[18] corresponding less acidic silver salts were also synthesized and tested. As a result, the 3,3′-di(2″,4″,6″-triisopropylphenyl)-substituted BINOL-phosphoric acid or its silver (I) salt proved to be effective for the ring expansion-type rearrangement of active enolate-type allylic cyclobutanols,[19] producing a series of spiroethers in very good enantioselectivities (74-98% ee) as well as yields (51-98%) (Scheme 11). We proposed that such an excellent stereoselectivity was possibly attributed to a double hydrogen-bonding interaction between substrate and catalyst, as illustrated in states **A** and **B** in Scheme 11.[20] It should be noted that additional silver-proton exchange process might exist prior to the state **A** for the silver salt catalyst.[19] This method provided an alternative powerful synthetic approach to chiral spiroether ketones.[21]



Scheme 11 Phosphoric Acid-Catalyzed Rearrangement of Allylic Alcohol

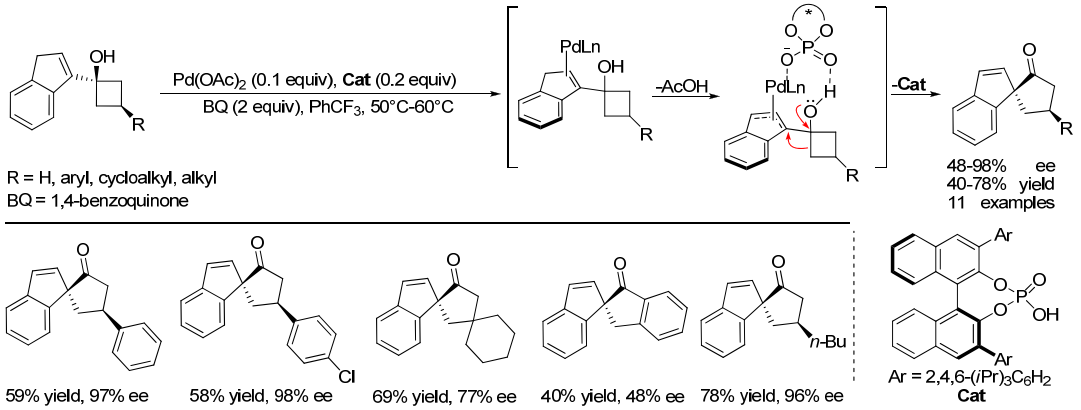
As for the catalytic asymmetric pinacol rearrangement of 1,2-diols, it was indeed much more difficult to access than the semipinacol-type rearrangement because of the likelihood of unselective carbocation formations and group migrations during reaction process, which would led to the formation of undesired products. To address this issue, a special substrate design was thus necessary for directing the expected regioselectivity. By designing a 1,2-diol connected to β-position of indole, Antilla and co-workers performed the Brønsted acid-catalyzed regioselective asymmetric pinacol rearrangement (Scheme 12).[22] During this process, the formation of expected carbocation could be favorably stabilized by resonance with

iminium ion of indole. With this concept, the use of H_8-BINOL-based chiral phosphoric acid as catalyst initiated the predicted asymmetric rearrangement in excellent ee values (91-96%) as well as isolated yields (83-99%). A double hydrogen-bonding interaction in reaction process was also proposed for the stereo-controlling step. This approach might provide an alternative strategy for the synthesis of chiral 3-substituted indole-type alkaloids.



Scheme 12 Phosphoric Acid-Catalyzed Asymmetric Piancol Rearrangement

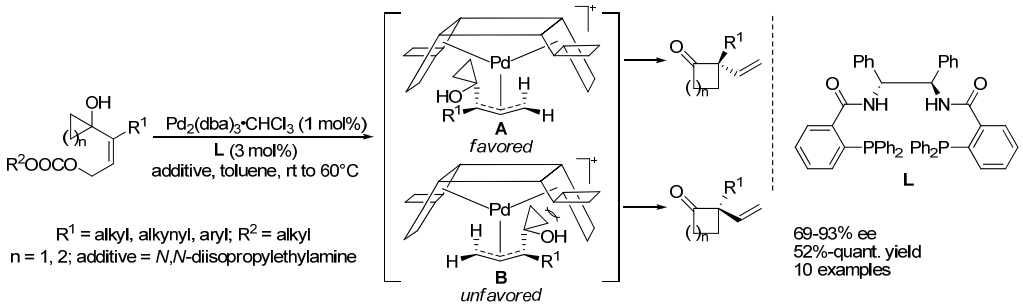
It also should be mentioned in this subtopic that an oxidative Brønsted acid catalyzed enantioselective C-H activation / semipinacol rearrangement of allylic alcohol was realized by Rainey and Chai (Scheme 13).[23] In this approach, when the indene-type allyl cyclobutanols was treated with 3,3′-di(2″,4″,6″-triisopropylphenyl)-substituted BINOL-phosphoric acid / $Pd(OAc)_2$ / 1,4-benzoquinone (BQ) system at heating temperature (50-60ºC), an oxidative rearrangement took place, generating the chiral indene-spiroketones in very good enantioselectivities (48-98% ee) and moderate yields (40-78%) in most cases. This method showed promising synthetic potential for the spiroketone-containing natural molecules and chiral ligands.[24] Furthermore, a deuterium labeling experiment indicated that the transition metal species $Pd(OAc)_2$, instead of the proton of phosphoric acid catalyst, coordinated first with the double bond of allyl moiety. Subsequently, a Pd-π allyl complex was formed through an allylic proton eliminated to form AcOH. This cationic allyl complex under coordination of chiral phosphoric acid induced a ring expansion-type rearrangement of the cyclobutanol moiety to give the spiroketones. The released Pd(0) species was then reoxidized by BQ back to Pd(II) to complete the catalysis cycle.



