

Review

Recent Advances in Dynamic Kinetic Resolution by Chiral Bifunctional (Thio)urea- and Squaramide-Based Organocatalysts

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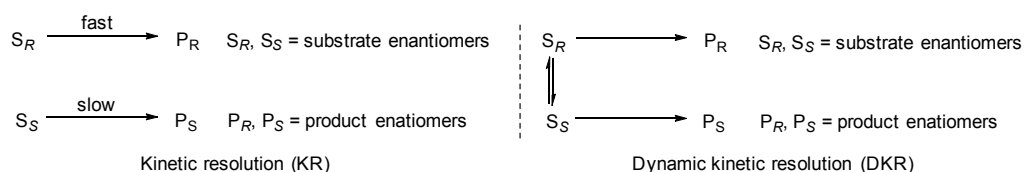
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Abstract: The organocatalysis-based dynamic kinetic resolution (DKR) process has proved to be a powerful strategy for the construction of chiral compounds. In this feature review, we summarized recent progress on the DKR process, which was promoted by chiral bifunctional (thio)urea and squaramide catalysis via hydrogen-bonding interactions between substrates and catalysts. A wide range of asymmetric reactions involving DKR, such as asymmetric alcoholysis of azlactones, asymmetric Michael–Michael cascade reaction, and enantioselective selenocyclization, are reviewed and demonstrate the efficiency of this strategy. The (thio)urea and squaramide catalysts with dual activation would be efficient for more unmet challenges in dynamic kinetic resolution.

Keywords: dynamic kinetic resolution; (thio)urea; squaramide

1. Introduction

The synthesis of optically pure compounds is increasingly in demand in the pharmaceutical, fine chemicals, and agriculture industries [1–8]. Resolution of racemates is one of the most important industrial approaches to obtain enantiomerically pure compounds [9,10]. Kinetic resolution (KR) is a process in which one of the enantiomers of a racemic mixture is transformed to the corresponding product faster than the other one (Scheme 1) [11–13]. If the KR process is efficient, one of the enantiomers of the racemic mixture is completely transformed to the desired product while the other remains unchanged. Therefore, the critical drawback of KR process is the maximum theoretical yield of 50%. The dynamic kinetic resolution (DKR) process is an attractive strategy without this limitation, which efficiently combines the process of KR and the racemization of the slowly reacting enantiomer in a one-pot system with 100% theoretical yield (Scheme 1) [14–20]. This powerful strategy has been widely applied to a great many asymmetric catalytic reactions for the access of chiral compounds [21–29].



Scheme 1. Kinetic resolution (KR) and dynamic kinetic resolution (DKR).

Asymmetric organocatalysis has been made significant advances in the last decades [30–32], and numerous asymmetric transformations were broadly applied to construct natural products [33] and industrial products [34]. Until now, various activation strategies have been developed, such as noncovalent catalysis via hydrogen-bonding [35], Brønsted base [36,37], Brønsted acid [38,39], phase transfer [40], and covalent catalysis via Lewis base [41]. Metal catalytic DKR has dominated in this research field during the end of the last century [42], and organocatalytic asymmetric reactions have reached maturity in recent years with impressive progress [43–52]. Among these chiral organocatalysts, chiral bifunctional (thio)ureas and squaramides catalysts have been intensively investigated to promote asymmetric reactions via dual hydrogen-bonding interactions which worked along with a Lewis acid functional group to achieve the activation of both the nucleophile and the electrophile [53]. Since the early research of primary amine–thiourea catalyzed the process of DKR in 2006 [54–56], DKR catalyzed by (thio)urea and squaramide has achieved tremendous advances [57–66]. The goal of the present review is to cover the recent developments concerning chiral (thio)ureas and squaramides (Figure 1) catalytic reactions through DKR. This review is subdivided into two sections according to the types of organocatalysts employed in these asymmetric reactions involving the process of DKR.

