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氮杂环卡宾催化实现的动力学拆分近期研究进展

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摘要 动力学拆分是获得手性化合物的最常用方法之一. 在过去的二十年里, 氮杂环卡宾催化的动力学拆分得到了快速的发展, 作者曾在 2017 年发表的综述文章中进行了一次总结. 自此以后, 该领域取得了一系列新的研究进展, 将阐述这一研究领域自 2017 年年中至 2023 年的最新研究进展.
关键词 动力学拆分; 氮杂环卡宾; 不对称催化; 消旋体; 对映体富集化合物

Kinetic Resolutions Enabled by *N*-Heterocyclic Carbene Catalysis: An Update

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Abstract Kinetic resolution is one of the most commonly used methods allowing access to enantioenriched compounds. The last two decades have seen the rapid development of kinetic resolutions enabled by *N*-heterocyclic carbene catalysis, and part of the achievements have been summarized in our previous review paper published in 2017. Since then, a series of new advances have been realized, and this review will provide an update of this field covering reports from mid-2017 to 2023.
Keywords kinetic resolution; *N*-heterocyclic carbene; asymmetric catalysis; racemates; enantioenriched compounds

1 Introduction

The huge demand for optically pure substances from organic chemistry, chemical engineering, medicinal chemistry, agrochemistry, and material chemistry urges the development of new methods to furnish chiral molecules in a diverse, concise, efficient, and environmentally benign fashion. Among the currently widely used strategies allowing access to optically pure molecules, kinetic resolution serves as a reliable and robust technique to produce compounds with high enantiopurity.[1] One of the outstanding advantages of classical kinetic resolution (KR) is that by controlling the conversion of a reaction, one can get highly enantioenriched compounds that can meet certain strict requirements such as those from the pharmaceutical industry.[2] Furthermore, to overcome the 50% yield issue of a classical KR, the technique of dynamic kinetic resolution (DKR) has been developed.[3] Moreover, parallel kinetic resolution (PKR) and divergent reactions on racemic mixtures (divergent RRM) have also been proposed, and in these processes both enantiomers of a racemate react with chiral reagents or catalysts at similar rates and deliver two enantioenriched products, which is advantageous in delivering molecules in a diversified approach.[4] Therefore, despite the great achievements that have been made by asymmetric catalysis, kinetic resolutions will continue playing irreplaceable roles in obtaining chiral substances.

The last two decades have witnessed an explosive development of *N*-heterocyclic carbene (NHC) organocatalysis, and the unique umpolung property, diversified activation modes, broad substrate scope, and fruitful product types have made NHC catalysis a prominent field.[5] In this context, kinetic resolutions mediated by NHC catalysis have also received extensive attention, and various enantioenriched molecules have been accessed through NHC-catalyzed different activation modes. Early in 2017, we

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have published a review comprehensively summarizing the NHC-catalyzed kinetic resolutions from the first report appeared in 2004 to mid-2017.[6a] Since then, several research groups have published reviews containing NHC-catalyzed kinetic resolutions in 2018[6b,6c] and 2019,[6d] respectively. As a continuation of our research interest in NHC catalysis and with the purpose to provide an update of our previous review, we herein describe the recent advances made by NHC-catalyzed kinetic resolutions from mid-2017 to 2023, and the content is arranged according to the different active intermediates involved in the resolution processes, which are acyl azoliums, *α*,*β*-unsaturated acyl azoliums, Breslow intermediates, azolium enolates, homoenolates, and *β*-azolium ylides.

The structures of the intermediates discussed in this review, their relationships, and their reactivities are shown in Figure 1. The Breslow intermediate, which is formed from the reaction of aldehyde and free carbene, is the origin of many other intermediates in NHC catalysis. When there is an oxidant in the system, acyl azolium is generated. Acyl azolium can also ben formed through the reaction of carbene with aldehydes having *α*-leaving group (LG) or carbonyl substrates bearing leaving groups. When acyl azoliums have *α*-protons, then after deprotonation in the presence of bases, azolium enolate intermediates generate. On the other hand, when aldehyde is *α*,*β*-unsaturated one, homoenolate is formed. Then in the presence of oxidants, *α*,*β*-unsaturated acyl azolium is produced. Similarly, such kind of intermediate can also be afforded directly through the reaction of carbene with enals having *α*-LG. *β*-Azolium ylide is a newly developed intermediate in NHC catalysis, which is generated from the addition of free carbene to activated C＝C double bond. Breslow intermediate is prone to undergo benzoin reaction and Stetter reaction due to the polarity umploung. The most common reaction for acyl azolium intermediate is esterification and amide formation, and for *α*,*β*-unsaturated acyl azolium, it is easy to proceed Michael addition-aldol reaction-lactonization sequence because of three sequential active sites. The *β*-position of homoenolate intermediate is nucleophilic and can attack electrophiles, followed by carbonyl esterification. Correspondingly, the *α*-position of azolium enolate intermediates reacts with electrophiles and then undergoes carbonyl estrification or amide formation.

2 Kinetic resolutions mediated by acyl azoliums

In this section, we will describe NHC-catalyzed kinetic resolutions using acyl azolium intermediates. Such type of intermediate is nucleophilic and can be attacked by various hydroxy and amino groups, thus enables the design of many kinetic resolution reactions.

γ-Lactams are core skeletons in many biologically active compounds, therefore, the synthesis of *γ*-lactams in an efficient and stereoselective fashion has received considerable attention. In 2017, Bolm *et al.*[7] conducted a kinetic resolution of *trans*-*γ*-lactams using the NHC-catalyzed acyl azolium process (Scheme 1). Although the *ee* values were moderate, the study showed opportunities for further investigations regarding the kinetic resolution of *γ*-lactams affected by chiral NHC catalysts.

Chiral 1-arylethane-1,2-diols and their derivatives are widely used in the preparation of natural products with

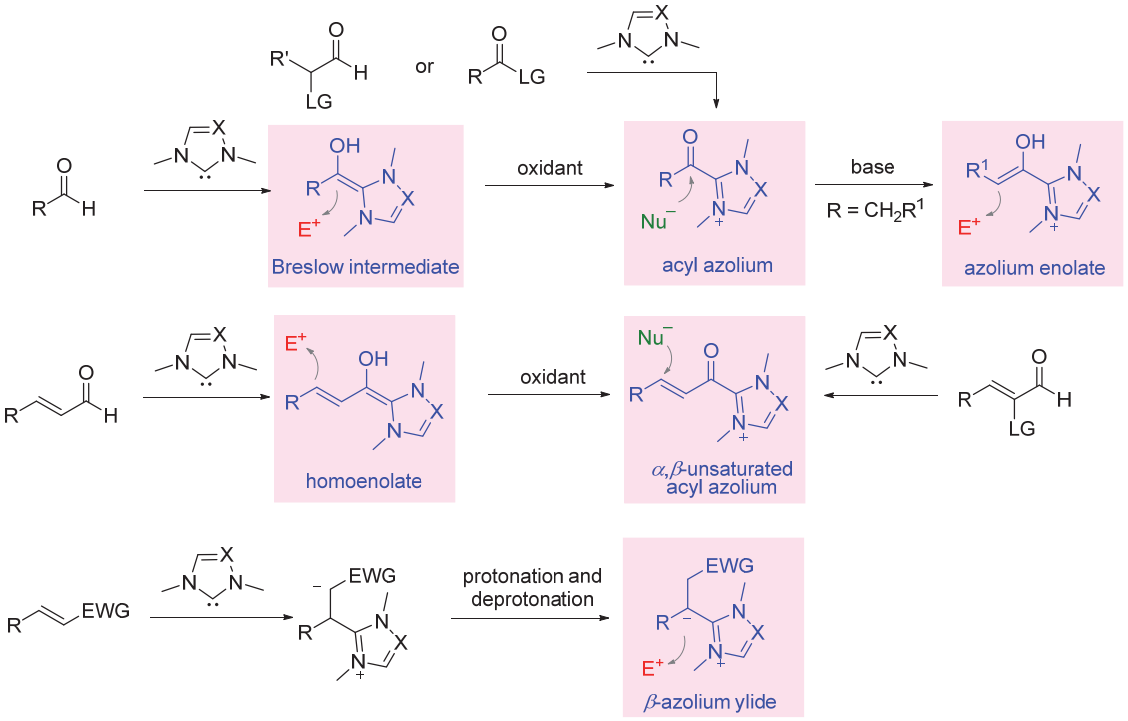
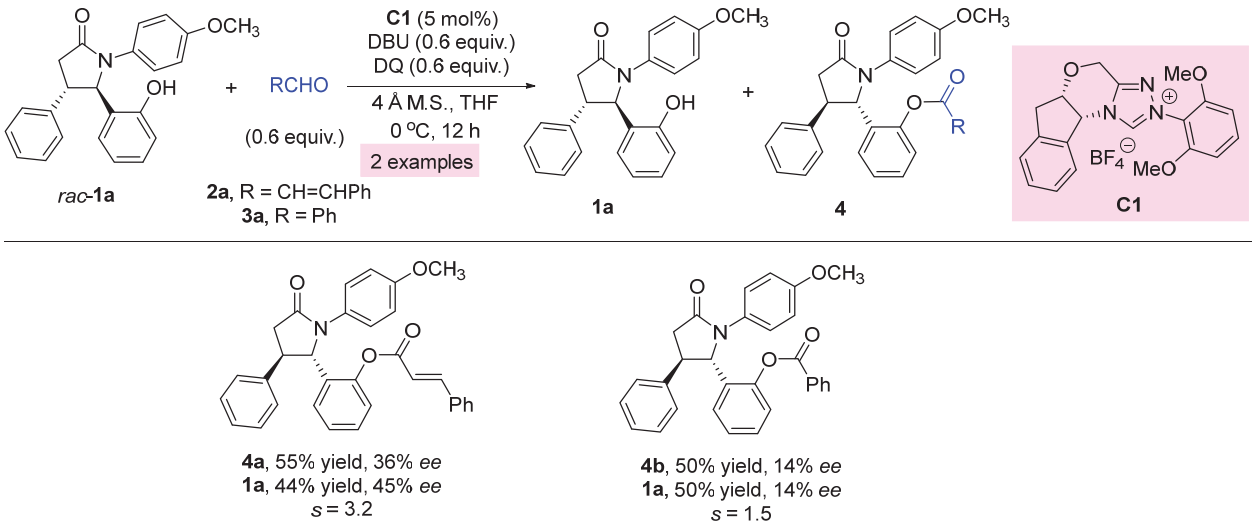


Figure 1 Structures, relationships, and reactivities of various NHC intermediates

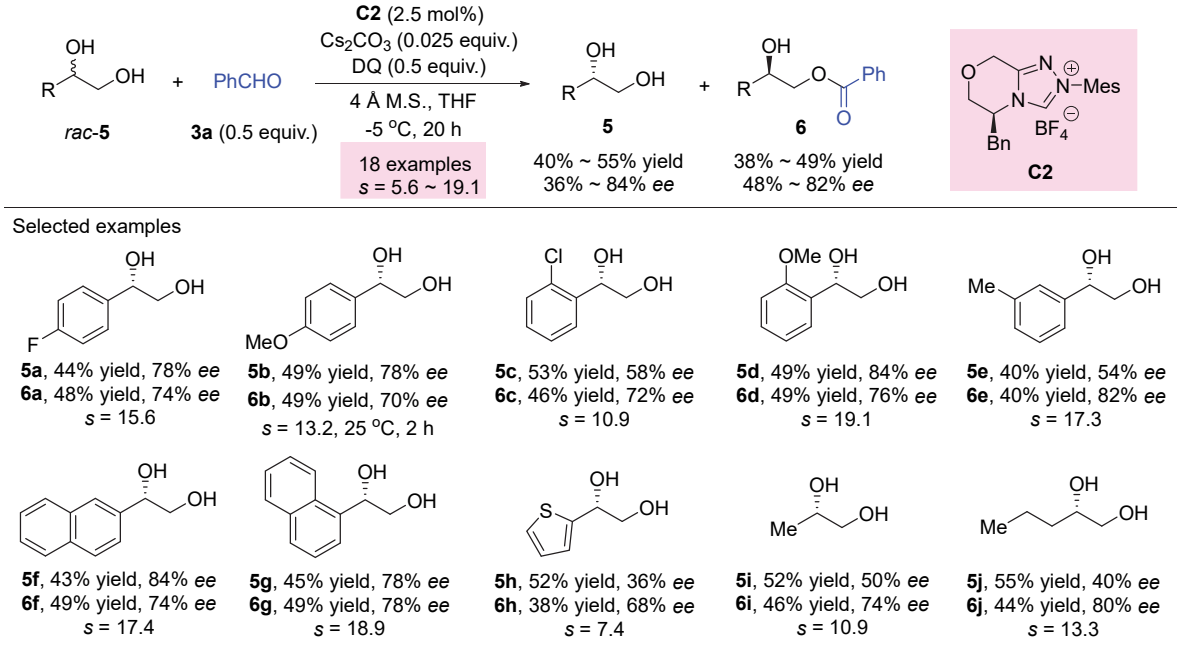


Scheme 1 Kinetic resolution of *trans*-γ-lactams

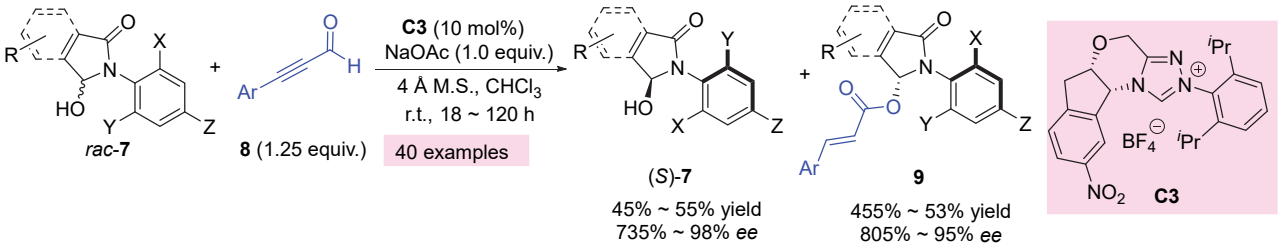
biological activities, therefore, the preparation of chiral 1-arylethane-1,2-diols has been a hotspot of chemists. In 2018, Chi *et al.*[8] reported for the first time a site- and enantioselective kinetic resolution of 1,2-diols bearing both a secondary and a primary alcohol motif (Scheme 2). By using an NHC-catalyzed oxidative acylation reaction as the key step, they could obtain 1,2-diols and their monoester derivatives in moderate to high enantioselectivities. In addition, both enantiomers of the product **6a** could be isolated with excellent optical purities after a sequential kinetic resolution using *ent*-**C2** as the catalyst. Non-covalent interactions involving the secondary alcohol may affect the regioselectivity and kinetic resolution.

Axially chiral anilides are very important in pharmaceutical and medicinal areas. The development of new catalytic methods for the preparation of axially chiral anilides is quite necessary. Wang's group[9] incorporated a hemiaminal functional group into the anilide skeleton and applied the NHC-catalyzed acylative kinetic resolution into the synthesis of axially chiral anilides (Scheme 3). The two enantiomers of anilides were separated efficiently. The corresponding acylated products were obtained in high to excellent enantioselectivities (up to 95% *ee*). An acyl azolium-participated mechanism was proposed.