Scheme 13 Phosphoric Acid and $Pd(OAc)_2$-Catalyzed Oxidative Semipinacol Rearrangement

Besides the chiral phosphoric acid, some other chiral ligand modified Pd(0) complex also could catalyze the asymmetric semipinacol rearrangement of allylic cycloalcohols, also categorized as Wagner-Meerwein shift. Early in 2001,[25] Trost and co-workers reported that the complex of Pd(0) with Trost's ligand **L** could catalyze a selective ring expansion-type semipinacol rearrangements of allylic cycloalkanols, yielding the chiral α-alkyl-α-vinyl cycloketones (Scheme 14). In this reaction, after the carbonate ester group $R'OCO_2^-$ was eliminated, the resulting Pd-complexed allyl carbocation

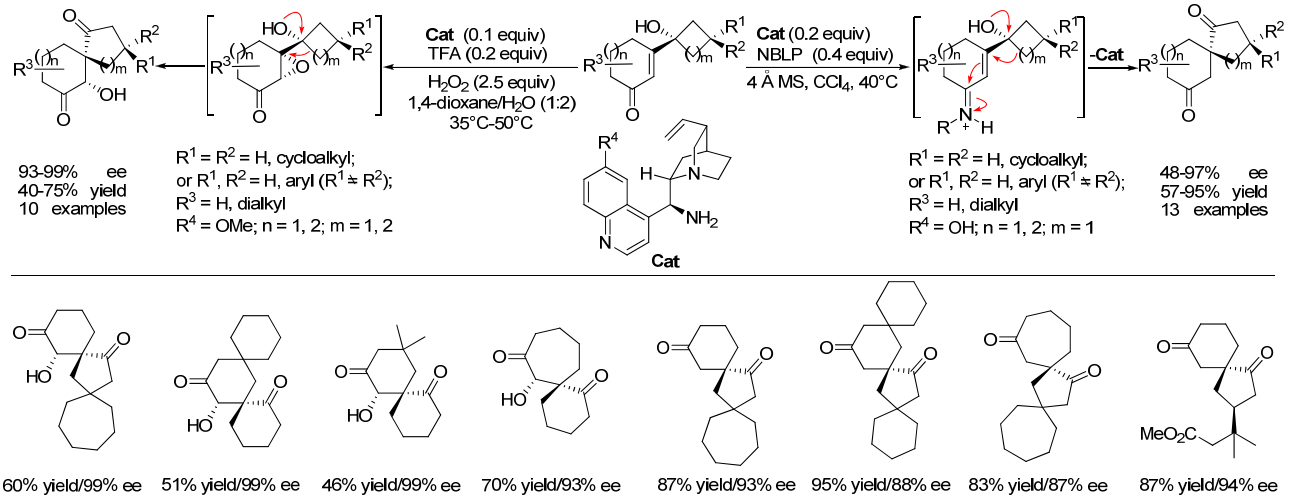
underwent a ring-expansion of cycloalkanols to produce the ring-expanded cycloketones. The stereospecification could be understood at the stage of two possible Pd-π allyl coordinate transition states **A** or **B**. Because of the steric hindrance in **B**, reaction preferred to take state **A** and led to the formation of predominant (*S*)-products. As a result, a series of chiral α-alkyl-α-vinyl cyclobutanones and cyclopentanones were obtained in 69-93% ee as well as 52%-quantitive yields.



Scheme 14 Pd(0)-Catalyzed Asymmetric Rearrangement of Allylic Alcohols

Organocatalytic Rearrangement and Epoxidation / Rearrangement of Vinylogous α-Ketols

With the emerging of organocatalysis concept,[26] asymmetric epoxidation[27] and aziridination[28] of α,β-unsaturated aldehydes or ketones have been accomplished through the catalysis with chiral amine, which generally involved a formation of iminium-enamine intermediate as key stereo-controlling step. Inspired by this background, we speculated that if an α,β-enone was designed to connect with a tertiary alcohol, such a vinylogous α-ket-*tert*-ol substrate, when subjected to chiral amine catalysis condition in acidic medium, would generate a cationic iminium intermediate, which subsequently induced a stereo-specified semipinacol rearrangement. To achieve this, a systematic optimization of substrates, amine catalysts and reaction conditions was performed. Fortunately, the quinine derivative catalyst in acidic medium (NBLP) enabled the desired asymmetric ring-expansion-type rearrangement of the cyclic vinylogous α-ket-*tert*-ols, providing various spirocyclic 1,4-diones in very good enantioselectivities (48-97% ee) as well as yields (57-95%) in most cases (Scheme 15, right half).[2] This transformation established a novel and highly efficient synthetic approach to chiral poly-spirocycle systems.[29]



Scheme 15 Rearrangement and Epoxidation /Rearrangement of Vinylogous α-Ketol

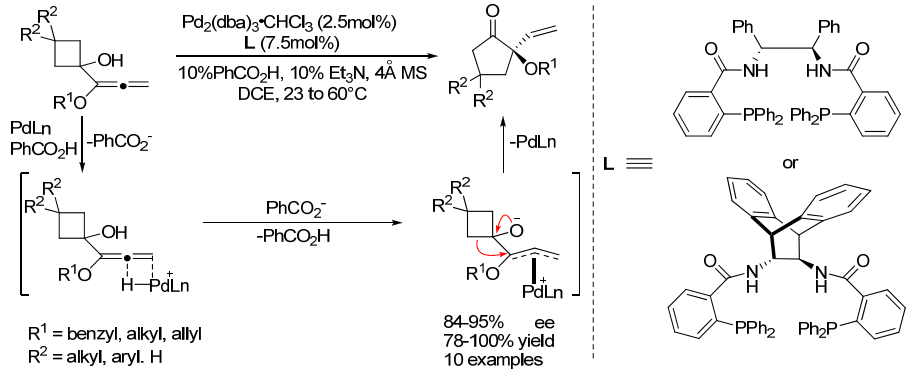
Since the ring-opening / rearrangement of epoxide has been extensively investigated in our group for efficiently constructing the 1,3-disubstituted-2-quaternary motifs,[30] we then turned to perform a one-pot asymmetric epoxidation / rearrangement of vinylogous α-ketol for synthesizing the chiral spirocycles with three oxygen-containing functional groups (Scheme 15, left half). Such a more complex product would possess more significant utilities for synthesis of both natural products and chiral ligands, for example the spirocyclo-1,3-diol.[30b,31] Accordingly, a range of vinylogous α-ket-*tert*-ol substrates were subjected to the organocatalyzed epoxidation with H_2O_2 / **Cat** in acidic (TFA) dioxane solvent, followed by addition of large amount of water / TFA, yielding the spirocycles in excellent enantioselectivities (93-99% ee) and