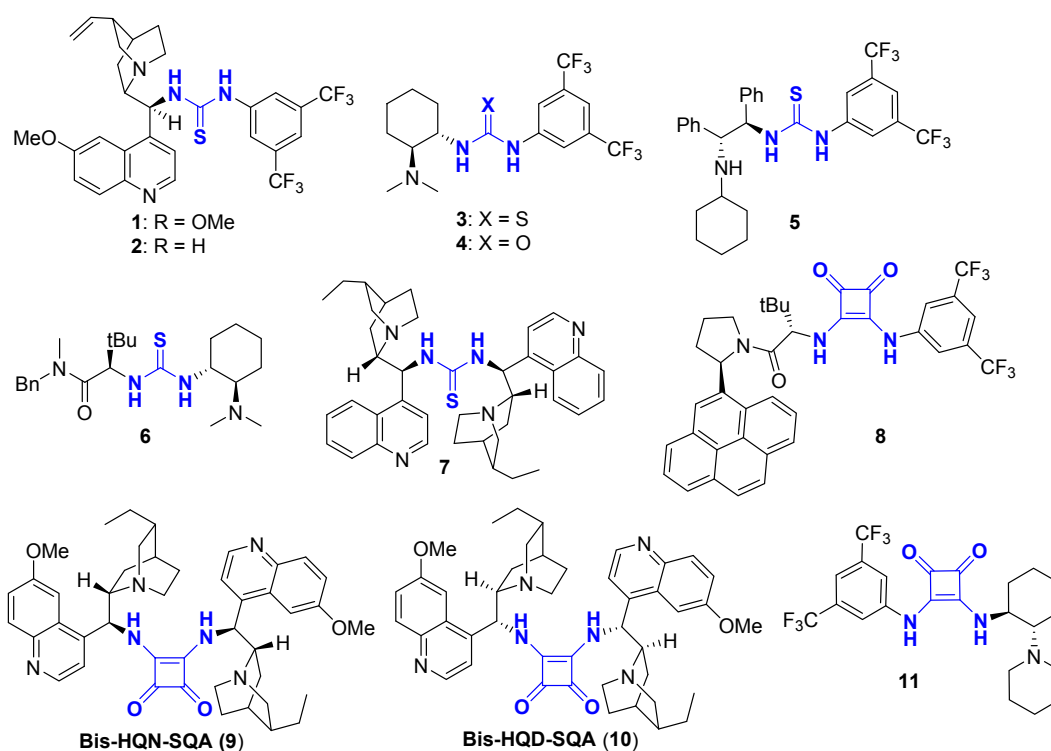
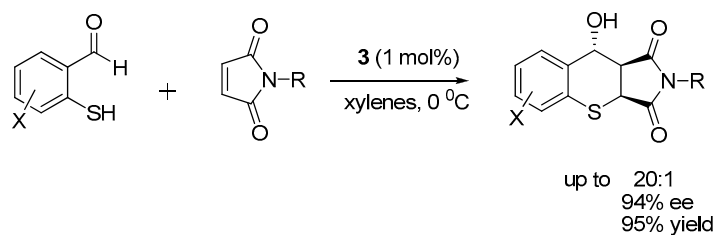


Figure 1. Selected reported representative (thio)urea and squaramide catalysts.

2. (Thio)urea Organocatalyst for DKR

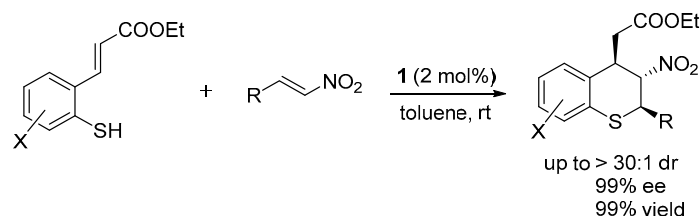
2.1. Thio-Michael–Michael Cascade Reaction

Asymmetric (thio)urea catalyzed Michael–Michael cascade reactions are one of the most powerful strategies for the efficient construction of chiral complex molecules with multiple bonds' formation and multistereogenic centers' creation [67,68]. In 2007, Wang and his coworker explored the novel thio-Michael–aldol reaction, which employed 2-mercaptobenzaldehydes and maleimides as template substrates and ligand **3** as catalyst. With the standard conditions, excellent yield and good stereoselectivity was achieved (90% yield, 84% ee, 10:1 dr). Further examination of the scope proved that this new methodology was a general approach to the preparation of a range of substituted thiochromanes (Scheme 2) [67].