The catalytic divergent formation of stereoisomers from one common precursor represents an efficient approach for the rapid construction of molecules with multiple stereocenters. Wang's group[10] developed a chiral NHC-catalyzed dynamic kinetic enantio- and diastereoselective acylation for the preparation of optically pure dihydropyranones (Scheme 4). The rate of equilibration between the two isomers is faster than the acylation, which is important for



Scheme 2 Site- and enantioselective kinetic resolution of 1,2-diols



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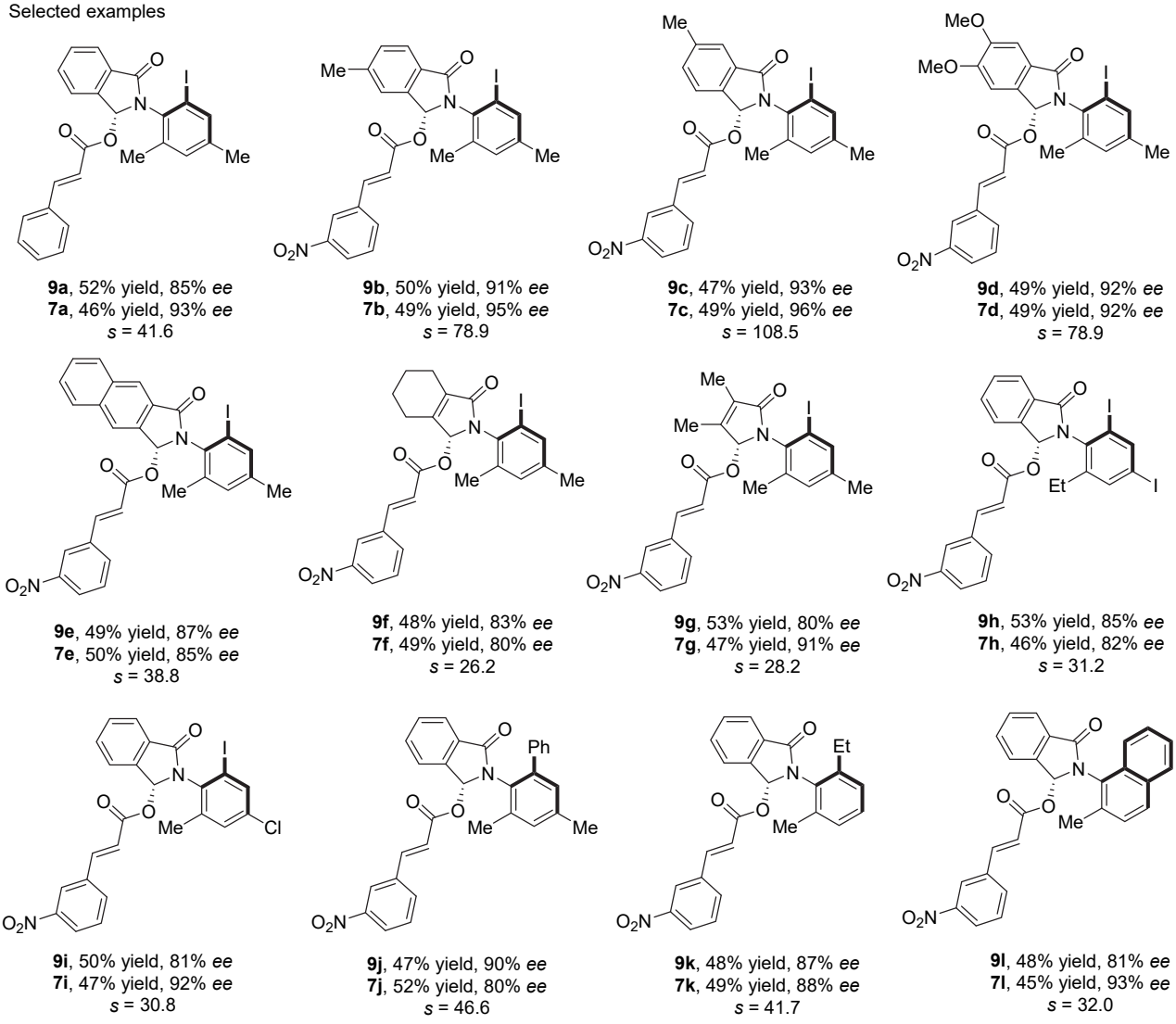
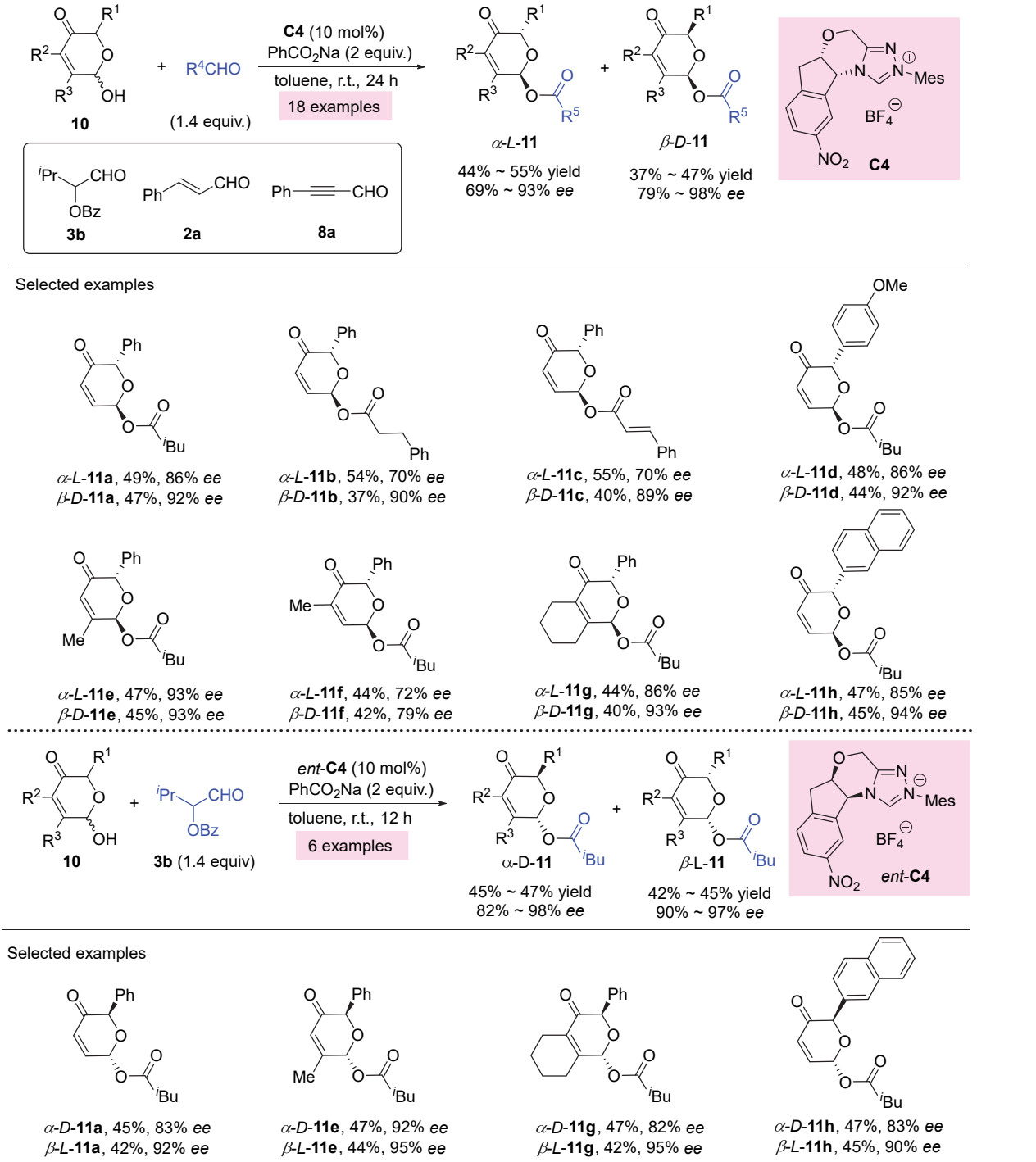


Scheme 3 Synthesis of axially chiral anilides via kinetic resolution

the dynamic kinetic resolution. By changing catalysts, another two isomers of dihydropyranones were obtained from the common racemic precursor. It is worth mentioning that the acyl azolium intermediate could be generated from carbene-catalyzed redox reaction of α-substituted aldehydes, enals, and alkynals.

Compared with the extensive use of 1,1'-bi-2-naphthol (BINOL) and its derivatives as chiral ligands in asymmetric catalysis, the analogs of 1,1'-biaryl-2,2'-amino alcohol (NOBIN) are less used mainly because of certain limitations in the preparation such as limited scope, low efficiency, and lengthy synthetic route. Developing a highly efficient strategy to synthesize this kind of amino phenols is still very necessary. In 2019, Zhao and Rong *et al.*[11] presented a highly efficient NHC-catalyzed atroposelective acylation of amino biphenols to prepare various NOBIN analogs in high yields with excellent enantioselectivities (Scheme 5). They believe that the combination of desymmetrization and a secondary kinetic resolution is responsible for the high enantioselectivity of the reaction. To confirm the hypothesis, they prepared some racemic monoesters and subjected them to the kinetic resolution conditions. The monoesters

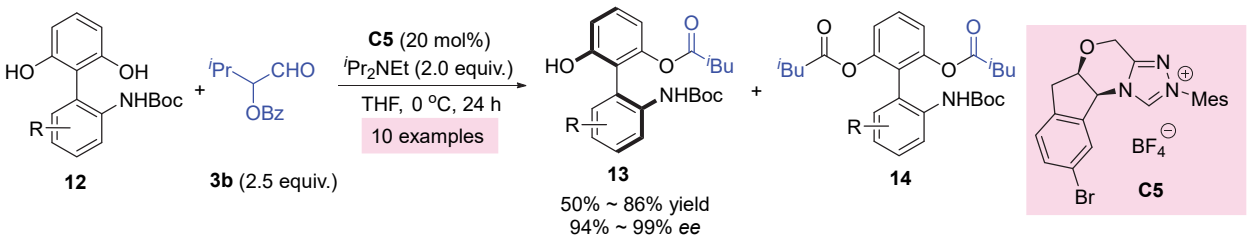


Scheme 4 Preparation of optically pure dihydropyranones via divergent strategy

could be obtained with 76%～99% *ee*.

Wang's group[12] also reported an NHC-catalyzed atroposelective synthesis of axially chiral biaryl amino-alcohols via a cooperative strategy of desymmetrization followed by kinetic resolution (Scheme 6). Different from Zhao's study, the acyl azolium intermediate was generated through oxidation of the corresponding Breslow intermediate (acyl anion). They also conducted control experiments and postulated the mechanism.

Recently, Gao *et al.*[13] developed a transition-metal free cascade protocol for the construction of NOBIN analogs by employing direct *O*-arylation of arylhydroxylamines with diaryliodonium salts to form transient *N*,*O*-diarylhydroxylamines which could subsequently undergo [3,3]-sigmatropic rearrangement and rearomatization. A NHC-catalyzed kinetic resolution was also successfully achieved for the preparation of enantiopure NOBIN analogs under mild conditions (Scheme 7).



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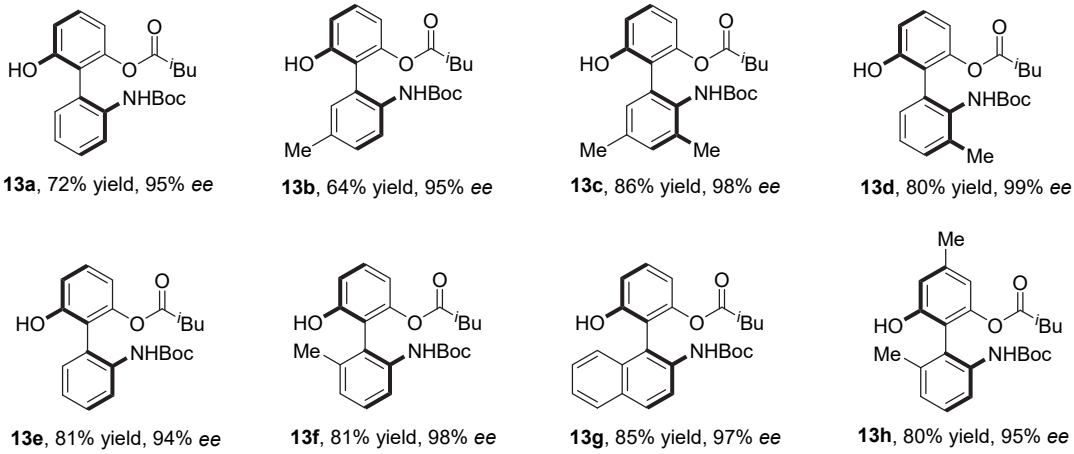
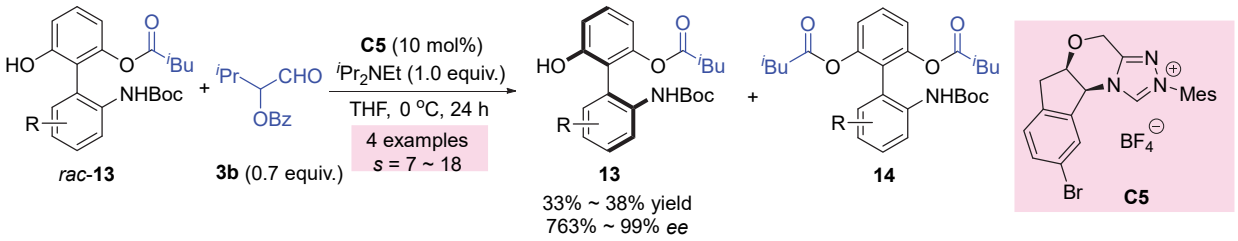
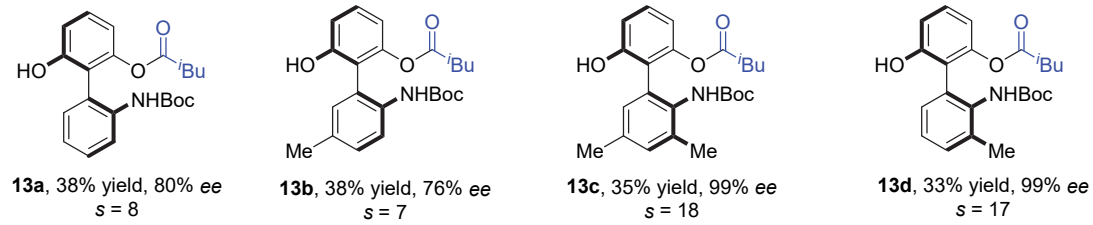




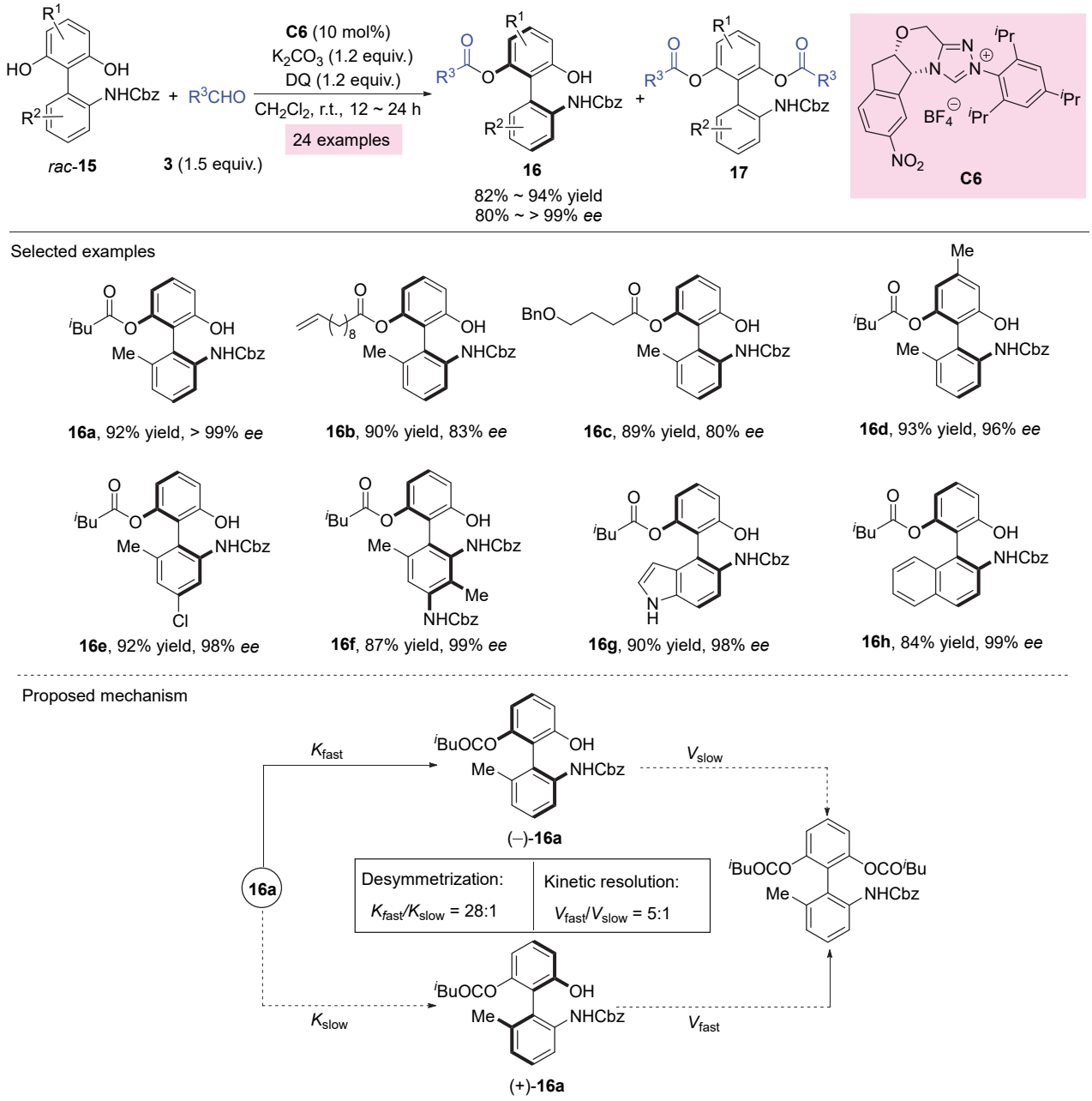


Scheme 5 NHC-catalyzed atroposelective acylation of biphenols

Acylated hydroxyphthalides have found applications especially as prodrugs. However, it is a great challenge to build chiral ketal units in hydroxyphthalides efficiently because they contain a labile chiral center. A carbene-catalyzed dynamic kinetic resolution process was developed for the rapid construction of enantiomerically enriched acylated hydroxyphthalides by Chi *et al.*[14] recently (Scheme 8). An equilibrium of formylbenzoic acid and the corresponding racemic hydrophthalide is key for the dynamic kinetic resolution to be realized. The method worked well for a broad range of substrates and allowed quick access to useful pharmaceuticals such as talosalate with up to 98% *ee*.