moderate isolated yields (40-75%).[32] During this process, a strong acid like TFA was necessary for completion of the transformation. Otherwise, the desired rearrangement step was difficult to proceed continuously, and the reaction would give the epoxide intermediate as the major product, which could be isolated and identified with NMR spectroscopy.

Catalytic Asymmetric Rearrangement of Alkynyl and Allenyl Cycloalkanol

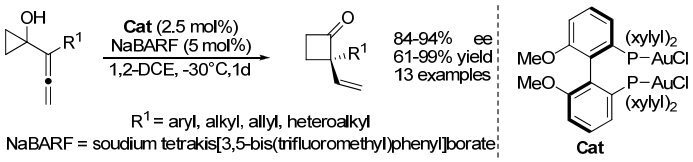
During the past two decades, transition metal complexes and their catalyzed reactions, especially those involving a 1,2-migratino process, have been an active field of chemistry due to their unique and diverse properties.[33] Normally the carbon-carbon double and triple bonds of allenyl and alkynyl tertiary cycloalkanols can easily coordinate with transition metal, which then generates a carbocation and thus induces the ring-expansion of the cycloalkanol moiety (also categorized as Wagner-Meewein shift by Trost and Toste). The products formed here are a sort of synthetically useful α-alkyl (or hetero) vinyl cycloalkanones. This section describes three kinds of related asymmetric protocols.

Following the earlier success in Pd(0) complex-catalyzed asymmetric Wager-Meewein shift of allylic cycloalkanols (Scheme 14),[25] Trost's group further performed a similar catalytic asymmetric reaction of alkyloxyallenyl cyclobutanols by screening Pd(0) complex derived from the Trost's ligands **L** (Scheme 16).[34] This process involved the formation of a π-allyl palladium cation intermediate and then a ring expansion-type rearrangement. Like what they have observed before,[35] both acid (10% $PhCO_2H$) and base (10% Et_3N) as additives played a role for achieving the good reactivity and selectivity of this transformation. The key enantio-controlling was carried out at the π-allylpalladium cation stage which could be illustrated in the similar manner as state **A** in Scheme 12. Accordingly, a series of substrates with varying alkyloxyls and substituents at cyclobutyl motif could rearrange to corresponding chiral α-alkyloxyvinyl cyclopentanones in 84-95 % ee and up to quantitative yield (Scheme 16).



Scheme 16 Pd(0)-Catalyzed Asymmetric Rearrangement of Alkyloxyallenyl Cyclobutanols

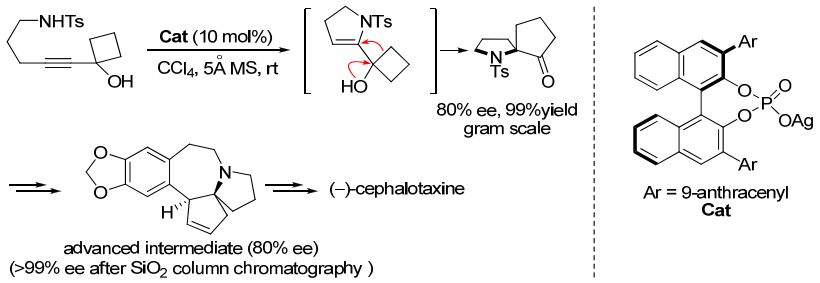
By using the chiral phosphine ligand-modified gold(I) complex, the cationic (R)-MeO-DM-BIPHEP$(AuCl)_2$, Toste and co- workers accomplished the catalytic asymmetric ring expansion-type rearrangement of a range of alkylallenyl cyclopropanols, providing the chiral α-alkylvinyl cyclobutanones, the similar type of products Trost reported in Scheme 14,[25] in synthetically useful yields (61-99%) and good to excellent enantioselectivities (84-94% ee) (Scheme 17).[36] In this transformation, because of the use of an electrophilic gold reagent, no extra proton from acid additive like the reaction in Scheme 16 was required. Accordingly an initial coordination of gold complex with the C=C bond of allene was proposed, and further induced ring expansion of cyclopropanol. Following that, a proton was released from OH of cyclopropanol to replace the gold complex. Notably, this reaction could tolerate both aliphatic R^1 with hetero atoms or C=C bond, and aromatic one bearing either electron rich or deficient substituents. Moreover, the reaction could be operated under air and / or moisture condition, which made this method suitable for the scalable synthesis of cyclobutane derivatives.