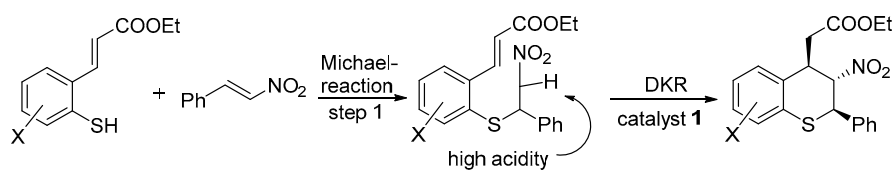
Scheme 2. Asymmetric thio-Michael–aldol cascade reaction of 2-mercaptobenzaldehydes with maleimides catalyzed by **3**.

In 2008, Wang and coworkers developed a highly stereoselective thio-Michael–Michael cascade reaction of *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester and *trans*- β -nitrostyrene catalyzed by a cinchona alkaloid-derived thiourea (**1**), which afforded chiral thiochromanes with three new stereogenic centers through one-pot access in excellent efficiency and stereoselectivity (Scheme 3, up to dr > 30:1, 99% ee, 99% yield) [68]. The generality of this cascade reaction was very wide, and a series of nitroalkenes can proceed well. In addition, this cascade reaction involved the DKR process, which has made great contributions to this transformation.



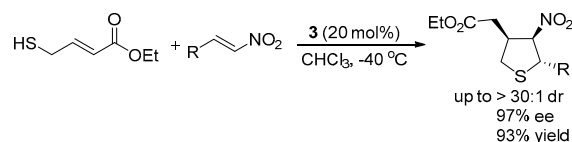
Scheme 3. Asymmetric thio-Michael–Michael cascade reaction of *trans*-3-(2-mercapto-aryl)-2-propenoic acid ethyl esters with nitroolefins catalyzed by **1**.

The initially formed Michael addition product, through reversible thia-Michael addition step 1 with strong acidity, went through deprotonation in the presence of bifunctional cinchona alkaloid-derived thiourea **1**, and then underwent a DKR process, which is mediated by the chiral bifunctional amine thiourea **1** and followed with retro-Michael–Michael–Michael process, providing chiral thiochromane product (Scheme 4). Moreover, this hypothesis was confirmed by the treatment of racemic first Michael adduct with catalyst **1** under the standard reaction conditions, affording similar reaction results.



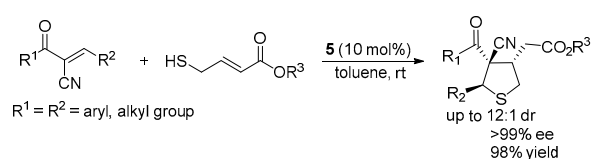
Scheme 4. Proposed pathway for asymmetric thio-Michael–Michael cascade reaction.

In 2011, Wang and coworkers established another asymmetric thio-Michael–Michael cascade reaction of *trans*-ethyl 4-mercapto-2-butenolate and *trans*- β -nitrostyrene catalyzed by Takemoto's bifunctional amine–thiourea catalyst (**3**), and the functionalized chiral trisubstituted tetrahydrothiophene products bearing three stereogenic centers through sequential C–S and C–C bond formation with high enantio- and diastereoselectivity (Scheme 5, up to >30:1 dr, 97% ee, 93% yield) [69]. Various aromatic nitroolefins performed smoothly in this transformation. The heteroaromatic and less reactive alkyl *trans*- β -nitroolefins were also well tolerated. In addition, an unprecedented activation mode of cooperative direct stereocontrol and similar DKR process was identified.



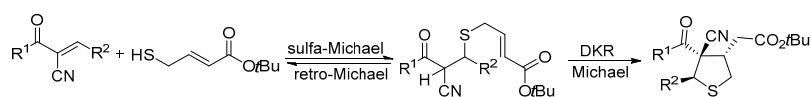
Scheme 5. Asymmetric thio-Michael–Michael cascade reaction of *trans*-ethyl 4-mercapto-2-butenate with nitroolefins catalyzed by amine–thiourea **3**.

In 2013, Lattanzi and coworkers successfully disclosed an efficient cascade double Michael reaction of *trans*- α -cyano- α,β -unsaturated ketone with *trans*-4-mercapto-2-butenate to construct chiral trisubstituted tetrahydrothiophenes catalyzed by amino thiourea **5** with excellent results (Scheme 6, up to 12:1 dr, >99% ee, 98% yield) [70]. The tetrahydrothiophene products contained three stereocenters, and one challenging all-carbon quaternary stereocenter was successfully created.