Ye *et al.*[15] realized the dynamic kinetic resolution of hemiaminals without *α*-hydrogen via NHC-catalyzed *O*-acylation of 3-hydroxy-3-trifluoromethylbenzosultams (Scheme 9). Noteworthy is that basic conditions are important for the racemization of hemiaminals without *α*-hydrogen. The resulting esters were obtained in high yields with good to high enantioselectivities.

Carboxylic acids and their derivatives bearing a chiral center at *α*-position widely exist in many bioactive reagents. Following their previous reports in NHC-catalyzed dynamic kinetic resolution of *α*-aryl-*α*-alkyl carboxylic esters, Chi's group[16] also studied the dynamic kinetic resolution of *α*-aryloxycarboxylic esters via a carbene catalyzed transesterification reaction (Scheme 10). Various *α*-aryloxycarboxylic esters could be obtained in 34%～99% yields with up to 98% *ee* under mild reaction conditions.

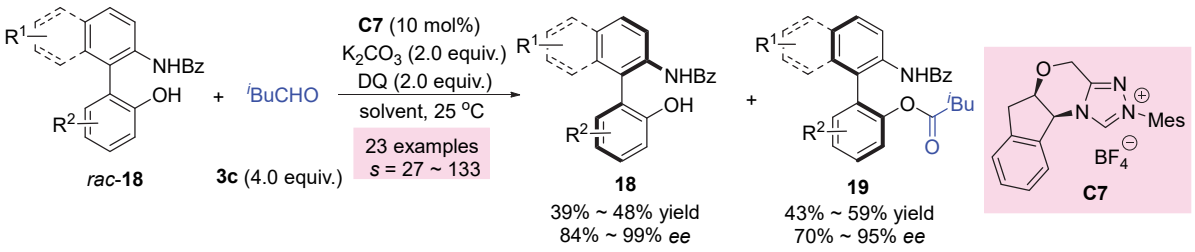


Scheme 6 NHC-catalyzed atroposelective synthesis of axially chiral biaryl amino-alcohols

Different stereoisomers of chiral *N*-acylated 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) often exhibit different or even contrary biological activities, thus the synthesis of enantioenriched *N*-acylated DHPMs has attracted the wide attention of chemists. Massi's group[17] realized the asymmetric *N*-acylation of DHPMs with enals via NHC-catalyzed kinetic resolution (Scheme 11). The method employed a set of mild conditions for the synthesis of Biginelli-type dihydropyrimidines, although in most cases the products were gotten with low to moderate *ee* values.

Enantioenriched acyclic *α*-substituted *β*-hydroxy amides are valuable pharmacophores and versatile precursors to enantioenriched 1,3-diols, 1,3-amino-alcohols, *β*-hydroxy acids and *β*-amino acids, but their enantioselective synthesis remains challenging. Recently, Guin *et al.*[18] realized the kinetic resolution of acyclic *α*-substituted *β*-hydroxy amides utilizing enantioselective acylation of primary alcohol via oxidative NHC catalysis (Scheme 12). The selectivity factor (*s*) was up to >200. The cyclic tertiary amine was key for the high selectivity. Diastereomeric transition state models for the process were proposed to rationalize the origin of enantioselectivity.

Aldol reaction is very important in forming chiral *β*-hydroxyl carbonyl compounds. However, due to the retro-aldol process, it is hard to improve the conversion and stereoselectivities. Chi *et al.*[19] developed a new catalytic strategy that attempted to control the product enantioselectivities via post-aldol processes (Scheme 13). The



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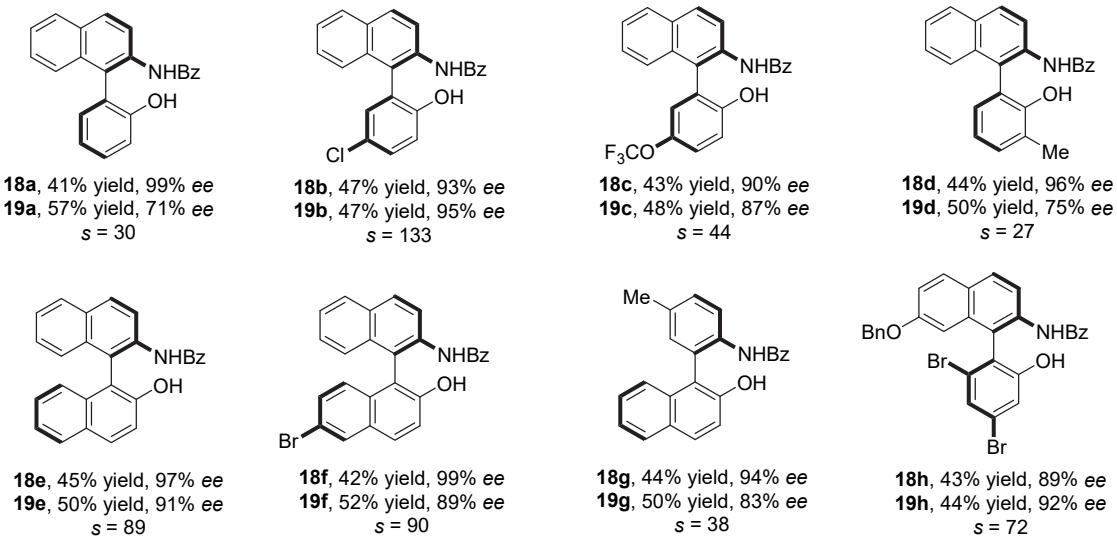
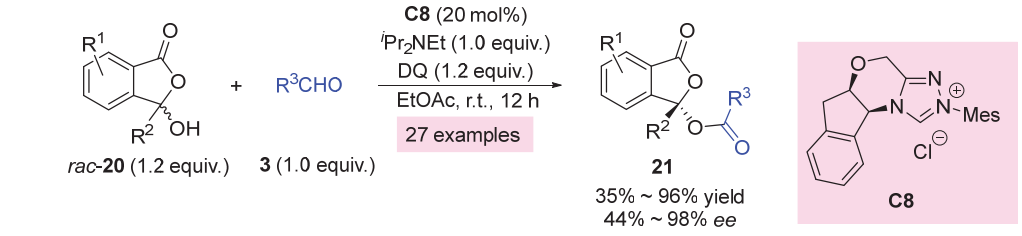


Scheme 7 NHC-catalyzed kinetic resolution of racemic NOBIN analogs



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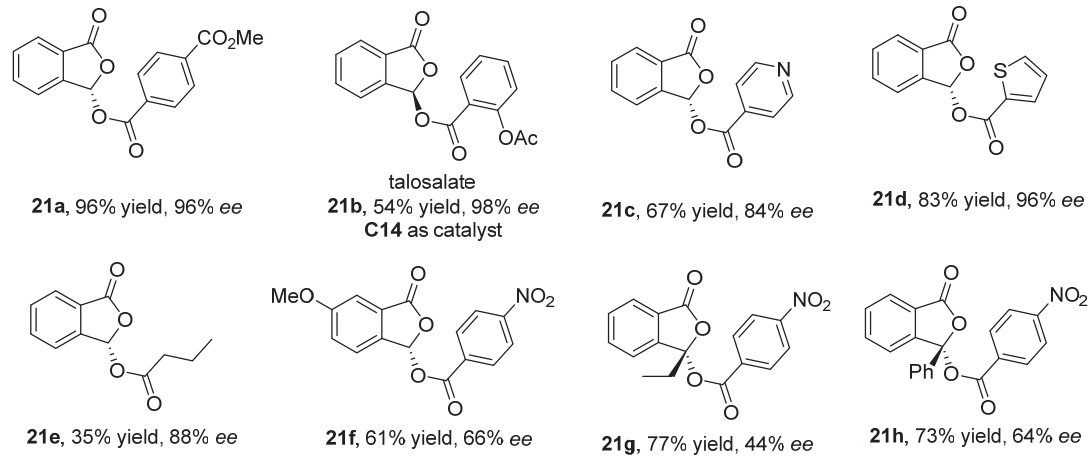
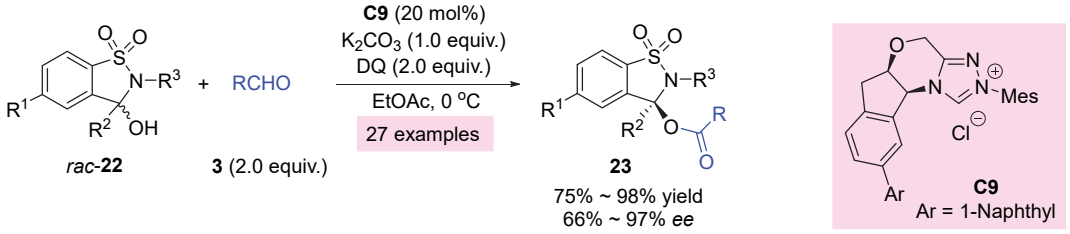


Scheme 8 NHC-catalyzed dynamic kinetic resolution of hydrophthalides



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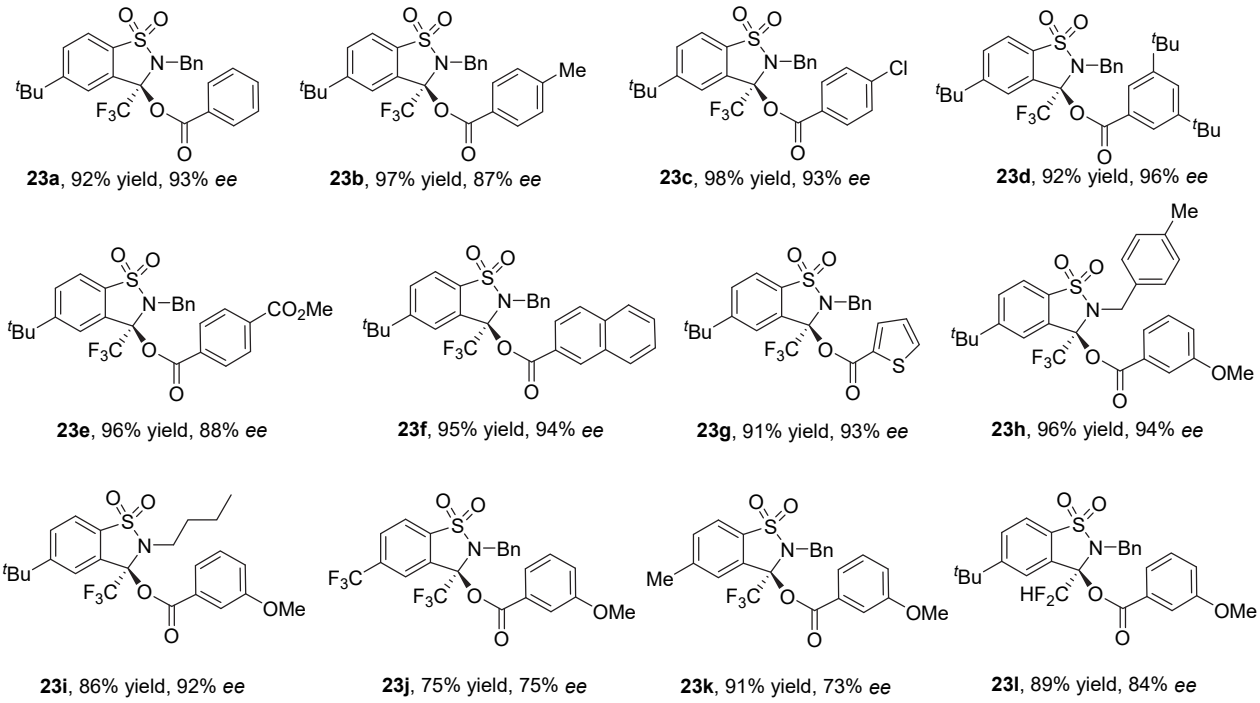
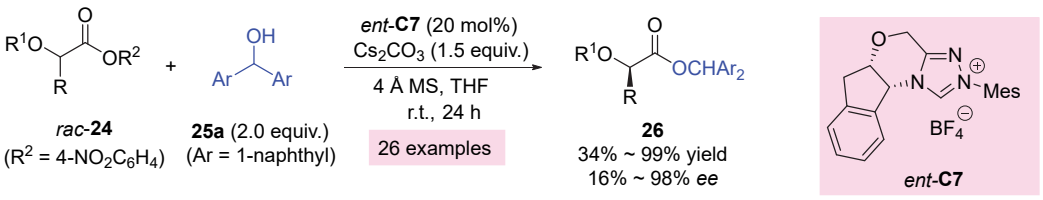


Scheme 9 NHC-catalyzed dynamic kinetic resolution of hemiaminals



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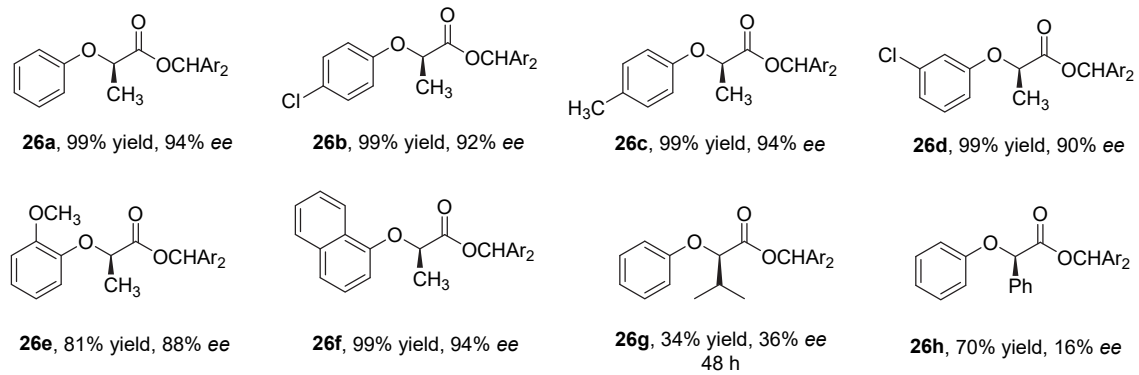
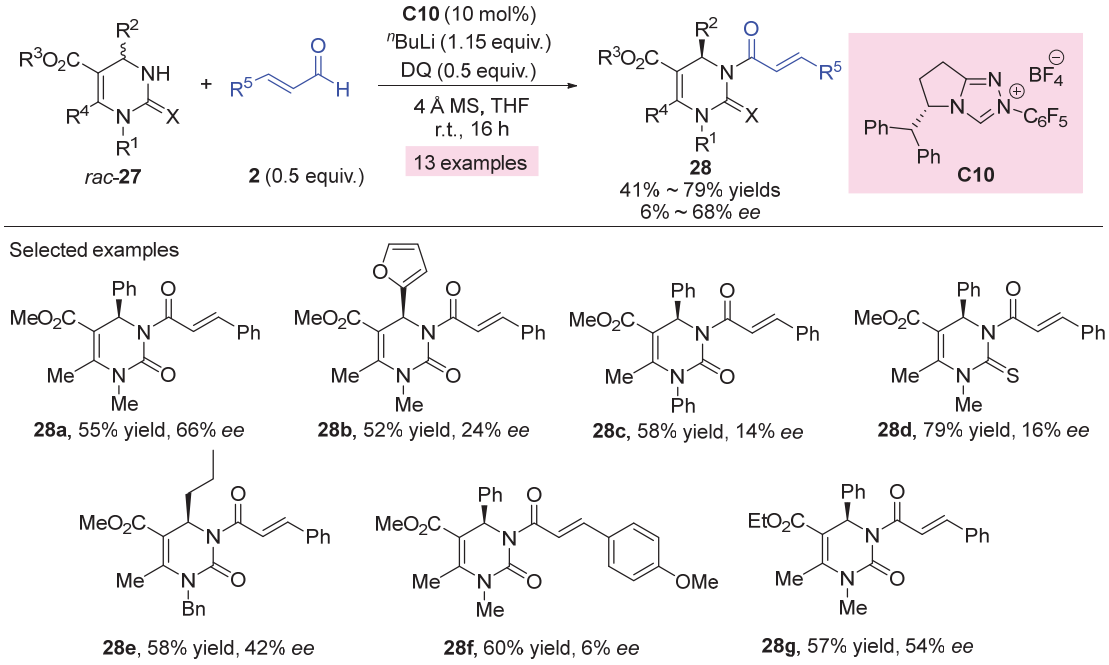
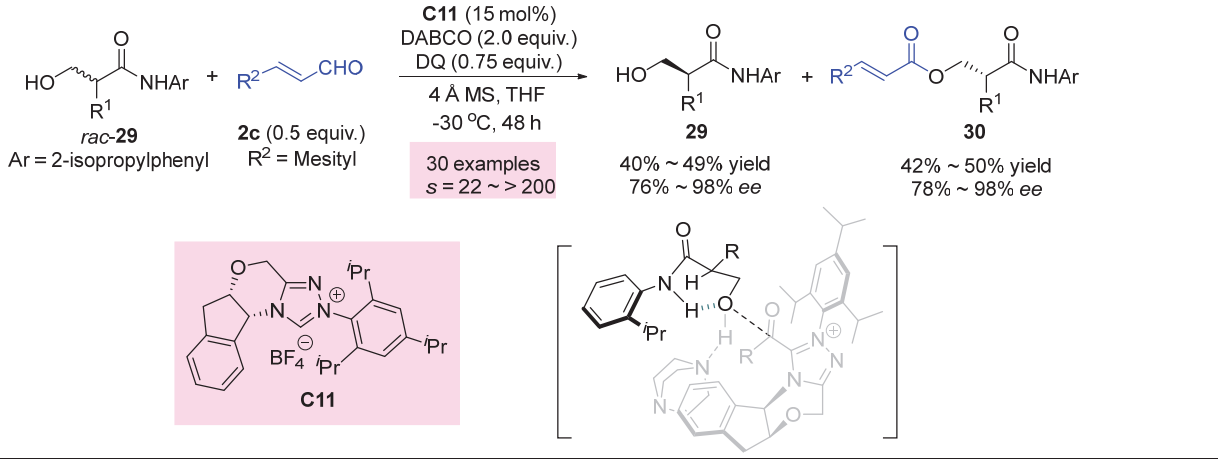