Scheme 17 Au(I) Complex-Catalyzed Rearrangement of Alkylallenyl Cyclopropanols

In the course of our synthetic study of the anti-cancer active alkaloid cephalotaxine, we have developed a novel formal synthetic approach by exploring a key tandem hydroamination / enantioselective semipinacol rearrangement of amino-propargyl

cyclobutanol,[37] which provided an efficient access to the chiral 1-aza-spiro[4.4]nonan-6-one intermediate.[38] After screening of the chiral catalysts, amino-protecting groups and reaction conditions, a Ag(I) salt of (*S*)-3,3′-dianthracenyl BINOL-derived phosphoric acid (10 mol%) has been proved to enable this catalytic asymmetric reaction, providing 1-aza-spiroketone intermediate in 80% ee and 99% isolated yield on a gram scale (Scheme 18). Subsequently, few conventional transformations of the 1-aza-spiroketone afforded the advanced pentacyclic intermediate with 80% ee, which could be converted to the target cephalotaxine following the literature report.[38] Interestingly, the optical purity of this intermediate could be increased to 99% ee simply by a double enantiomer enrichment through achiral silica gel chromatography.[39]

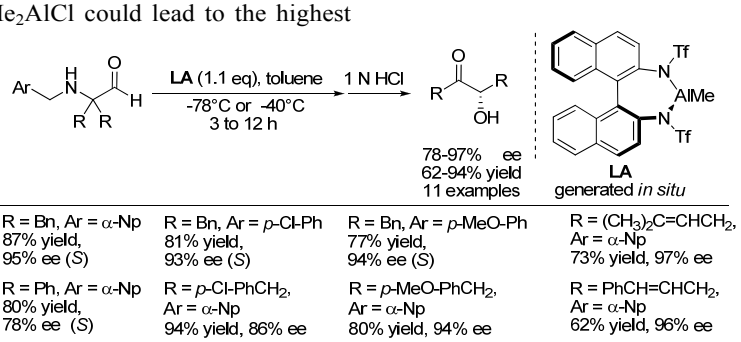


Scheme 18 Ag(I)-Catalyzed Rearrangement of Alkynyl Cyclobutanol and Synthetic Application

Lewis Acid-Catalyzed Rearrangement of α-Hydroxy and α-Amino Aldehydes

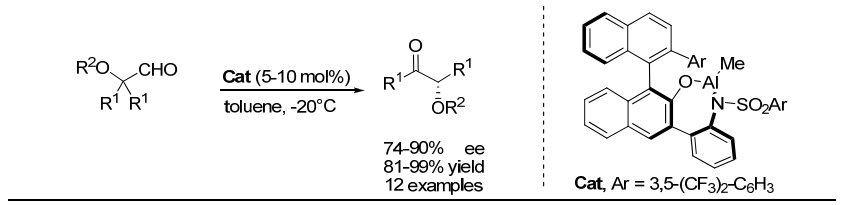
The α-ketol rearrangement (acyloin rearrangement) was also a class of 1,2-carbon migration reactions.[40] As one of the typical promoters, certain Lewis acid also could complex with carbonyl of the α,α-disubstituted-α- amino or hydroxy aldehyde to generate an α-carbocation amine or alcohol intermediate, which further underwent a semipinacol-like rearrangement to give the α-imino alcohol or α-hydroxy ketone. The former product could be readily converted to α-hydroxy ketone through *in situ* hydrolysis. Although the existence of two contiguously functional groups was favorable for asymmetric induction through coordination with chiral promoter, it was not until the beginning of this century that Maruoka and co-workers had succeeded in the first asymmetric version of this rearrangement type.[41] Since this transformation was a reversible process, the migration pattern largely depended on the substrate structure and reaction conditions, which were the main factor for performing the asymmetric version.

Initially, Maruoka examined a racemic rearrangement of *N*-benzyl-α,α-dibenzyl-α-amino aldehyde using several common Lewis acids, among which Me_2AlCl could lead to the highest yield (94%) of α-ketol. Then asymmetric rearrangement was accomplished under the catalysis of corresponding chiral organoaluminum Lewis acid, which was derived from the reaction of $AlMe_3$ and (*S*)-2,2'-di-(trifluoro-methanesulfonyl-amino)-1,1'-binaphthyl (Scheme 19).[42] As a result, a series of *N*-mono and α-di substituted α-amino aldehydes could be subjected to this asymmetric reaction in toluene at -78 to -40°C, providing corresponding α-ketols[43] in up to 97% ee and 94% yield. This rearrangement could tolerate a wide scope of substrates with both EWG and EDG-benzyl or allyl at *N*- or α-position, respectively. And both group R and substituent attached to nitrogen could significantly affect the reactivity and enantioselectivity of this transformation. Additionally, the existence of the zwitterionic iminium intermediate was confirmed by the ^{1}HNMR spectroscopy monitoring of the reaction process. Based on this observation, the key intermediate for pharmaceutically active compounds, *anti* 2-hydroxy-3-amino-1,4-diphenylbutane, was prepared readily with 95% ee and 90% yield by direct DIBAL-reduction of the *in situ* generated iminium intermediate.[44] However, it should be noticed that this asymmetric transformation required stoichiometric amount of the chiral Lewis acid (1.1 equiv).



Scheme 19 Lewis Acid-Promoted Rearrangement of α-Amino Aldehydes

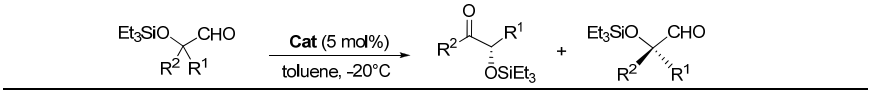
Subsequently, Maruoka's group further improved this protocol and accomplished the catalytically effective asymmetric rearrangement of α,α-disubstituted 2-silyloxyacetaldehyde under chiral organoaluminum catalysis.[45] To achieve this, Maruoka and co-workers designed another chiral organoaluminum catalyst, which was prepared *in situ* from $AlMe_3$ and the chiral amino alcohol ligand with the novel di-aryl-substituted binaphthyl framework (Scheme 20) in toluene at room temperature. Under the optimal catalytic (5-10 mol%) conditions, a series of α-trialkylsiloxy α,α-dialkyl-aldehydes rearranged smoothly, providing the chiral α-trialkylsiloxy ketones with up to 90% ee and 99% yield. This transformation represented a useful and highly efficient strategy for the syntheses of different α-ketols with high optical purities from tertiary α-hydroxy aldehydes. Furthermore, this rearrangement could tolerate the substrates with the simpler migrating alkyl groups, such as isobutyl and cyclohexyl.