Scheme 6. Asymmetric thio-Michael–Michael cascade reaction of *trans*- α -cyano- α,β -unsaturated ketones with *trans*-4-mercapto-2-butenates catalyzed by amino thiourea **5**.

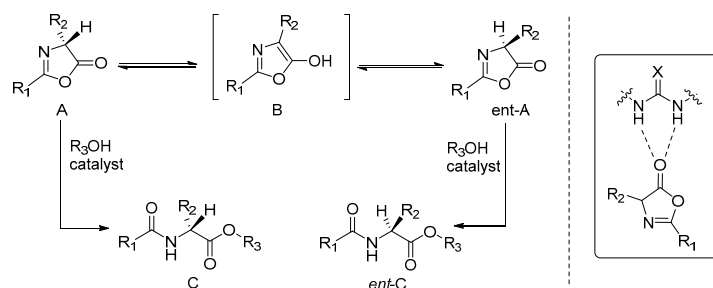
In addition, the control experiment confirmed that the DKR process was involved in this asymmetric cascade reaction (Scheme 7). The racemic mixture of diastereoisomers of the first sulfa-Michael product was treated under the optimized reaction conditions in the presence of catalyst **5**, and the result was the same with the *trans*- α -cyano- α,β -unsaturated ketone reacting with *trans*-4-mercapto-2-butenate directly.



Scheme 7. The cascade pathway involving DKR process.

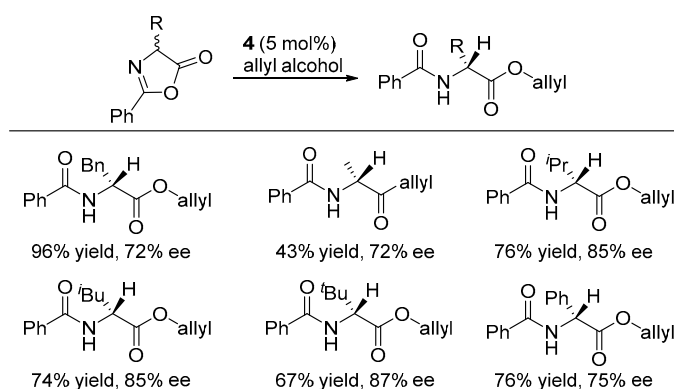
2.2. Asymmetric Ring Opening of Azlactones

Chiral α -amino acids have been widely used for the construction of pharmaceuticals, nature products, ligands, and organocatalysts [71–74]. The alcoholic dynamic kinetic resolution of azlactones has been regarded as an attractive and important way to generate the enantiomerically enriched α -amino acid derivatives (Scheme 8). The azlactones are readily prepared by the Erlenmeyer azlactone synthesis or from amino acids by N-acylation followed by cyclization–dehydration in the presence of condensation reagent [75].



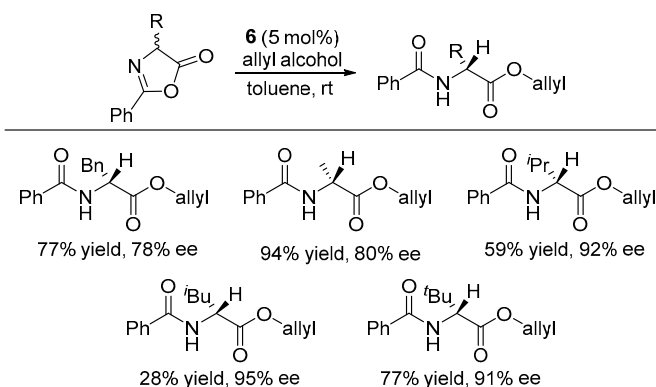
Scheme 8. Basis of the DKR of azlactones.

In 2005, Berkessel successfully developed asymmetric ring opening of azlactones with alcohol via the DKR process catalyzed by bifunctional amine urea catalyst **4** (Scheme 9) [76], which demonstrated the effective hydrogen-bonding activation of the (thio)urea moiety with the azlactone substrates. The NMR-spectroscopic studies also indicated that the catalyst activates the substrate azlactone by hydrogen bonding of the (thio)urea moiety directing to the carbonyl oxygen atom. The alcoholysis and ring opening of these substrate azlactones—derived from the aliphatic α -amino acids phenylalanine, alanine, valine, leucine and *tert*-leucine, and the aromatic α -amino acid phenylglycine—proceeded efficiently with good enantioselectivities catalyzed by amine urea **4** (72%–87% ee).