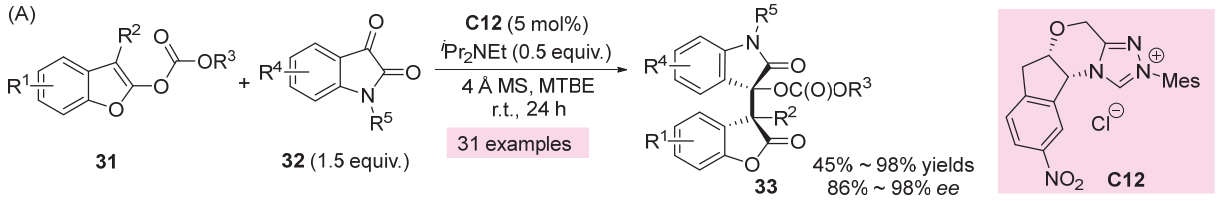
Scheme 10 Synthesis of *α*-aryloxycarboxylic esters via NHC-catalyzed dynamic kinetic resolution



Scheme 11 Catalytic *N*-acylation of 3,4-dihydropyrimidin-2-(1*H*)-ones with enals



Scheme 12 Hydrogen bonding assisted kinetic resolution of acyclic *β*-hydroxy amides



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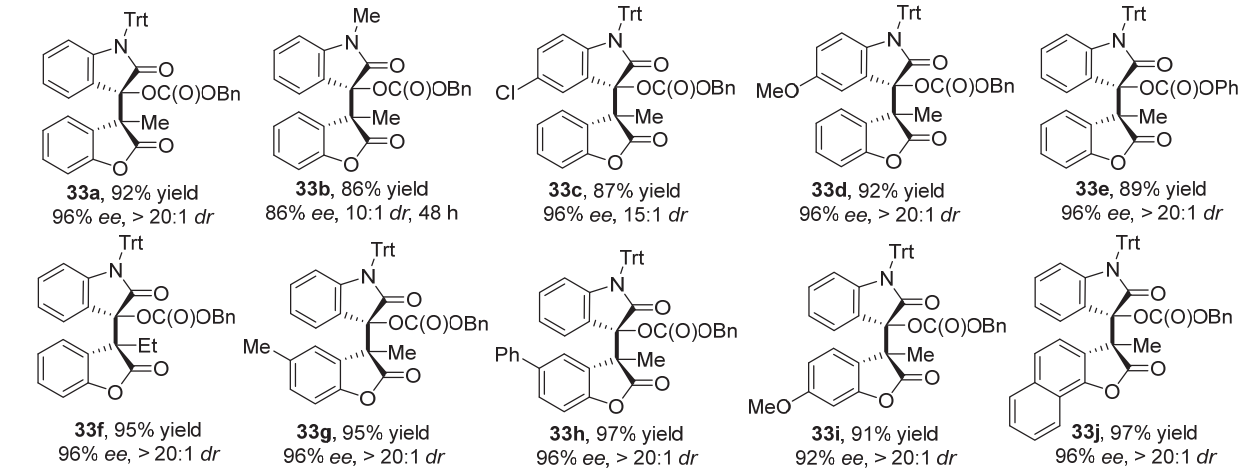
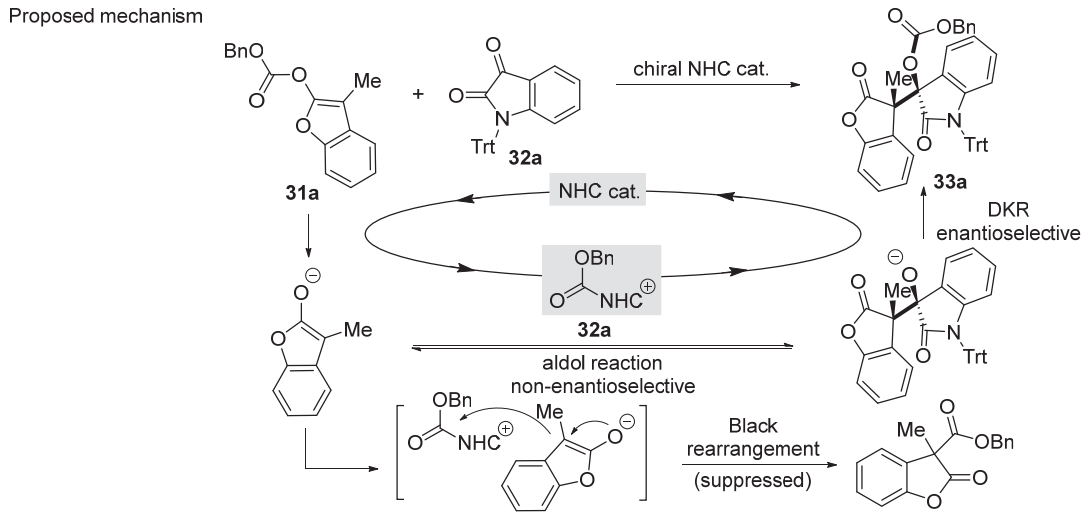


Proposed mechanism



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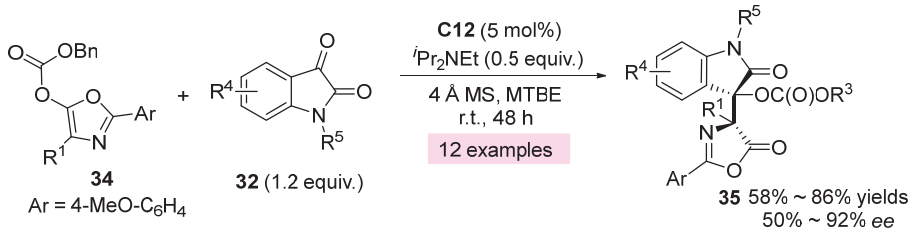

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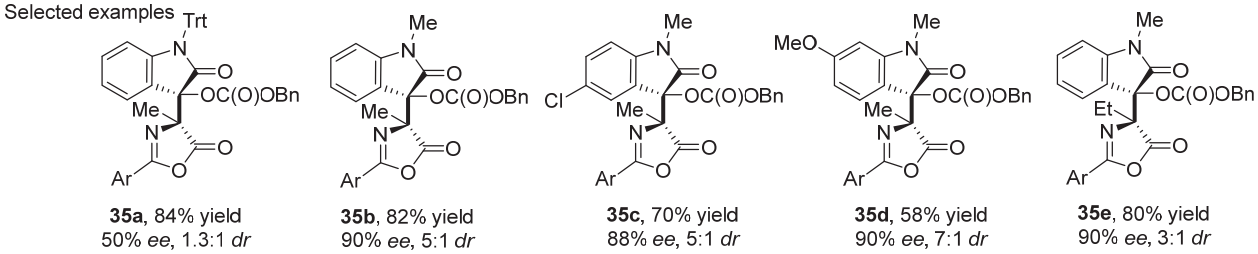


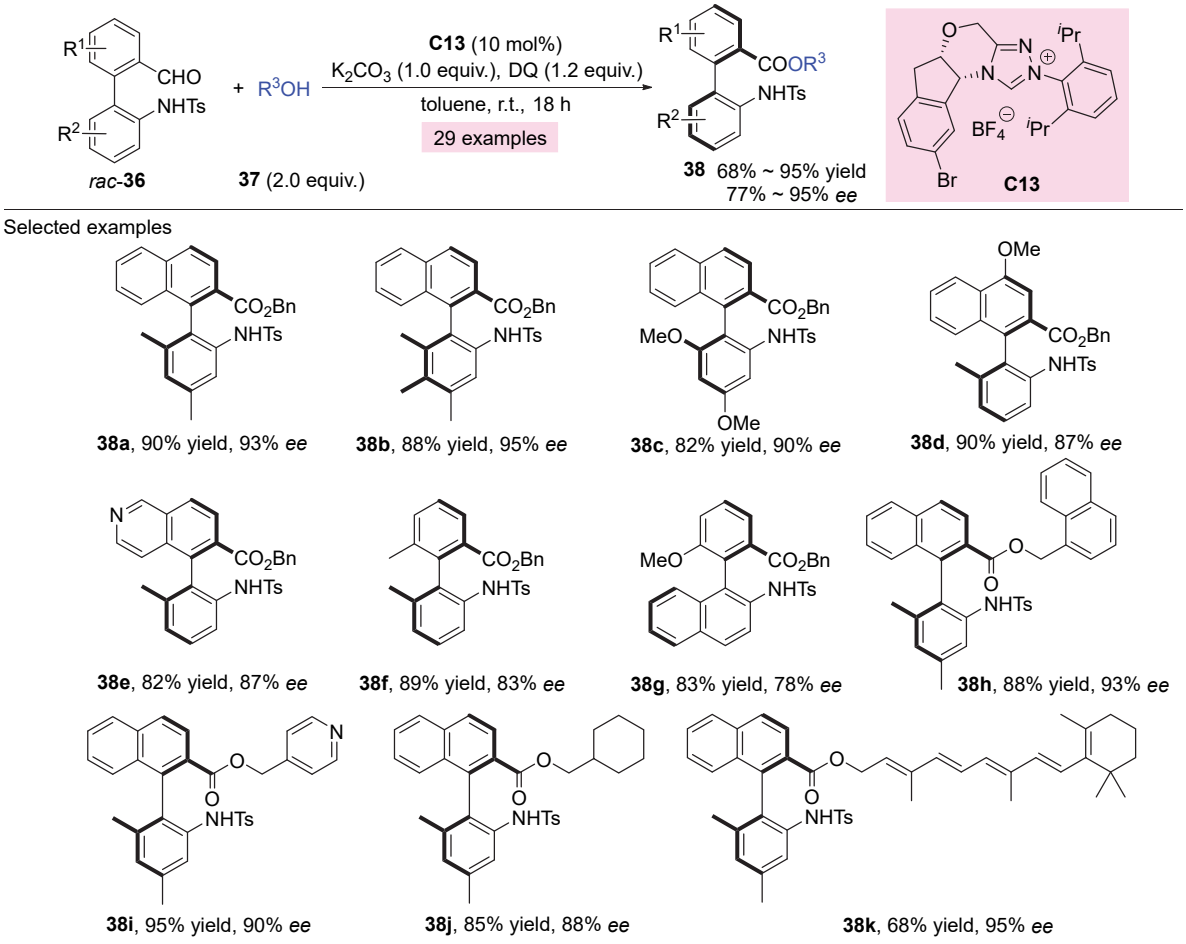
Scheme 13 Post-aldol stereochemistry control and formation of quaternary stereogenic centers

NHC catalyst plays dual roles in two catalytic steps, with the enantioselectivity controlled in a post-aldol DKR process. First, the NHC catalyst activates a masked enolate substrate to initiate the aldol reaction in a non-enantioselective manner. Then the aldol product is transferred to protected aldol product by subsequent step of acylation. The reversible aldol process is key to the dynamic kinetic resolution. The acylated aldol products bearing quaternary/tetrasubstituted carbon stereogenic centers were formed in good yields and high optical purities.

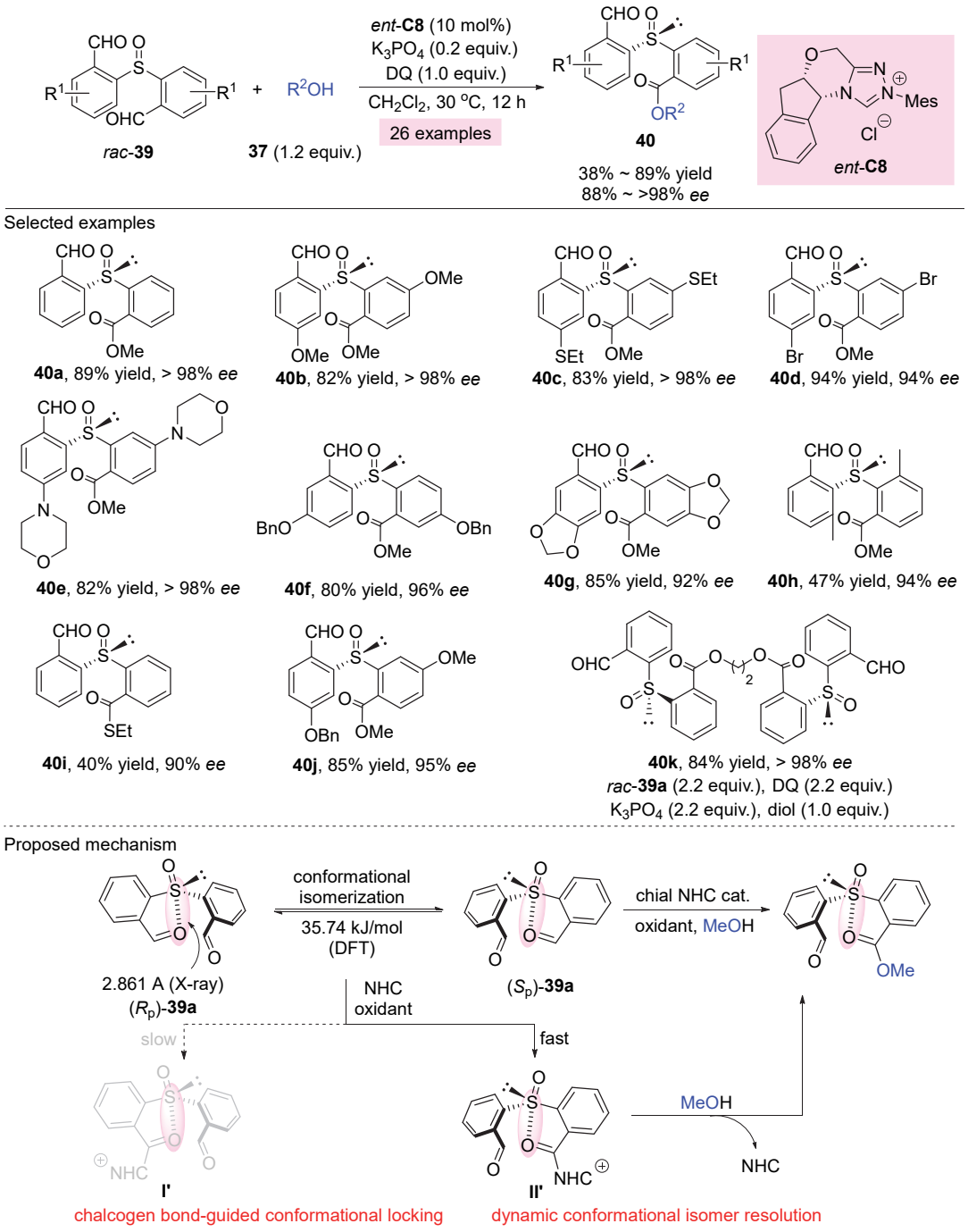
Axially chiral amino acids, which are different from natural and unnatural amino acids with central chirality, are important chiral catalysts and ligands in asymmetric syhthesis, moreover, their derivatives are important skeletons of many bioactive molecules. Therefore, the rapid construction of axially chiral amino acids is of great importance. Wang *et al.*[20] reported an atroposelective NHC catalyzed dynamic kinetic resolution via *in situ* hemiaminals to produce the axially chiral amino esters with high enantioselectivities (Scheme 14). The covalent bond formed between NHC and aldehyde can introduce chirality into the target structure, and the protocol provides a convenient strategy for realizing the enantioselective oxidation of aldehydes under mild conditions.

Chiral sulfoxides are widely used in medicines, agrochemicals and as ligands in asymmetric catalysis, they also work as platform scaffolds to make bioactive molecules and catalysts. Chi *et al.*[21] used chalcogen bond-guided confromational isomerization to realize the dynamic kinetic resolution, affording the corresponding chiral sulfoxides with excellent enantioselectivities (Scheme 15). It is noteworthy that the chalcogen bond breaks the symmetry of sulfoxide and makes it as a racemate by inducing a conformational locking effect. Interconversion of the two enantiomers via chalcogen bond-guided conformational isomerization was also estimated by DFT. Oxidation of Breslow intermediates to the corresponding acyl azolium intermediates was estimated (via DFT) to be the stereoselectivity-determining step in this dynamic kinetic resolution process.