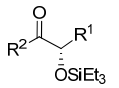
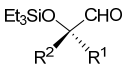


R^1 = Bn; R^2 = Me_3Si 96% yield, 77% ee	R^1 = Bn; R^2 = Et_3Si 99% yield, 87% ee	R^1 = *p*-MeO-$C_6H_4CH_2$; R^2 = Et_3Si 98% yield, 85% ee
R^1 = *c*-Hex; R^2 = Et_3Si 97% yield, 74% ee	R^1 = *p*-F-$C_6H_4CH_2$; R^2 = Et_3Si 97% yield, 90% ee	R^1 = *trans*-PhCH=$CHCH_2$; R^2 = Et_3Si 81% yield, 83% ee

Scheme 20 Catalytic Asymmetric Rearrangement of α-Siloxy Aldehydes

By the use of this protocol, the kinetic resolution of racemic α-siloxy aldehydes were also realized, leading to the chiral α-siloxy aldehydes and ketones with good ee values (Scheme 21).[45]



	R^1 = Bn R^2 = Ph	R^1 = Bn R^2 = *p*-F-Ph	R^1 = Bn R^2 = *p*-Me-Ph	R^1 = Bn R^2 = *c*-Hex	R^1 = *trans*-PhCh=$CHCH_2$ R^2 = Ph
	49% yield, 86% ee	49% yield, 86% ee	51% yield, 85% ee	55% yield, 77% ee	57% yield, 63% ee
	51% yield, 84% ee	51% yield, 85% ee	49% yield, 83% ee	44% yield, 88% ee	43% yield, 90% ee

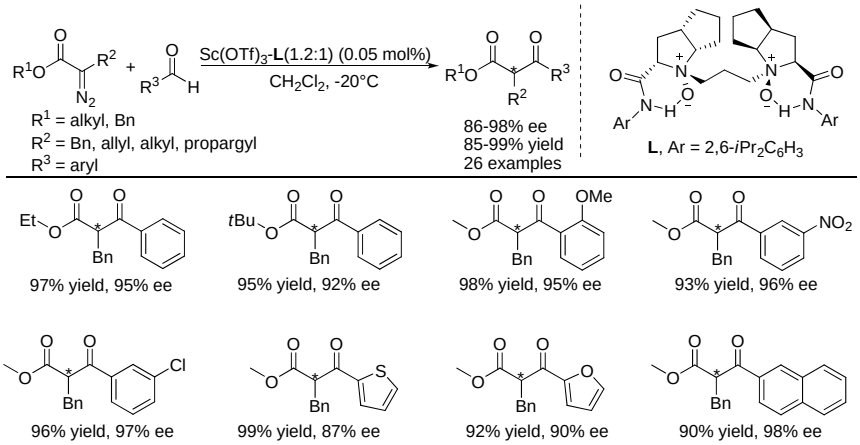
Scheme 21 Asymmetric Kinetic Resolution of α-Siloxy Aldehydes

Lewis Acid-Catalyzed Rearrangement of α-Diazo Alcohols

The α-diazo alcohol, an *in situ* formed adduct of diazo compound with aldehyde or ketone in the presence of Lewis acid, also could generate an α-hydroxy carbocation species, which then took a 1,2-carbon-to-carbon rearrangements providing structurally more complex ketone after the releasing of N_2. The process involved formally an insertion of diazo-connected carbon into C-H of aldehyde or C-C of ketone. This transformation generally was known as Tiffeneau-Demjanov rearrangement,[46] or Roskamp reaction for intermolecular fashion.[47,48] Since this rearrangement could lead to the product with a newly formed stereocenter, use of chiral catalyst may result in the establishment of corresponding chiral stereocenter.[49] For a long time, however, this rearrangement has been used mainly in racemic version.[50] There were two major reasons why its asymmetric version was difficult to access. The first was the chemoselectivity because of multiple possibilities of group migration patterns. The second was the easy racemization of the newly formed stereogenic center at α-position of carbonyl. Recently it has become possible to achieve the enantioselectivity of this kind of rearrangements as some novel chiral Lewis acids with particular stereoselectivity have been explored. In this section three kinds of representative catalytic systems were described.

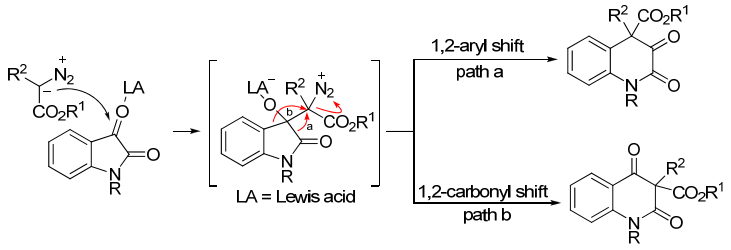
Feng's group first reported such a catalytic asymmetric addition / rearrangement reaction of α-alkyl-α-diazoesters with aromatic aldehydes.[51] After extensive screening of the reaction conditions, a promising Lewis acid $Sc(OTf)_3$ modified with novel and highly efficient dipole ligand developed by Feng's group[52] was used successfully to catalyze the asymmetric Roskamp reaction, providing excellent chemoselectivity, chemical yield (85-99%) as well as enantioselectivities (86-98%ee) (Scheme 22). Importantly, this reaction could be operated in gram scale without affecting the yield and

enantioselectivity. However, the use of aliphatic and α,β-unsaturated aldehydes (R^3 = alkyl, alkenyl) gave poor results, and the racemization of products was also observed during chromatography on silica gel. In 2012, Ryu's group also reported a similar type of transformations by the use of oxazaborolidinium catalyst, which further expanded the substrate scope with aliphatic aldehydes.[53]