Scheme 9. Asymmetric ring opening of azlactones with allyl alcohol by catalyst **4**.

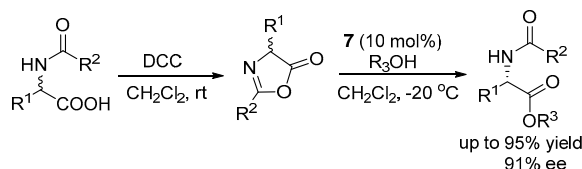
Based on their previous studies, Berkessel and coworkers envisioned that the reactivity and enantioselectivity of this transformation could be greatly improved by reasonable modified thiourea catalyst [77]. The initial catalyst-screening results of Takemoto-type bifunctional organocatalysts demonstrated that increasing the steric hindrance of the additional chiral center may contribute to enhancement of enantioselectivity. Therefore, they synthesized a series of the *tert*-leucine amide-derived catalysts, and catalyst **6** was identified to be the best one. Various azlactones derived both from natural and non-natural α -amino acids were investigated to examine the generality of substrates in the presence of catalyst **6**, and the enantioselectivity was up to 95% (Scheme 10). They successfully realized clean *stereoinversion* of natural and non-natural α -amino acids through this organocatalytic DKR.



Scheme 10. Asymmetric ring opening of azlactones with allyl alcohol by catalyst **6**.

(Thio)urea-based organocatalysts, to some extent, existed hydrogen-bonded aggregates, which led to realization that the reactivity and enantioselectivity were greatly dependent on concentration and temperature of reactions [78–80]. The enantioselectivity always dramatically decreased when the concentration was increased, and this was not conducive to their practical application. In 2012,

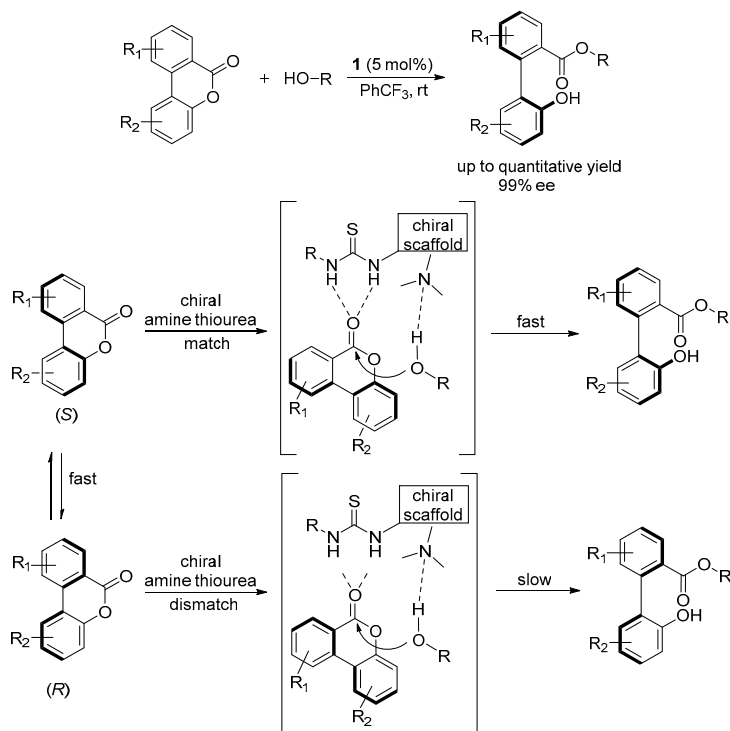
Song and coworkers reported that C2-symmetric bis-cinchona-alkaloid-based thiourea **7** was applied to catalyze the DKR of racemic azlactones available from N-protected racemic amino acids in one pot, affording various chiral non-natural α -amino esters (Scheme 11, up to 95% yield, 91% ee) [81]. The steric bulkiness of the two alkaloid moieties of catalyst **7** can prevent their self-aggregation and exhibited concentration-independent enantioselectivity in this transformation. Moreover, the experimental and NMR-spectroscopic studies and single crystal X-ray analysis confirmed that these kinds of bifunctional organocatalysts do not establish hydrogen-bonded self-aggregates in either solution or solid state.