Chiral α-hydroxycarboxylic acid derivatives are important building blocks in synthetic chemistry and also serve as synthetic units of chiral ligands. Among α-hydroxycarboxylic acid derivatives, the α-hydroxythioamide is an interesting and useful compound due to the versatility of the thioamide functionality. Yamada and Takasu *et al.*[22] developed the first catalytic kinetic resolution of α-hydroxythioamides using chiral NHC-catalyzed highly enantioselective acylation assisted by a newly 9-julolidinecarboxylate additive (Scheme 16). The enhanced molecular recognition by forming a hydrogen-bonded complex between the additive and α-hydroxythioamides, which



Scheme 14 Dynamic kinetic resolution to access axially chiral amino esters

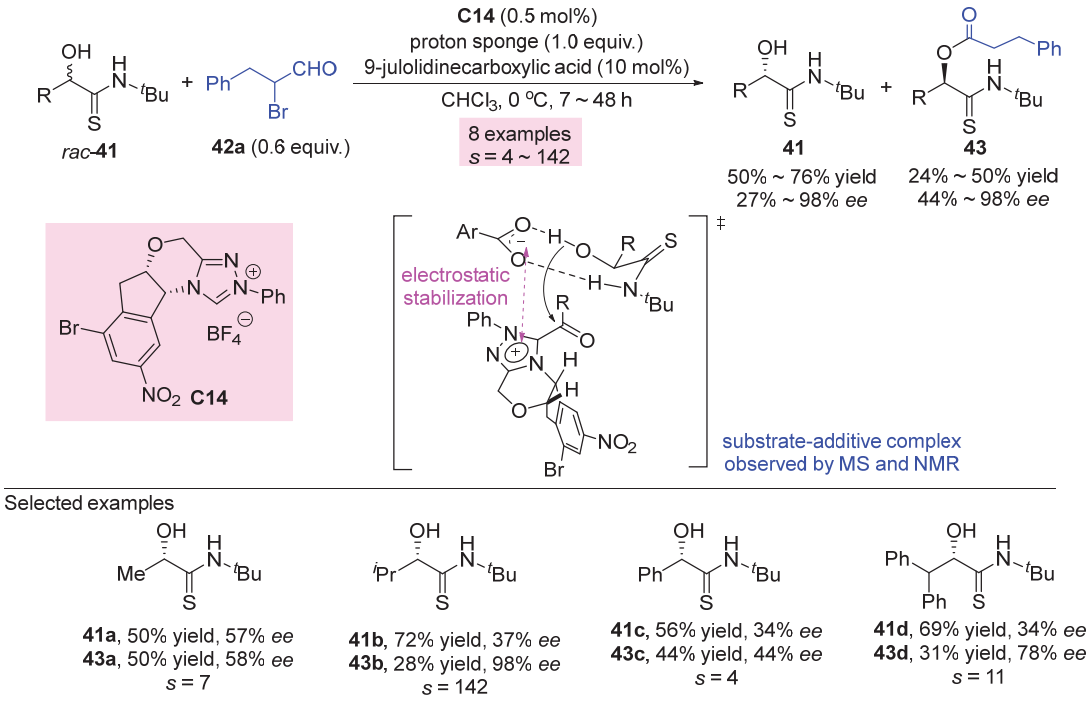


Scheme 15 Dynamic kinetic resolution of sulfoxides

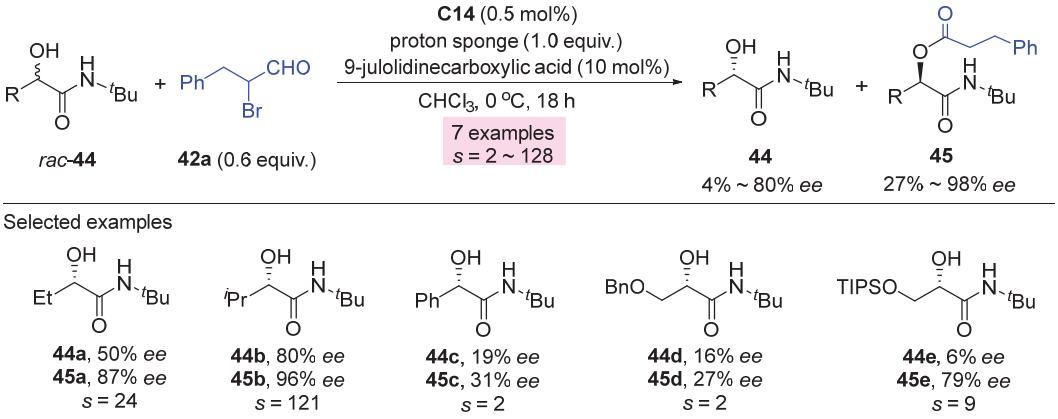
results in the increase of reaction rate and selectivity, is proved by mass spectra (MS) and nuclear magnetic resonance spectroscopy (NMR).

Yamada *et al.*[23] also realized the kinetic resolution of *α*-hydroxyamides (Scheme 17). *N*-*tert*-Butyl-*α*-hydroxyamides provided the best performance and underwent kinetic resolution through enantioselective acylation with the selectivity factor up to 128. Although the ability of amides to form a hydrogen-bonded complex with the substrate is likely lower than that of thiomides, comparable selelctivity was observed in the kinetic resolution. Amide bearing an oxygen functionality could also proceed the reaction smoothly, indicating that the bulky silyl protective group doed not affect the selectivity.

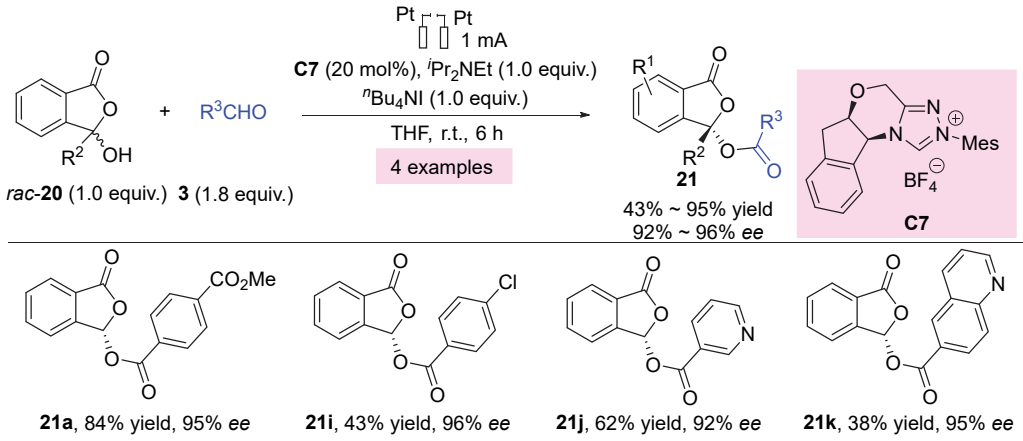
Zhu *et al.*[24] developed an iodide promoted electroredox NHC system and provided an effective way for electrochemical single-electron-transfer (SET) oxidation of Breslow intermediate towards versatile transformations. This method was also applied to the dynamic kinetic resolution of hydroxyphthalides, and various acylated hydroxyphthalides with different ester substituents were produced with excellent enantioselectivities (Scheme 18).



Scheme 16 Kinetic resolution of *α*-hydroxythioamides



Scheme 17 Kinetic resolution of *α*-hydroxyamides

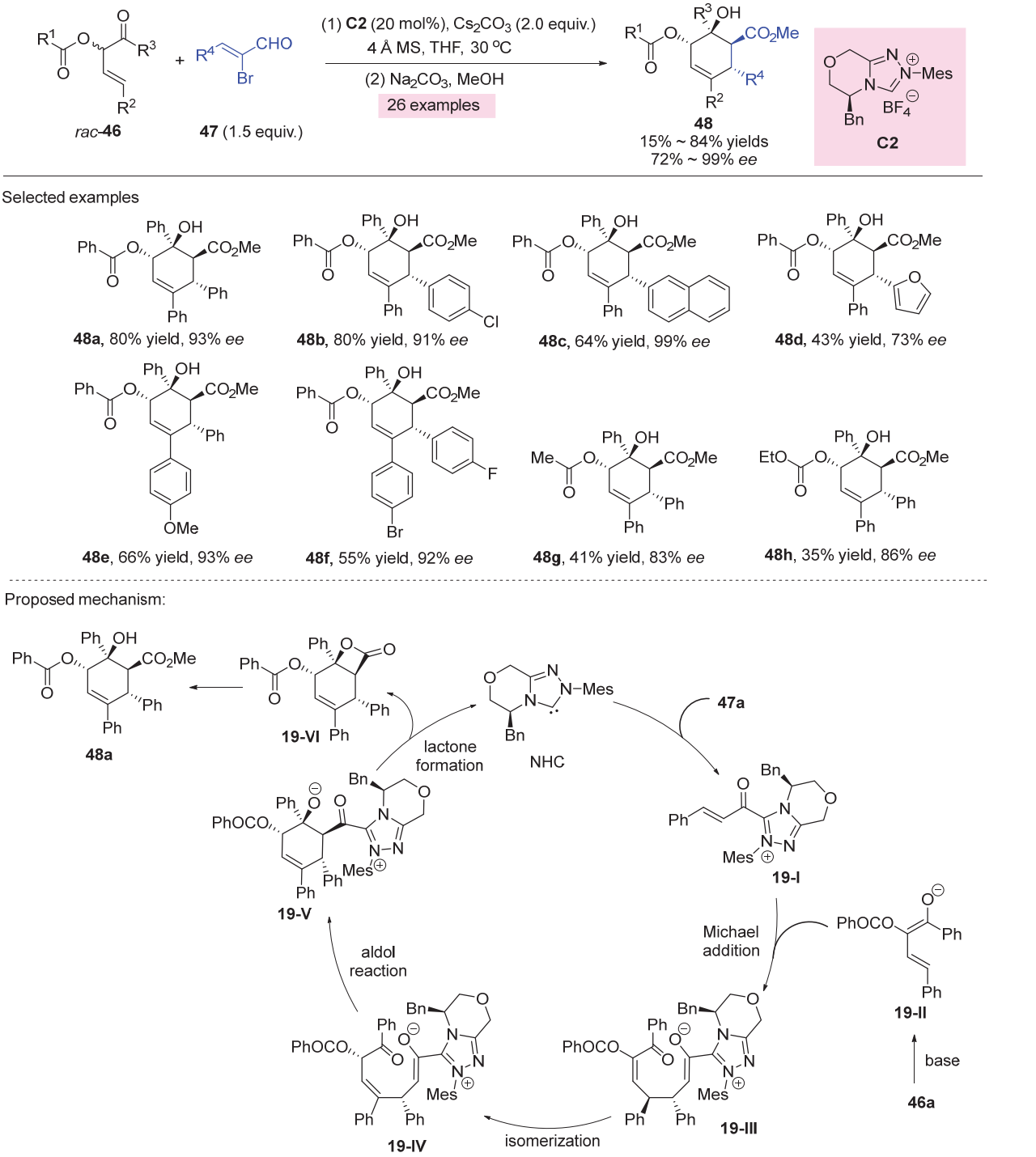


Scheme 18 Dynamic kinetic resolution of hydroxyphthalides using electroredox method

3 Kinetic resolutions mediated by *α,β*-unsaturated acyl azoliums

In this section, we will describe the kinetic resolutions involving *α,β*-unsaturated acyl azolium intermediates. These intermediates are featured by their ability of undergoing various cascade annulation reactions. Through rational design, racemic ketones or esters having nucleophilic sites can realize classical or dynamic kinetic resolutions.

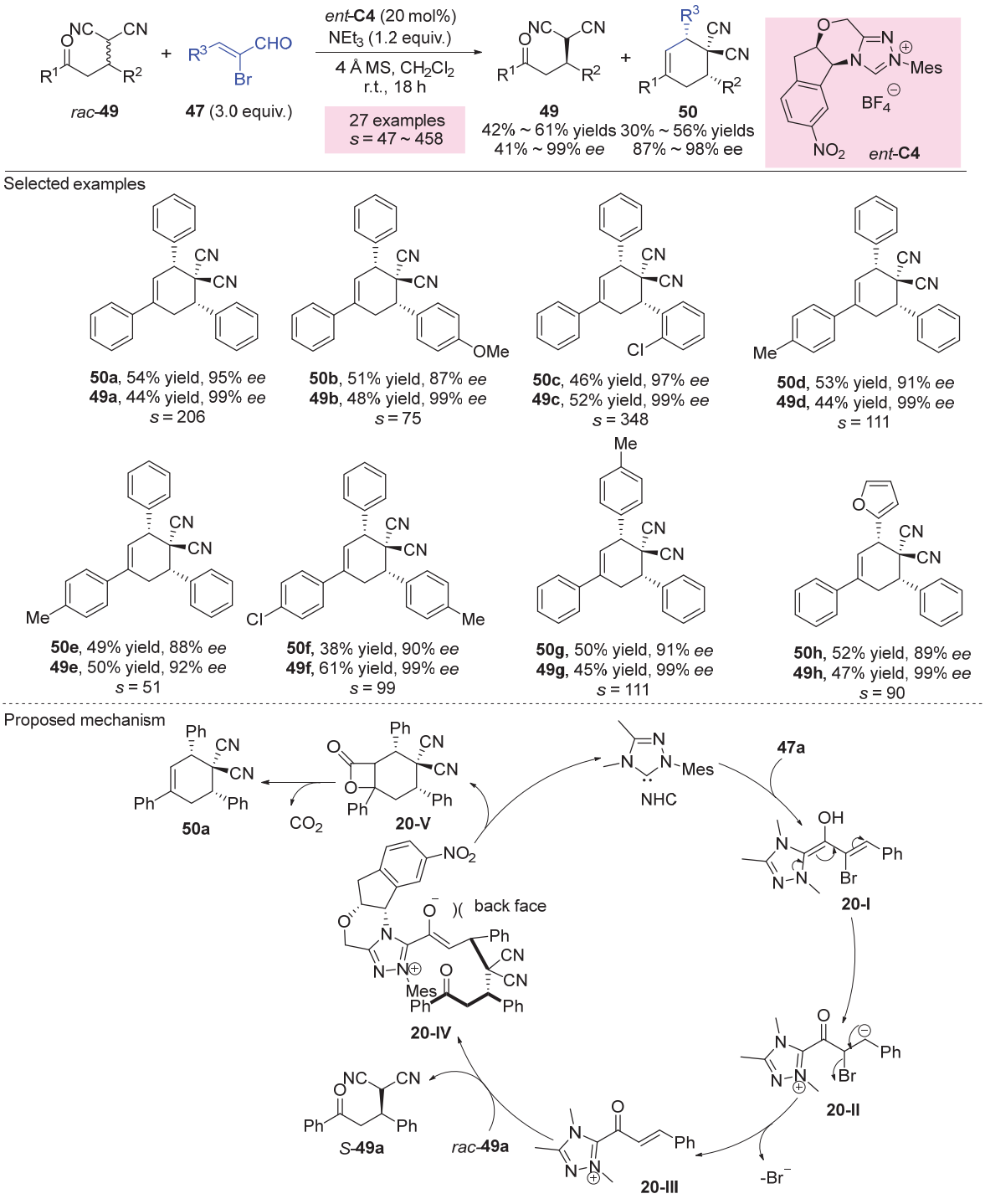
Cyclohexenes and their derivatives are useful building blocks for many biologically active molecules and natural products. In 2017, Fang's group[25] disclosed an NHC-catalyzed enantioselective formal intermolecular all-carbon [4+2] annulation between *in situ* generated acyclic dienolate and conjugated acyl azolium (Scheme 19). Racemic 2-acyloxy-3-butenones were used as the diene precursors and a formal dynamic kinetic resolution process was observed. A series of polysubstituted cyclohexenes were



Scheme 19 NHC-catalyzed intermolecular all-carbon [4+2] annulation

obtained with high to excellent diastereo- and enantioselectivities. They also proposed a mechanism for the reaction. Firstly, carbene reacts with enal to give *α*,*β*-unsaturated acyl azolium **19-I**. Then the Michael addition of **19-II** to **19-I** leads to the production of enolate **19-III**. **19-III** isomerizes to **19-IV**, and the intramolecular aldol reaction-lactonization occurs to release *β*-lactone **19-VI**. The opening of **19-VI** leads to the synthesis of **4a**. According to the proposed mechanism, the stereoselective isomerization is crucial to the formal dynamic kinetic resolution.