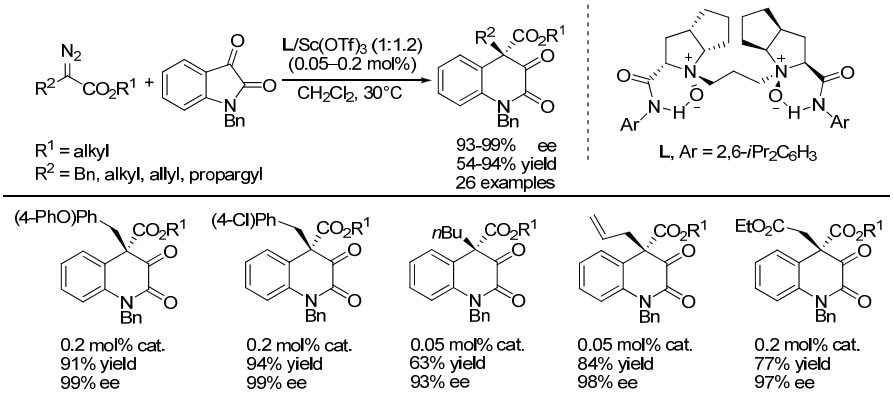
Scheme 22 Lewis Acid-Catalyzed Addition/ Rearrangement of Aldehydes with Diazoesters

Besides, Feng's group also investigated an asymmetric aryl and carbonyl 1,2-migration reaction of isatins with α-alkyl-α-diazoesters via the catalysis of the same chiral Sc(III)-complex above.[54] As shown in Scheme 23, because of the intrinsic structure feature of the isatins, a competition migration between aryl and carbonyl became possible. In order to achieve both good regioselectivity and enantioselectivity, choice of suitable catalytic system was crucial.



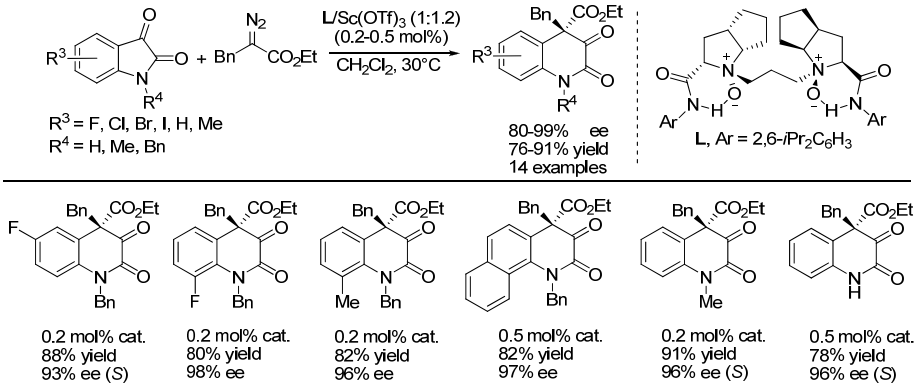
Scheme 23 Competing Migration Patterns between Aryl and Carbonyl

As indicated in Schemes 24/25,[54] under the same catalysis conditions as above (Scheme 22) the reaction took place dominantly in an aryl migration pattern and generated the 2,3-dicarbonyl-4-quaternary tetrahydroquinoline derivatives in both high yields and enantioselectivities. While the byproducts formed through carbonyl migration were obtained only in low yield, indicating aryl group had a stronger migration aptitude than carbonyl under this condition. Importantly, this reaction showed very broad substrate scope. For example, a large number of α-alkyl-α-diazoesters, with various R^2 groups like benzyl, propyl, allyl and propargyl, could give moderate to high yields (54-94%) and excellent ee (93-99%) (Scheme 24).



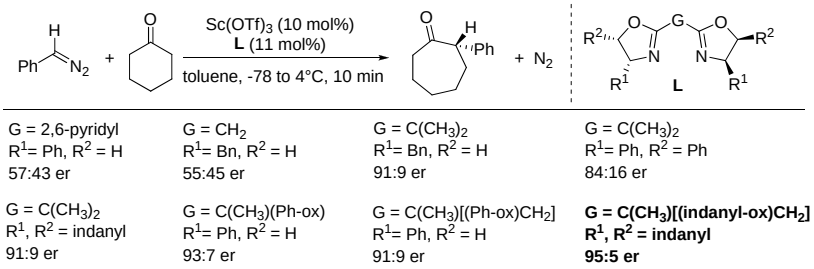
Scheme 24 Scope of α-Diazoesters in Addition/Ring Expansion with Isatins

While for the scope of substituted isatins,[54] the results showed some variations (Schemes 25). Though the electronic effect of substituent R^3 at aromatic ring didn't affect the reaction significantly, its location did affect the enantioselectivity and reactivity. For example, 5-substituted substrates clearly gave lower enantioselectivity (80-93% ee) than those with substituents at C6 and C7 positions (96-99% ee). Furthermore, switching the *N*-protecting group R^4 from Bn to Me or H didn't clearly vary the enantioselectivity. Overall, this reaction provided a promising method for synthesis of 4-quaternary 2-quinolones.