Scheme 11. One-pot procedure for the DKR reactions.

2.3. Atropo-Enantioselective Transesterification

Asymmetric synthesis of axially chiral biaryl compounds emerged as a challenging and attractive research area, where they were found to have broad applications for constructing various natural products, drugs, bioactive molecules, and chiral ligands [82–86]. There are numerous excellent synthetic methodologies to efficiently build chiral biaryl skeletons, such as chiral auxiliaries, asymmetric transformations, asymmetric oxidation homo couplings, and asymmetric Suzuki–Miyaura couplings [87–92]. DKR of configurationally labile biaryl lactones was a powerful and outstanding transformation to produce such chiral compounds and continues to receive increasing attention now [93–98]. Owing to great versatile application and highly effective activation mode of bifunctional chiral thiourea catalyst, the combination of DKR and organocatalysis is an attractive way to build chiral biaryl compounds.



Scheme 12. DKR of biaryl lactones via bifunctional amine thiourea (**1**)-catalyzed atropo-enantioselective transesterification.

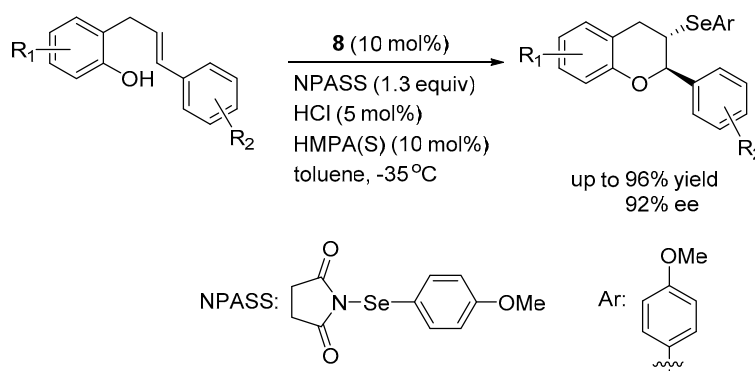
Recently, Wang and coworkers realized highly atropo-enantioselective transesterification of biaryl lactones catalyzed by chiral bifunctional amine thiourea **1** provided enantioenriched axially chiral biaryl compounds with a wide substrate scope under mild reaction conditions (Scheme 12, up to quantitative yield, 99% ee) [99]. Additionally, this asymmetric transformation involved a highly enantioselective DKR process, which was owing to synergistic activation of the biaryl lactones and alcohols/phenols by the thiourea **1** and amine groups (Scheme 12).

3. Squaramide Organocatalyst for DKR

Asymmetric organocatalysis employing a hydrogen-bonding activation strategy has been well-established for the synthesis of enantioenriched compounds. Chiral squaramides have been identified as a type of powerful bifunctional hydrogen-bonding catalysts, and promoted numerous catalytic asymmetric transformations [42–51]. They were also effective for the asymmetric reactions involving the DKR process.