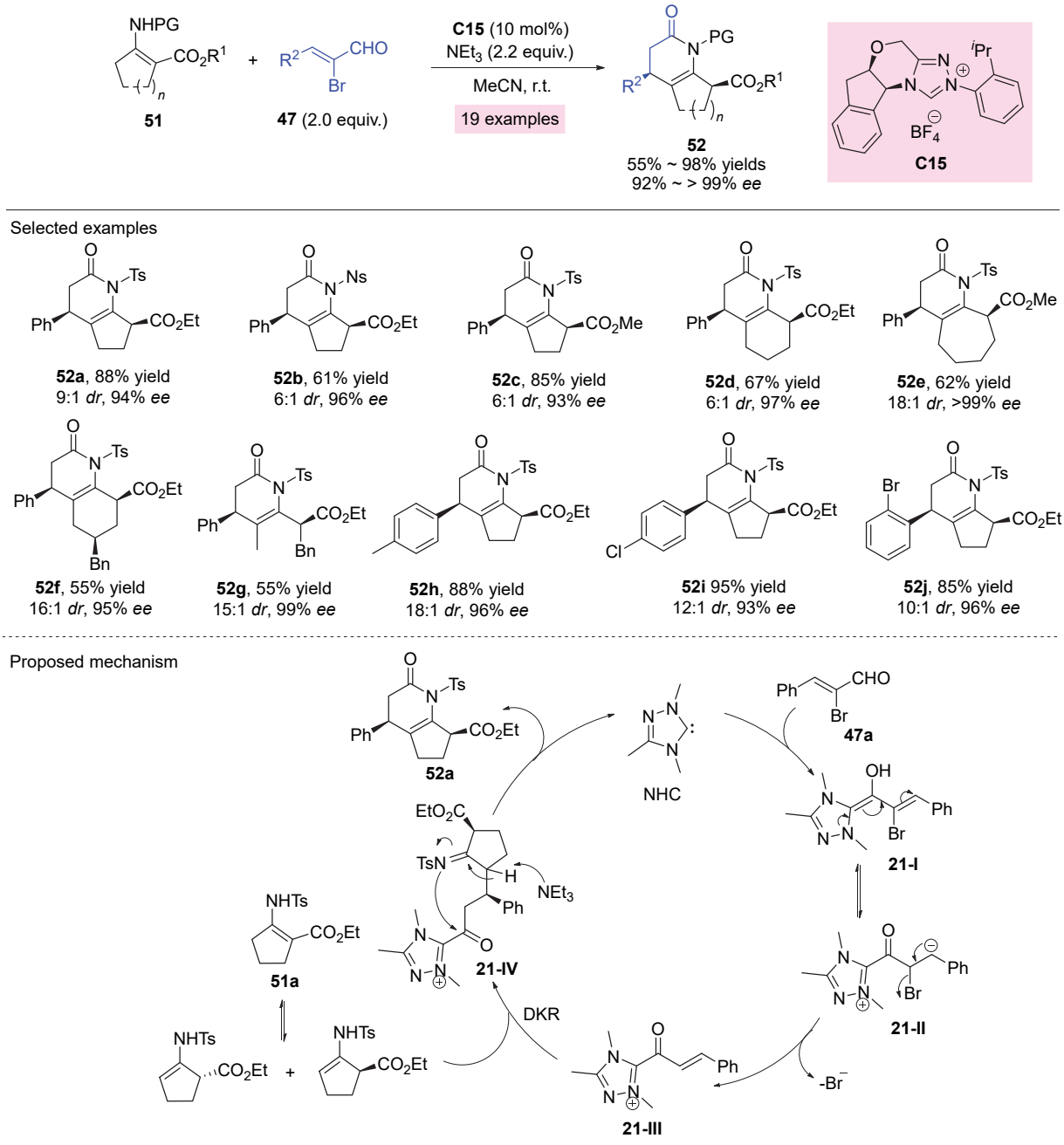
Before 2018, there is no efficient way to achieve the catalytic kinetic resolution of Michael adducts. Inspired by the synthetic importance of the cyclohexenes and Michael adducts, a highly enantioselective kinetic resolution of Michael adducts was realized by Enders *et al.*[26] through NHC catalysis, providing a new route to enantiomerically enriched cyclohexenes and Michael adducts in good yields with high enantiomeric excesses (Scheme 20). A plausible catalytic cycle is also depicted in Scheme 20. Breslow



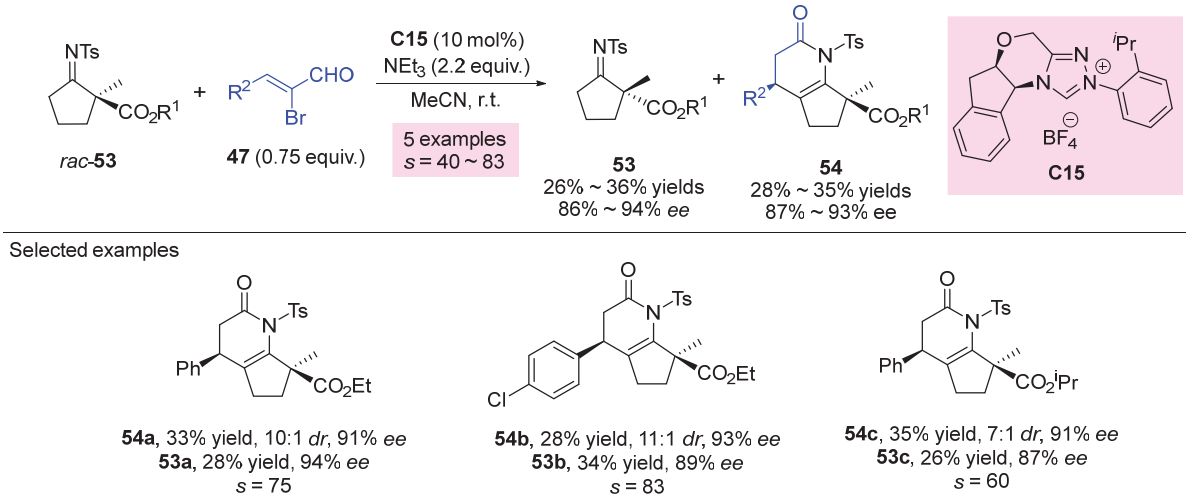
Scheme 20 Kinetic resolution of Michael adducts by Enders *et al.*

intermediate **20-I** is generated from the addition of the NHC catalyst to the *α*-bromoenal **2a**. **20-I** can tautomerize to intermediate **20-II** and then leads to the formation of unsaturated acyl azolium **20-III** through bromide elimination. The Michael addition of the Michael adduct *rac*-**49a** to the *α*,*β*-unsaturated acyl azolium **20-III** from the opposite side of the catalyst chiral backbone generates the azolium enolate **20-IV**. After lactonization and decarboxylation, **50a** is obtained.

Compared to the kinetic resolution of ketones, the dynamic kinetic resolution of imines or enamines is challenging because imines easily tautomerize to enamines. In 2019, Ye *et al.*[27] developed an NHC-catalyzed [3＋3] annulation of *α*-bromoenals with enamines by dynamic kinetic resolution (Scheme 21-1). A series of cyclopentene-, cyclohexene-, and cycloheptene-derived enamines and the acyclic enamines worked well in the reaction, producing polysubstituted dihydropyridones with good diastereoselectivities and high enantioselectivities. According to the proposed mechanism, unsaturated acyl azolium is generated in the same way as before. The isomerization of enamine and Michael addition to intermediate **21-III** are the key steps in dynamic kinetic resolution. The subsequent lactamization affords **52a**. Noteworthy is that a classical kinetic resolution of disubstituted imines was also developed to give both the dihydropyridones and the recovered disubstituted imines with high enantioselectivities (*s* factor up to 83, Scheme 21-2).



Scheme 21-1 Dynamic kinetic resolution of enamines



Scheme 21-2 Classical kinetic resolution of disubstituted imines

The resolution of α-functionalized ketones has been a long-term challenge since the first report by Woodward in 1941. Both stoichiometric and catalytic methods have been developed, but less satisfactory results have been obtained.[28] In 2020, an efficient kinetic resolution protocol affording 11 classes of chiral α-functionalized ketones with up to 684 of the selectivity factor (s) was disclosed by Fang and co-workers using a two-key-step resolution mode (Scheme 22).[29] α-Methylated, α-benzylated, α-allylated, α-estermethylated, α-aminomethylated, and α-thiomethylated ketones, and ketones with α-acetamino, α-alkylthio, α-alkyoxy, α-deuterium, and α-fluoro groups were all accessible with high enantioselectivities. The addition of aminolactam additive plays a crucial role in achieving the resolution. Mechanistic studies showed a two-key-step resolution mode, in which the real kinetic resolution happened at the second aldol step and the enantioenriched ketones were recovered by the first reversible Michael process.

4 Kinetic resolutions mediated by acyl anions (Breslow intermediates)

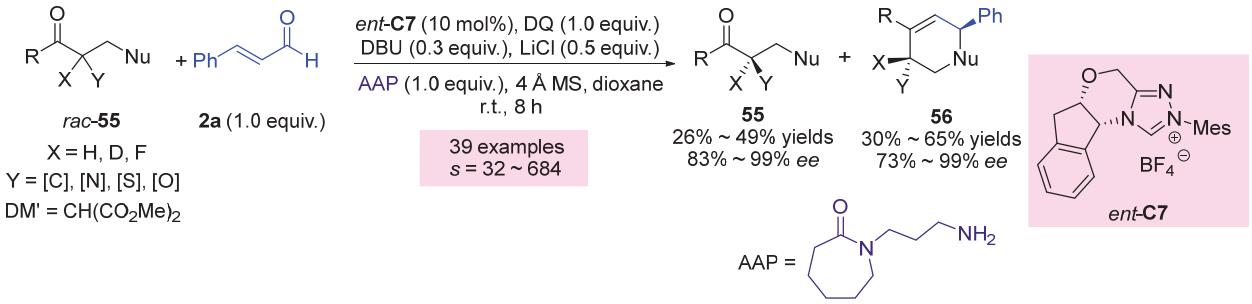
In this section we describe the kinetic resolutions involving acyl anion (Breslow) intermediates. Most of the successful kinetic resolutions using Breslow intermediates are benzoin reactions. The Fang's group conducted systematic studies on kinetic resolutions through benzoin reactions, and reazlied the rapid asymmetric synthesis of various tetralone derivatives having multiple stereocenters.

Racemic mixtures of four stereoisomers are easily formed but less used because of the challenges to separate the four stereoisomers efficiently. Fang's group[30] developed an NHC-catalyzed divergent dynamic kinetic resolution (DDKR) protocol to achieve the separation of racemic mixtures of four stereoisomers (Scheme 23). A series of tetralone products with three stereocenters were formed in a divergent fashion. Mechanistic studies showed two key points for the success of resolution: (1) rapid conversions between (2*S*,3*S*)/(2*R*,3*S*) and (2*R*,3*R*)/(2*S*,3*R*) happened quickly under the reaction conditions, and (2) rapid annulations occurred for (2*S*,3*S*)-**57a** and (2*S*,3*R*)-**57a** to afford the benzoin products, and slow reactions happened for other two isomers.

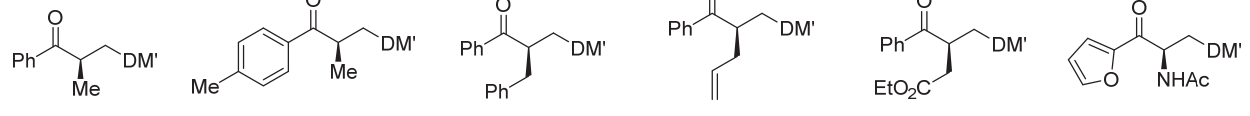
2-Hydroxy-2,3-dihydronaphthalene-1,4-diones (HDNDs) are important skeletons of many natural products possessing antibacterial and antimicrobial activities. Fang's group[31] also employed benzoin reaction-mediated divergent reaction on racemic mixture to synthesize both stereoisomers of 2-hydroxy-2,3-dihydronaphthalene-1,4-diones (Scheme 24). Both *cis*- and *trans*-products could be obtained with good to excellent enantioselectivities in a single step. Noteworthy is that direct catalytic methods are hard to afford HDNDs with two stereogenic centers.

Chiral β-ketoesters and 1,3-diketones possessing fully substituted carbon stereocenters are very useful synthons in both synthetic chemistry and industrial field. In 2019, Fang and co-workers[32] achieved an NHC-catalyzed kinetic resolution of α,α-disubstituted β-ketoesters using intramolecular benzoin reaction, deriving a series of previously unavailable β-ketoesters with all-carbon quaternary stereocenters in good to excellent enantioselectivities (Scheme 25). The reaction tolerated two different α-benzyl or α-allyl groups, and the ketone unit could be aryl or alkyl group. It is worth to be mentioned that catechol additive is crucial in enhancing the selectivity of the resolution.

Using the same strategy, Fang *et al.* [33] also accomplished the kinetic resolution of 2,2-disubstituted 1,3-diketones through Breslow intermediate participated annulations (Scheme 26). Various chiral tetralone derivatives and 1,3-diketones, which were not easily accessible via conventional asymmetric catalysis can be obtained with high enantioselectivities. Two basic kinetic resolution modes exist in the reaction: (1) classical kinetic resolution happens when the two ketone moieties have apparent different reactivities (Scheme 26A), and (2) divergent reaction on



Selected examples



55a, 48%, 98% *ee*
56a, 49%, 98% *ee*
50% conv., *s* = 458

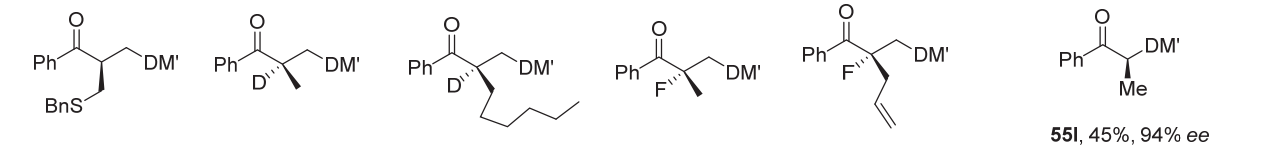
55b, 46%, 93% *ee*
56b, 46%, 99% *ee*
48% conv., *s* = 684

55c, 46%, 98% *ee*
56c, 48%, 93% *ee*
51% conv., *s* = 127

55d, 48%, 98% *ee*
56d, 46%, 98% *ee*
50% conv., *s* = 458

55e, 46%, 95% *ee*
56e, 45%, 96% *ee*
50% conv., *s* = 183

55f, 26%, 99% *ee*
56f, 65%, 75% *ee*
57% conv., *s* = 35



55g, 39%, 83% *ee*
56g, 52%, 96% *ee*
46% conv., *s* = 128

55h, 48%, 97% *ee*
56h, 49%, 96% *ee*
50% conv., *s* = 207

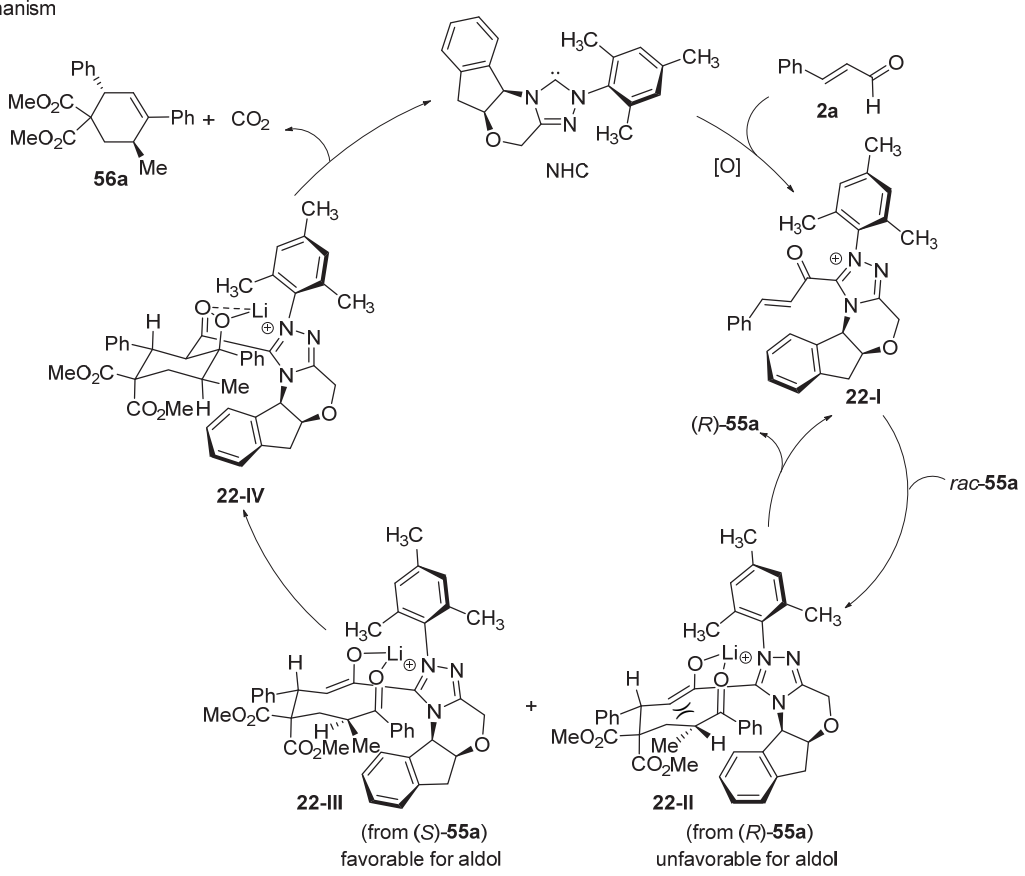
55i, 47%, 98% *ee*
56i, 48%, 98% *ee*
50% conv., *s* = 458

55j, 40%, 99% *ee*
56j, 50%, 73% *ee*
58% conv., *s* = 32
2a (1.2 equiv.)
DQ (1.2 equiv.)