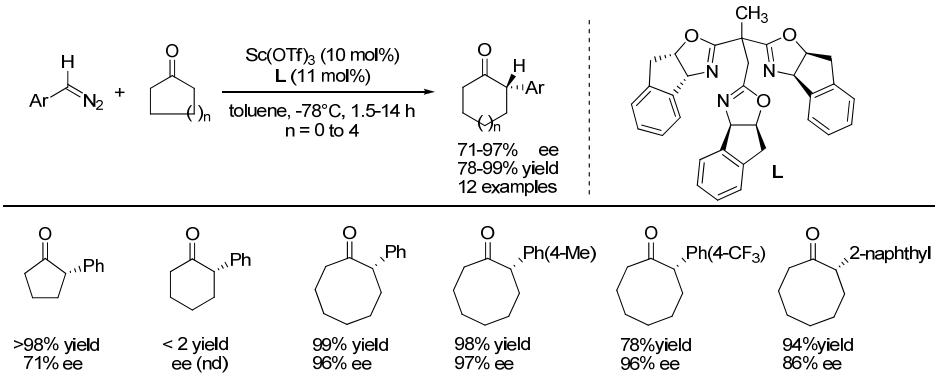
Scheme 25 Scope of Isatins in Addition/Ring Expansion with Diazoesters

Kingsbury and co-workers also accomplished such an enantioselective addition / rearrangement of α-aryldiazoalkane and cycloketone using tris(oxazoline)-modified[55] Sc(III) complex as catalyst.[56] This catalyst could be prepared *in situ* with a slight excess of chiral ligand. Screening of reaction conditions indicated that the structure of the linker G of ligand could vary the acidity of the complex and thus affect the stereoselectivity of the reaction (Scheme 26). Further experiments indicated that using tris(oxazoline) as ligand and toluene as solvent could accomplish this asymmetric transformation with the best results at -78°C. In addition, the presence of moisture would lower the selectivity of this reaction, which was confirmed by NMR study of the catalyst solution.



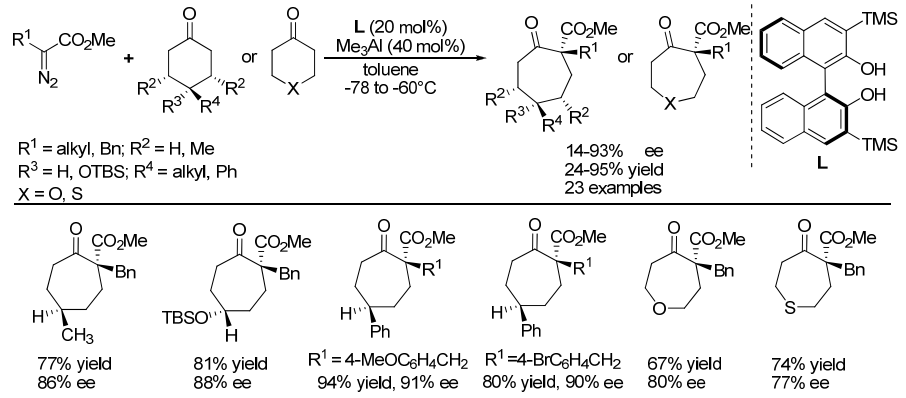
Scheme 26 Screening of Ligand for Ring-Expansion of Cycloketones

During the further substrate scope investigations, the cycloketone structure demonstrated to clearly influence the enantioselectivity of the reaction. Although the initial use of cyclobutanone led to only moderate ee value (71%), this result was still of value because the product normally racemized on silica gel.[57] In addition, the reaction of cyclopentanone only gave trace amount of desired product due to that the mono-insertion product was more reactive than the starting material. Nevertheless, the cycloketones bearing six to nine-membered rings could smoothly react with several aryl diazomethanes to produce the desired ring-expanded products with excellent yield (78-99%) and ee (85-97%) regardless of the electronic and steric effect of the substituents at aryl group (Scheme 27). In addition, this reaction also proved to be scalable. However, this reaction did not well tolerate heteroaromatic diazomethane substrates, and results obtained showed low enantioselectivity, which was probably resulted from the disruption of the optimum geometry of the transition state caused by the coordination of the metal center with the heteroatom.



Scheme 27 Scope of Ring Expansion of Cycloketones with Diazoalkane

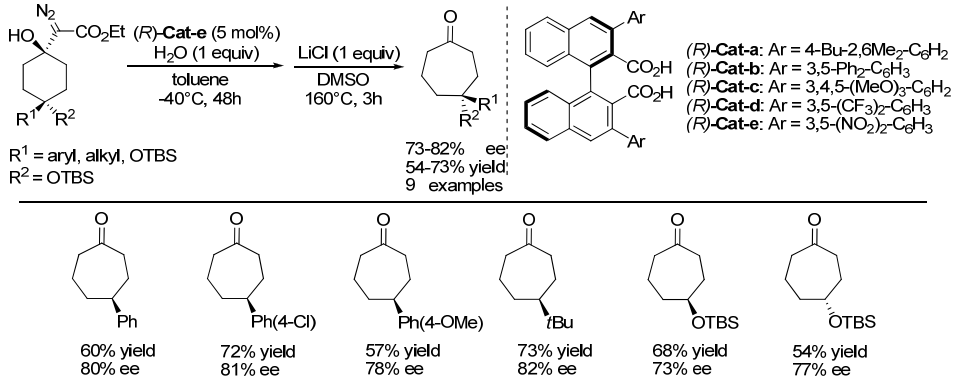
At the same time of Feng and Kingsbury's reports, Maruoka also developed an interesting asymmetric addition / ring expansion of cyclohexanones with α-diazo esters under the catalysis of chiral BINOL-modified Lewis acid.[58] After optimization, use of aluminum Lewis acid modified with chiral 3,3′-di-(trimethylsilyl)-BINOL[59] proved to be effective, with the ratio 2:1 of Me_3Al and BINOL derivative being the best. And the use of strong and hard Lewis acid was advantageous for the ring expansion. Consequently, a series of chiral cycloheptanone derivatives with an α-quaternary carbon could be efficiently furnished in up to 95% yield and 93% ee (Scheme 28). Furthermore, the substitute R^1 of α-diazo esters and the reaction temperature also were the key factors affecting the enantioselectivity, and the best result could be achieved with benzyl-type substitution at -78°C. Also, the cyclohexanone substrates with 4-substituent or 4-oxa or thio analogues were tolerable to this reaction, affording good to excellent yields (52-94%) and enantioselectivity (60-93% ee). However, 4-silyloxy cyclohexanone substrate resulted in a lower enantioselectivity and an opposite δ-stereochemistry of the product. Over all, this method offered a novel and applicable strategy for the synthesis of chiral substituted cycloheptanones.