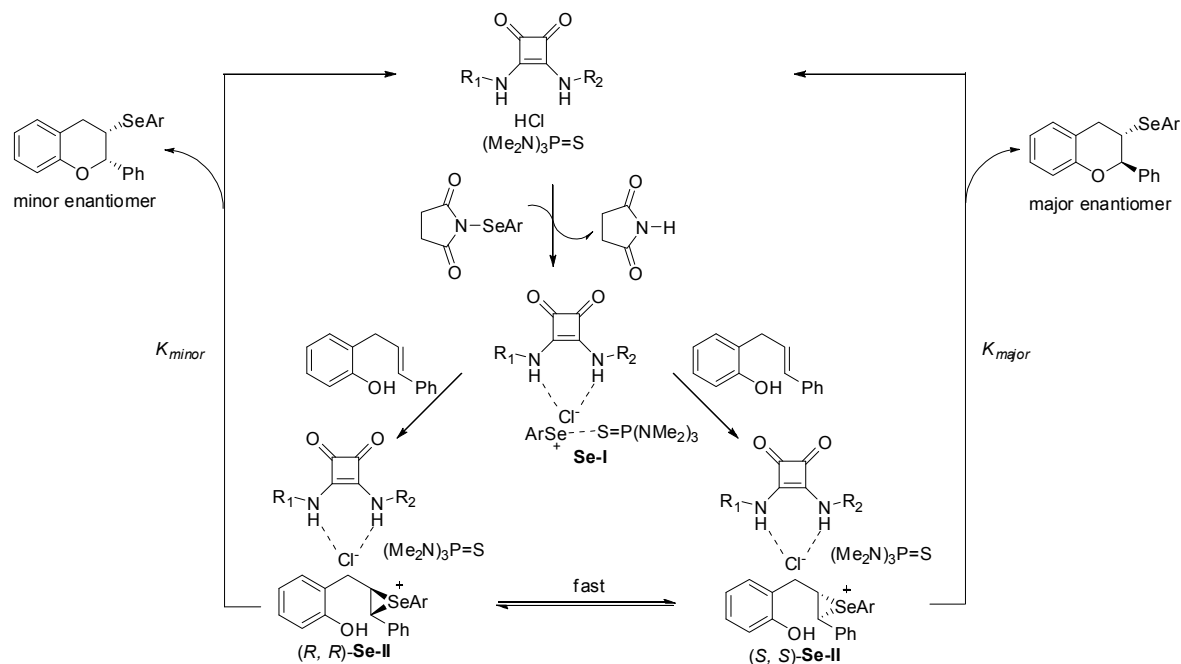
3.1. Enantioselective Selenofunctionalization Reactions

Asymmetric selenofunctionalization of alkenes was regarded as an attractive and challenging methodology to produce chiral selenide compounds in organic synthesis [100–106]. Due to the configurational instability of seleniranium ions, the rapid seleniranium racemization can contribute to promotion of the DKR process. In 2014, Jacobsen and coworkers successfully established highly enantioselective selenocyclization reactions of *o*-allyl-substituted phenol via the DKR process of seleniranium ions by chiral squaramide catalyst **8** (Scheme 13, up to 96% yield, 92% ee) [107]. They made use of *N*-phenylselenenyl succinimide (NPSS) as the selenium donor, and hydrogen chloride and tris-(dimethylamino)phosphorus sulfide (HMPA(S)) as cocatalysts. The substrates with different substituent patterns performed smoothly, affording cyclization products in high yield and enantioselectivity. However, the *ortho* substituent of the hydroxyl group substrate obtained poor enantioselectivity, which suggested that the possible interaction between the hydroxyl group and catalyst that may play an important role in the mechanism of enantioinduction, and such an interaction may be sensitive to the steric environment around the hydroxyl group.



Scheme 13. Asymmetric selenocyclization via DKR of seleniranium ions by squaramide catalyst **8**.

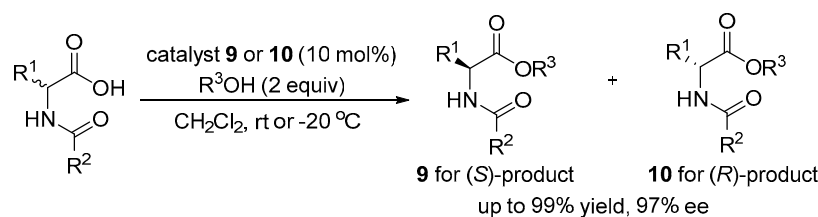
According to the proposed activation strategy of this asymmetric selenocyclization, cooperative Lewis base and Brønsted acid activation of the electrophilic selenium reagent formed a reactive ion pair (**Se-I**), which may be associated with the squaramide catalyst **8**. This intermediate reacted with *o*-allyl-substituted phenol substrate and formed chiral seleniranium ions (*R,R*)-**Se-II** and (*S,S*)-**Se-II**. These two seleniranium ions equilibrated very rapidly, and subsequently went through cyclizations with different rates due to the association with chiral squaramide **8**, resulting in formation of products with excellent enantioselectivities (Scheme 14).



Scheme 14. Proposed possible catalytic cycle.