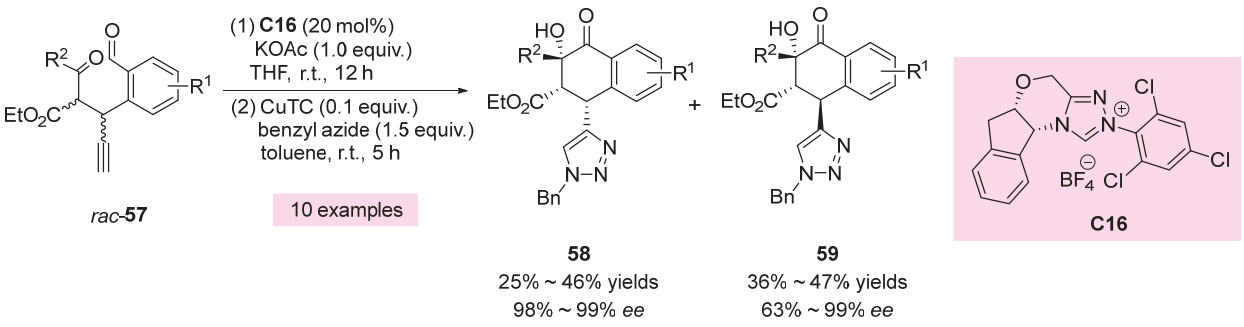
55k, 45%, 99% *ee*
56k, 49%, 91% *ee*
52% conv., *s* = 111
2a (1.2 equiv.)
DQ (1.2 equiv.)

55l, 45%, 94% *ee*
56l, 50%, 83% *ee*
53% conv., *s* = 38
2a (1.5 equiv.), *ent*-**C7** (20 mol%)
DQ (1.2 equiv.), DBU (0.4 equiv.)
LiCl (5 equiv.), AAP (0.1 equiv.)

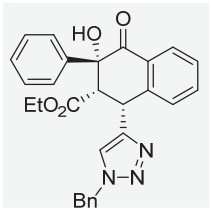
Proposed mechanism



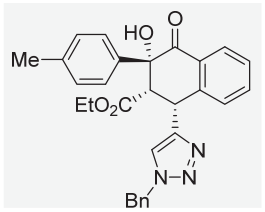
Scheme 22 Kinetic resolution of various α-functionalized ketones



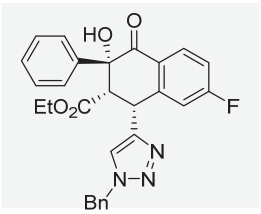
Selected examples



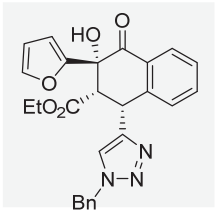
58a
38% yield
99% *ee*



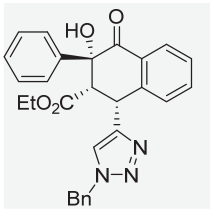
58b
35% yield
99% *ee*



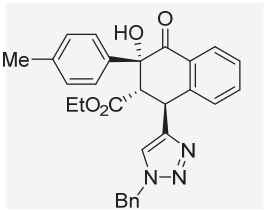
58c
26% yield
98% *ee*



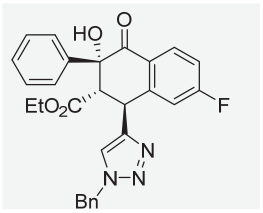
58d
25% yield
99% *ee*



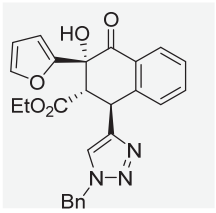
59a
42% yield
90% *ee*



59b
43%yield
85% *ee*

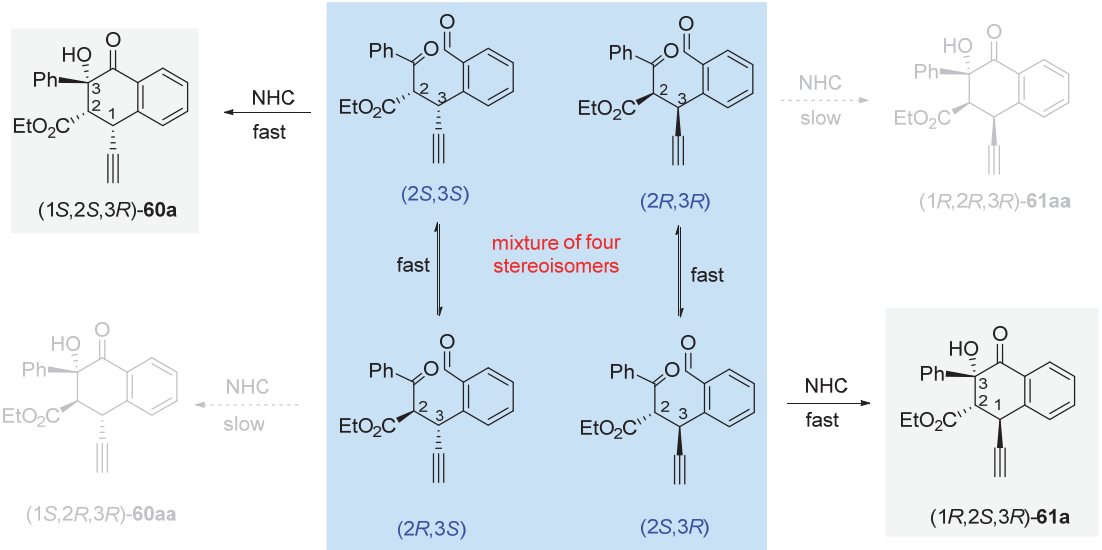


59c
37% yield
89% *ee*

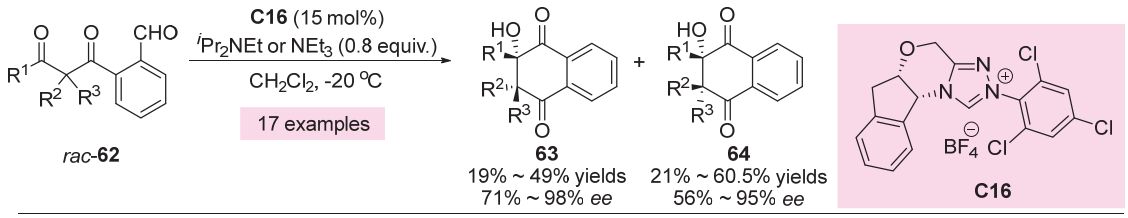


59d
39%yield
88% *ee*

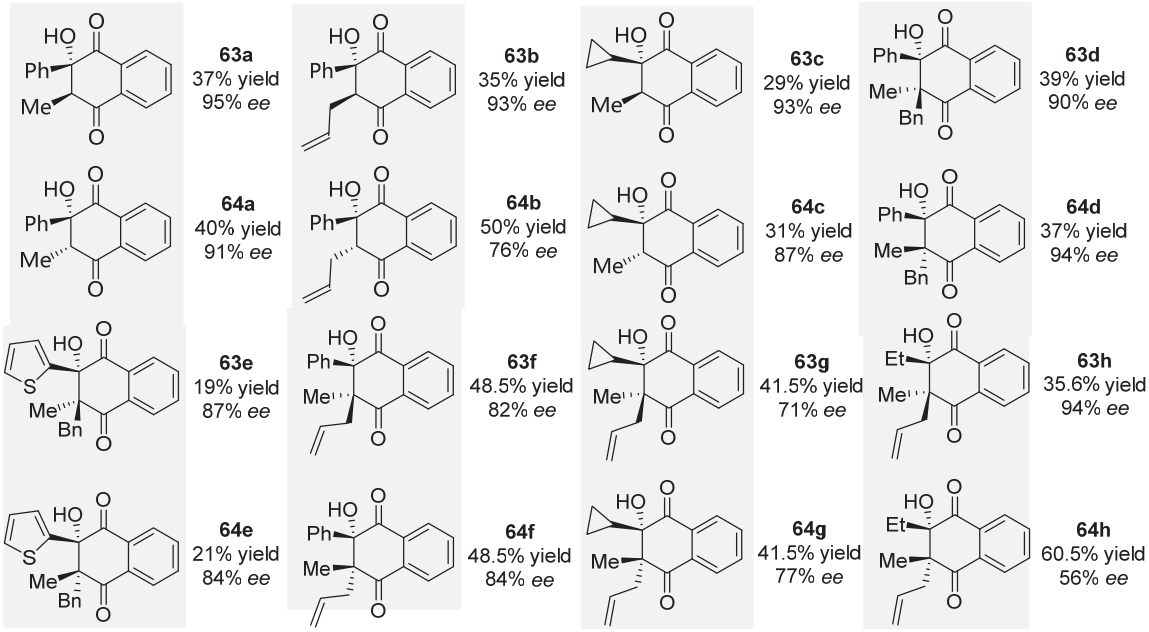
Proposed mechanism



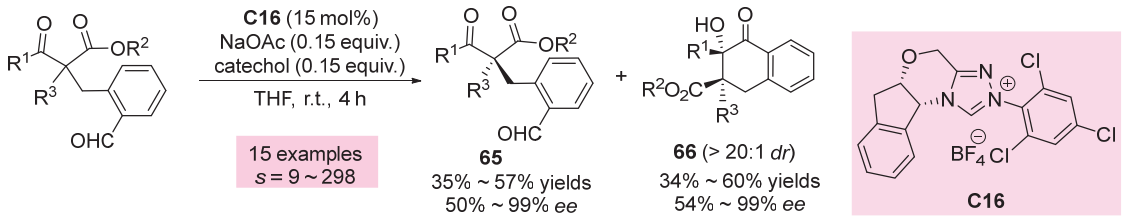
Scheme 23 One-step separation of racemic mixtures of four stereoisomers



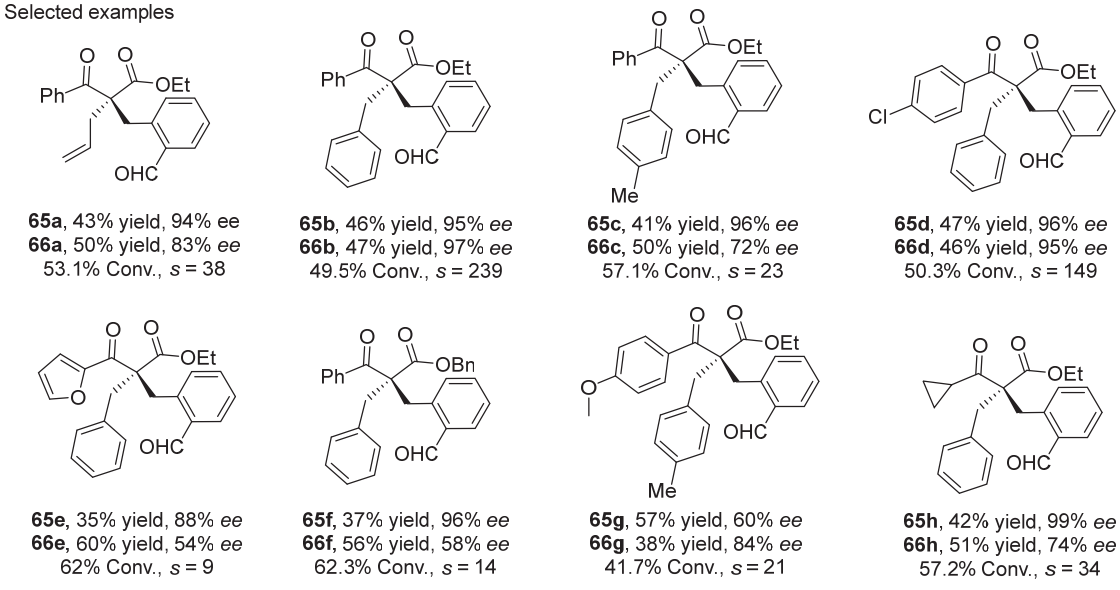
Selected examples



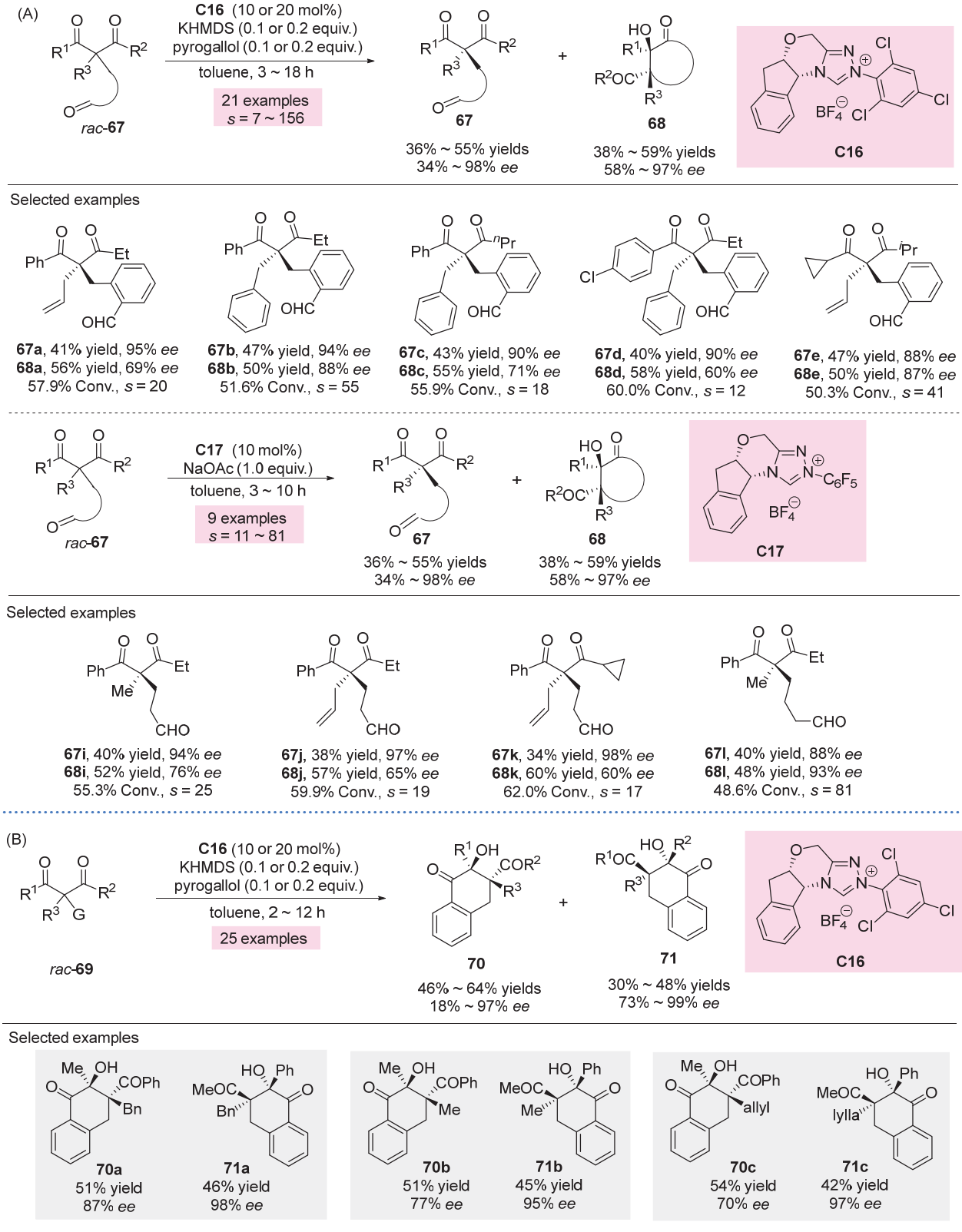
Scheme 24 Synthesis of *cis*- and *trans*-HDNDs



Selected examples



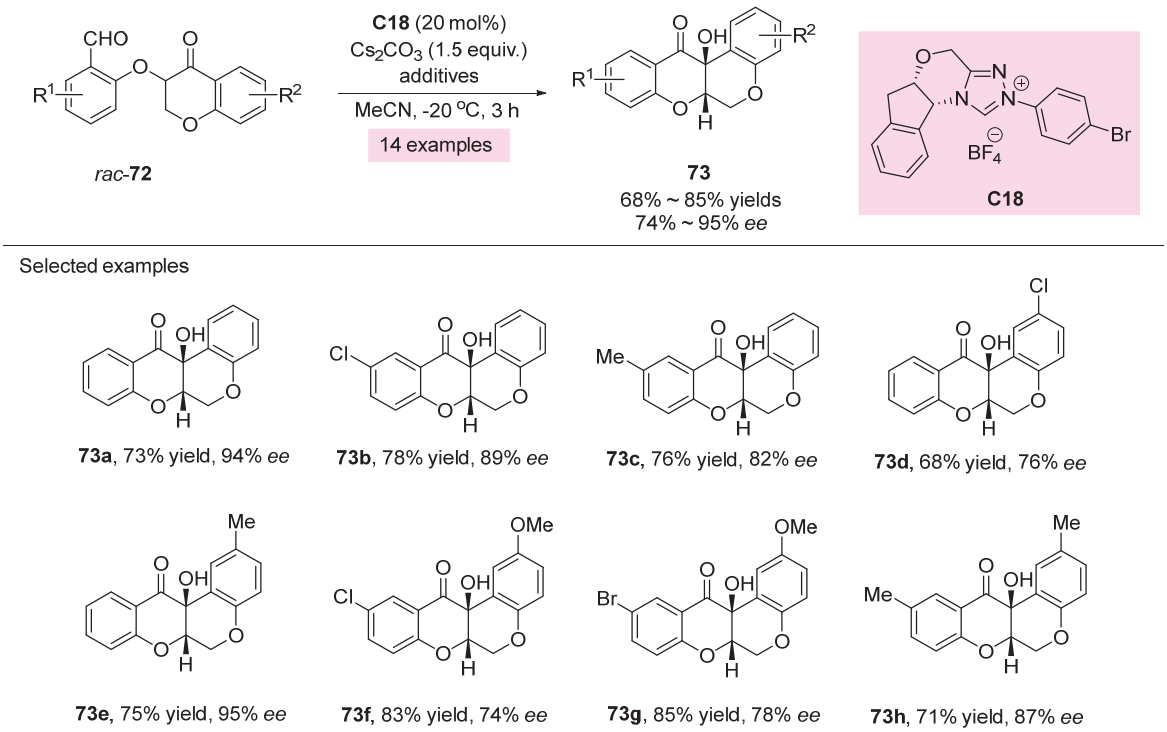
Scheme 25 Kinetic resolution of α,α-disubtituted β-ketoesters



Scheme 26 Classical kinetic resolution and divergent reaction of 1,3-diketones

racemic mixture (divergent RRM) happens when the two ketone units show comparable reactivities (Scheme 26B).