Scheme 28 Asymmetric Ring Expansion of Cycloketones by Diazoesters

Following the above success, Maruoka and co-workers further attempted an intramolecular desymmetric ring-expansion rearrangement of cyclohexane-substituted β-hydroxy-α-diazo carbonate esters using chiral Brønsted acids as catalyst (Scheme 29).[60] This reaction was initiated by a key enantioselective protonation of C=N bond, forming actually a β-hydroxy diazonium cation species.[61] Subsequent stereo-controlled ring expansion of the cyclohexane moiety followed by a decarboxylation gave the chiral cycloheptanone. Reaction condition optimization indicated that this reaction was clearly affected by the catalyst, solvent and reaction temperature. Among the axially chiral catalysts screened, the sterically hindered binaphthyl carboxylic acid with 3,3′-di(3,5-dinitrophenyl) substituents could afford the best result in toluene at -40°C. Interestingly, the existence of stoichiometric amount of water was favorable to obtain the high and reproducible stereoselectivity, which was further supported by the adverse effect caused by adding molecular sieves. By the use of this method, a variety of substrates with *cis*-substituents R, such as aryl, alkyl or siloxyl group, could rearrange to the desired cycloheptanones in moderate yield (57-73%) and good ee (73-82%). While the *trans*- substrates showed the discrepant results between the 4-OTBS and 4-phenyl substitutions. The former gave 77% ee and 54% yield with the opposite

stereochemistry, but the latter was inert under the standard conditions, which might be worth to further investigate.

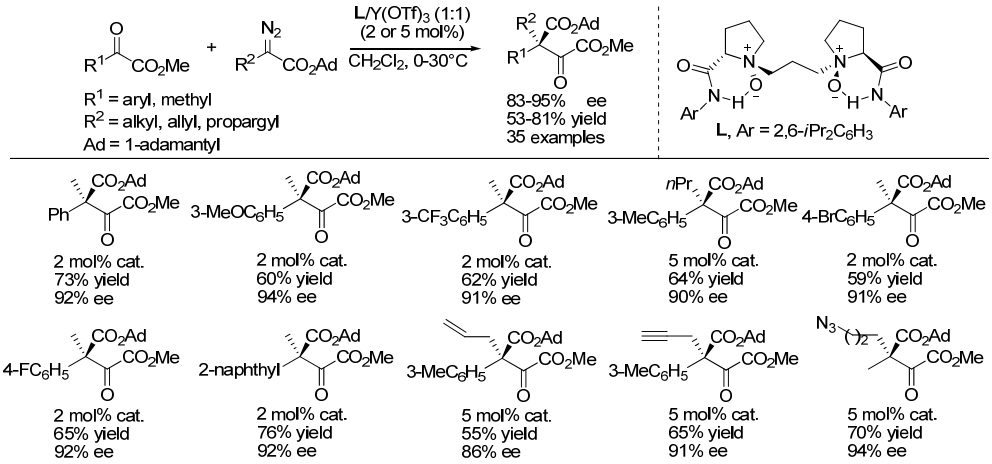


Scheme 29 Asymmetric Ring Expansion of Cyclic β-Hydroxy-α-Diazo Esters

In 2013, Feng and co-workers further extended the scope of this type of asymmetric protocol to acyclic ketones with an ester group (Scheme 30).[62] Different from their previous results, catalyst made from $Y(OTf)_3$ and L-proline derived dipole ligand gave the satisfactory results in CH_2Cl_2. Furthermore, the presence of a bulky group at the ester part of the α-diazoester substrate was also the key factor for the realization of good enantioselectivity and yield. Accordingly, a series of methyl or aryl substituted α–ketomethylester and 1-adamantyl α–diazoester with different substituents like alkyl, allyl and propargyl could be subjected to this reaction giving moderate to good yield (53-81%) and moderate to excellent ee (83-95% ee). Besides, this reaction can be carried out in gram scale, and it is not sensitive to air and moisture, which further expand its potential for future practical utility in the enantioselective synthesis of quaternary carbon containing compounds.

Conclusion

After years of assiduous efforts of several groups, great progress in developing catalytic asymmetric semipinacol rearrangement has been achieved. More and more asymmetric semipinacol rearrangement types and catalytic systems are emerging, and their application for synthesis of important organic molecules presents great potential and considerable prospect.



Scheme 30 Asymmetric Roskamp Reaction of Acyclic α–Ketomethylester

Acknowledgements

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Notes and references

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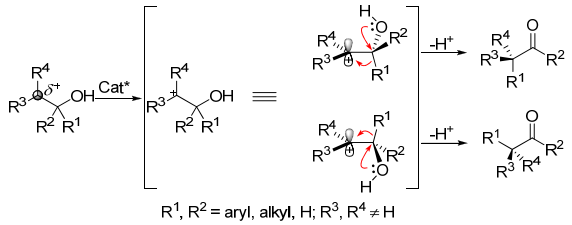
Table of Content entry:



Recent progressions of catalytic asymmetric semipinacol rearrangements are summarized in this Feature Article.