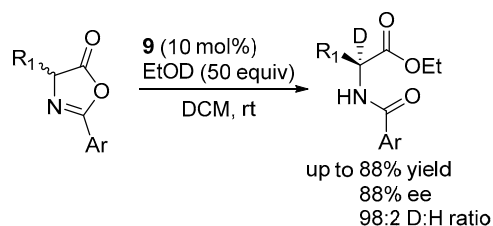
3.2. Asymmetric Ring Opening of Azlactones

Numerous thiourea-organocatalytic DKRs of racemic azlactones have been widely investigated, but few examples concerning DKR of racemic azlactones promoted by squaramide-organocatalysts were reported. Song and coworkers developed a novel catalytic DKR of ring-opening reactions of racemic azlactones with various alcohols by the bifunctional squaramide-based dimeric cinchona alkaloid catalysts **9** and **10** (Scheme 15) [108]. These catalysts displayed unprecedented catalytic activity, as well as enantioselectivity in the DKR reaction of a broad range of racemic azlactones (up to 99% yield, 97% ee). The recyclability of the catalysts was examined, and the enantioselectivity and activity were not decreased even after fifth run.



Scheme 15. DKR of the racemic azlactones with alcohols by squaramide-based dimeric cinchona alkaloid catalysts.

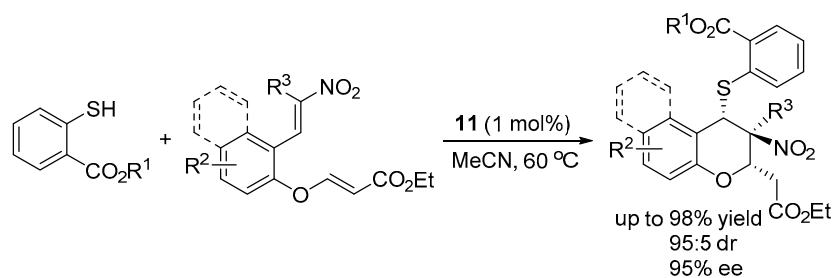
Inspired by the aforementioned results, Song and coworkers further employed this protocol for the preparation of α -carbon deuterium-labeled α -amino acids with EtOD as a nucleophile as well as a deuterium source catalyzed by bifunctional squaramide-based dimeric cinchona alkaloid catalyst **9** (Scheme 16) [109]. Various α -deuterated amino esters were afforded with good enantioselectivities and yields (up to 88% yield, 88% ee). In addition, most of the *N*-protected α -deuterated amino ester products were obtained with a deuterium content greater than 95%, and their optical purity can be improved to >99% ee after a single recrystallization.



Scheme 16. Catalytic DKR of various azlactones with ethanol-*d*.

3.3. Cascade Sulfur-Michael–Michael Reaction

Chroman is a kind of fundamental heterocyclic skeleton and widely found in natural products and medical molecules with great importance [110–112]. Organocatalytic cascade reactions were regarded as a straightforward and efficient method to construct chiral chroman framework [113]. In 2013, Du and coworkers developed an efficient asymmetric cascade sulfa-Michael/Michael addition of thiosalicylates with nitroalkene enoates to build chiral chromans catalyzed by a chiral bifunctional squaramide-tertiary amine catalyst **11** (Scheme 17, 98% yield, 95:5 dr, 95% ee) [114]. The highly functionalized chiral chroman products contained three contiguous stereocenters, including one quaternary center. Based on the results of control experiments, they proposed a reasonable reaction pathway of sulfa-Michael/retro-sulfa-Michael/sulfa-Michael/Michael reactions involving the DKR process.



Scheme 17. Squaramide-catalyzed asymmetric cascade sulfa-Michael/Michael addition of thiosalicylates to nitroalkene enoates.

4. Conclusions

Asymmetric organocatalysis is one of the most important research areas in organic synthesis and applicable in a broad variety of reaction types, which includes those reactions involving the DKR process. In this review, we have summarized recent significant developments on the catalytic asymmetric reactions via the DKR process promoted by the (thio)urea and squaramide organocatalysts. These reaction examples have confirmed that (thio)urea and squaramide organocatalysts bearing hydrogen-bonding donors as catalysts have played an important role in achieving excellent results from the transformations involving the DKR process. In addition, further exciting and significant discoveries of (thio)urea and squaramide organocatalytic DKR process and developments with this versatile type of bifunctional organocatalysis are to be expected in the near future with the advent of more systematic studies.

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Conflicts of Interest: The authors declare no competing financial interest.

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