Rotenoids, which are famous because of its insecticidal, anticancer, and antiplasmodial activities, are a class of isoflavonoids that arises in nature by oxidative cyclization of 2'-methoxyisoflavones. Recently, Fang and co-workers successfully realized the concise construction of the *cis*-fused tetrahydrochromeno[3,4-*b*]chromene core structure of rotenoids through NHC-catalyzed dynamic kinetic resolution (Scheme 27).[34] A series of annulation products



Scheme 27 Construction of tetrahydrochromeno[3,4-*b*]chromenes by dynamic kinetic resolution

containing rotenoid key structures were rapidly assembled using this method. The protocol enabled the modular synthesis of a variety of rotenoid natural products in a highly convergent fashion, and the concise asymmetric total synthesis of tephrosin, the first asymmetric total synthesis of 12a-hydroxymunduserone, milletosin, and 12a-hydroxyrotenone, and the formal synthesis of deguelin were accomplished (Scheme 28).

The rapid construction of axially chiral benzonitriles and their derivatives remains challenging and thus limits the further applications. Chi and co-workers[35] disclosed an unprecedented dynamic kinetic resolution method using racemic 2-arylbenzaldehydes and sulfonamides as the substrates to afford axially chiral benzonitriles in good to excellent yields and enantioselectivities (Scheme 29). DFT calculations suggest that the loss of *p*-toluenesulfinate group is both the rate-determining and stereo-determining step. They also postulated a mechanism for the reaction.

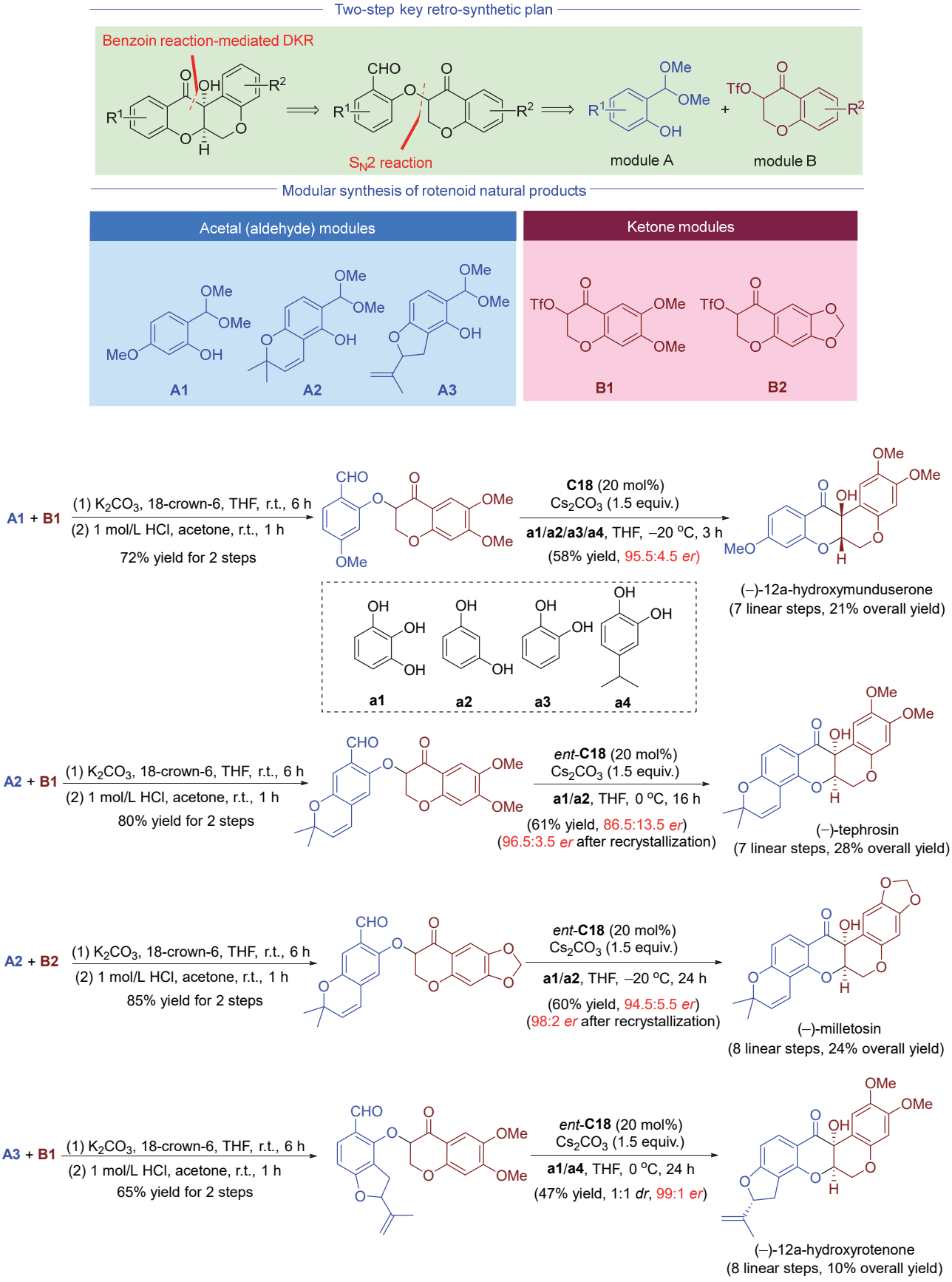
Racemic 2-arylbenzaldehyde can condense with $TsNH_2$ to deliver the racemic imines (±)-**74aa**. The addition of NHC to imime is reversible to give aza-Breslow intermediates **29-I** and **29-III**. The loss of the *p*-toluenesulfonyl anion from the aza-Breslow intermediate is predicted to be rate-determining and stereo-determining. The carbonitrile product is finally generated by deprotonation process (Scheme 29).

5 Kinetic resolutions mediated by azolium enolates

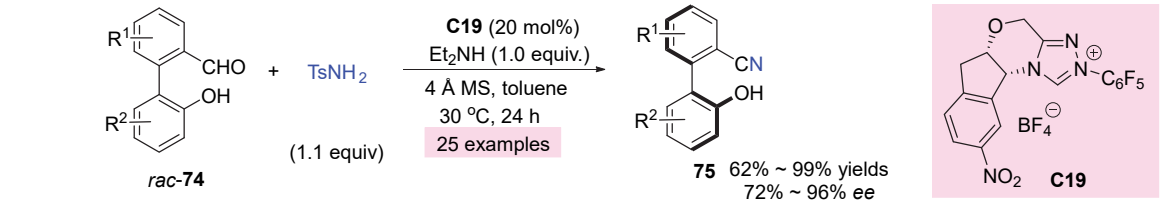
In this section we describe the kinetic resolutions involving azolium enolate intermediates. This class of intermediates are nucleophilic and can attack ketones and imines. So using this character, some annulation reactions can be designed and kinetic resolutions are observed in the reactions.

In 2017, Biju *et al.*[36] realized the dynamic kinetic resolution of acyclic ketoacids through NHC-catalyzed enantioselective aldol lactonization (Scheme 30). The cyclopentane-fused *β*-lactones having three contiguous stereocenters could be obtained with moderate to good yields, diastereoselectivities, and enantioselectivities. Mechanistic study shows that the NHC-bound enolate **30-IV**, which is generated under basic conditions from acyl azolium **30-II** or the ketene intermediate **30-D**, is key for the reaction. **30-IV** proceeds intramolecular aldol reaction of enolate to afford intermediate **30-E**. The *β*-lactonization of **30-E** delivers the final product **77**.

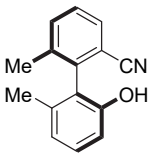
Chi *et al.*[37] realized the activation of *γ*-carbon in cyclopropylcarbaldehydes for the first time to proceed Mannich reaction with *N*-sulfonyl *α*-iminoesters (Scheme 31). The reaction can produce a series of enantiomerically enriched *δ*-lactams with up to 98% *ee* via dynamic kinetic asymmetric transformation. The ring-opening process of the Breslow Intermediate **31-I** to form the chiral azolium enolate intermediates, the dynamic kinetic asymmetric transformation of the chiral azolium enolate intermediates through asymmetric Mannich reaction and the second dynamic kinetic resolution of **31-IIIa** and **31-IIIb** through a stereoselective lactam formation process are crucial to the stereoselective control of the reaction.



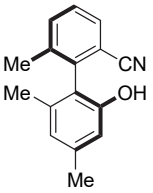
Scheme 28 Total synthesis of 12a-hydroxymunduserone, tephrosin, milletosin and 12a-hydroxyrotenone



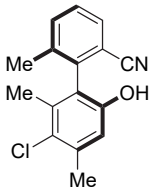
Selected examples



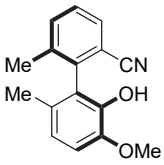
75a, 96% yield, 96% *ee*



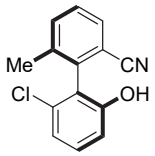
75b, 97% yield, 96% *ee*



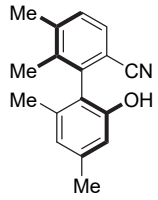
75c, 98% yield, 72% *ee*



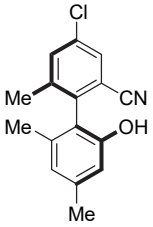
75d, 85% yield, 80% *ee*
1-naphthylphenol (0.2 equiv.)
0 °C, 36 h



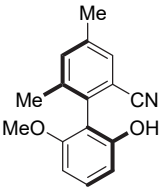
75e, 89% yield, 90% *ee*
1-naphthylphenol (0.2 equiv.)
0 °C, 36 h



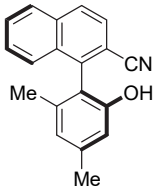
75f, 82% yield, 94% *ee*



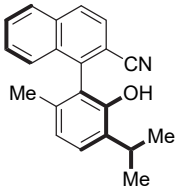
75g, 62% yield, 88% *ee*



75h, 90% yield, 86% *ee*

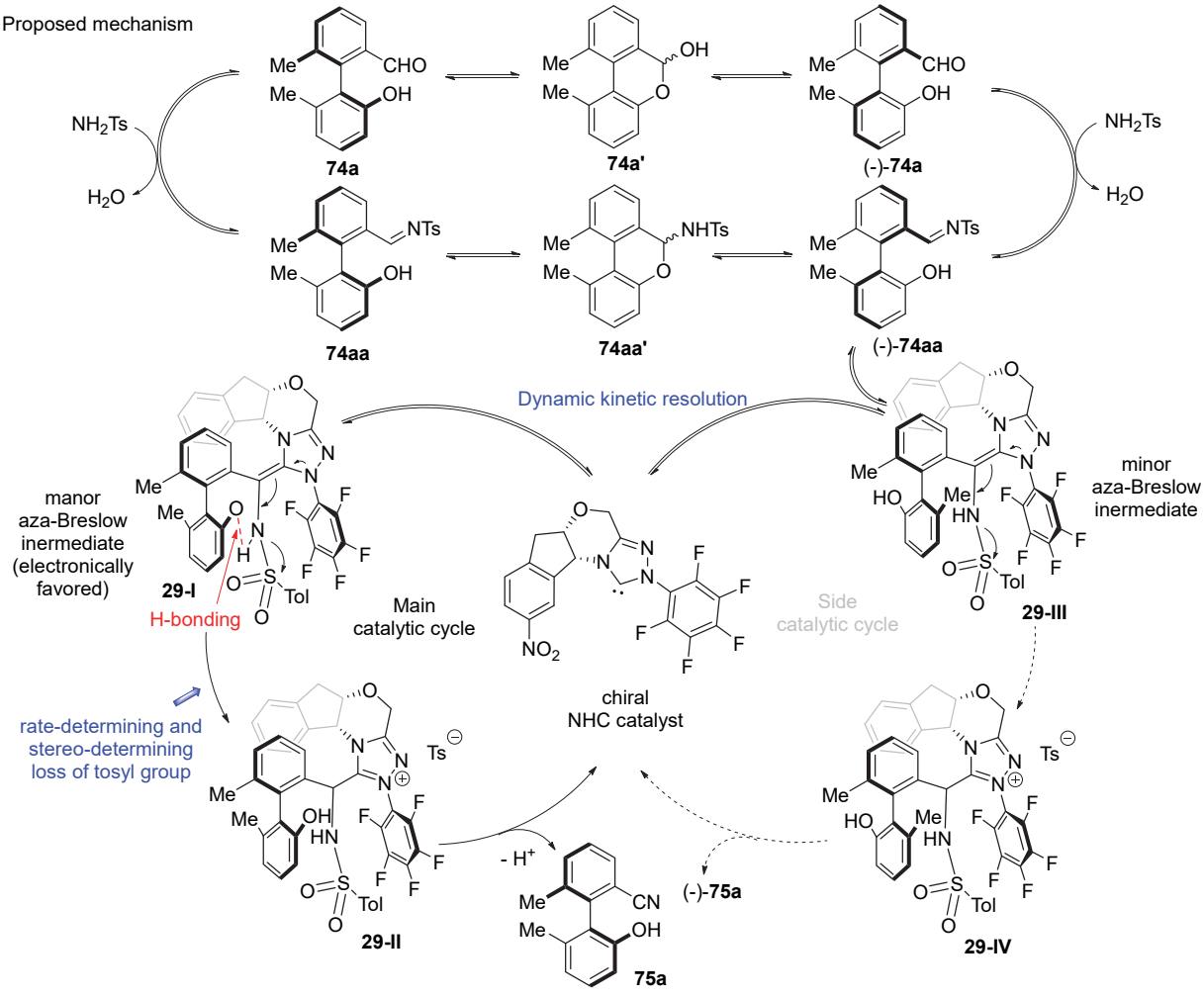


75i, 99% yield, 86% *ee*
1-naphthylphenol (0.2 equiv.)
0 °C, 36 h

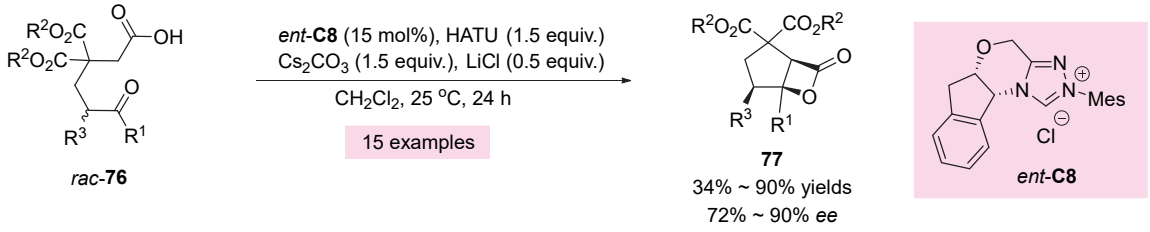


75j, 94% yield, 80% *ee*
1-naphthylphenol (0.2 equiv.)
0 °C, 36 h

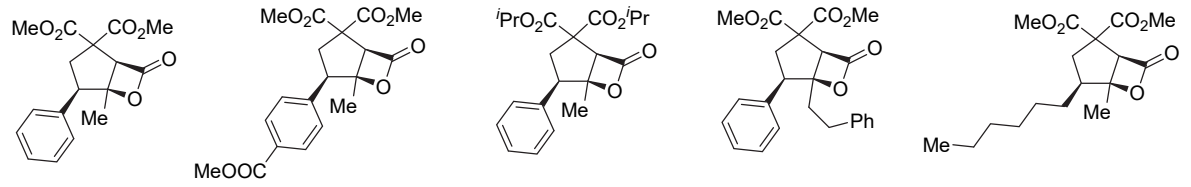
Proposed mechanism



Scheme 29 Atroposelective synthesis of axially chiral benzonitriles



Selected examples



77a, 70% yield
10:1 *dr*, 90% *ee*

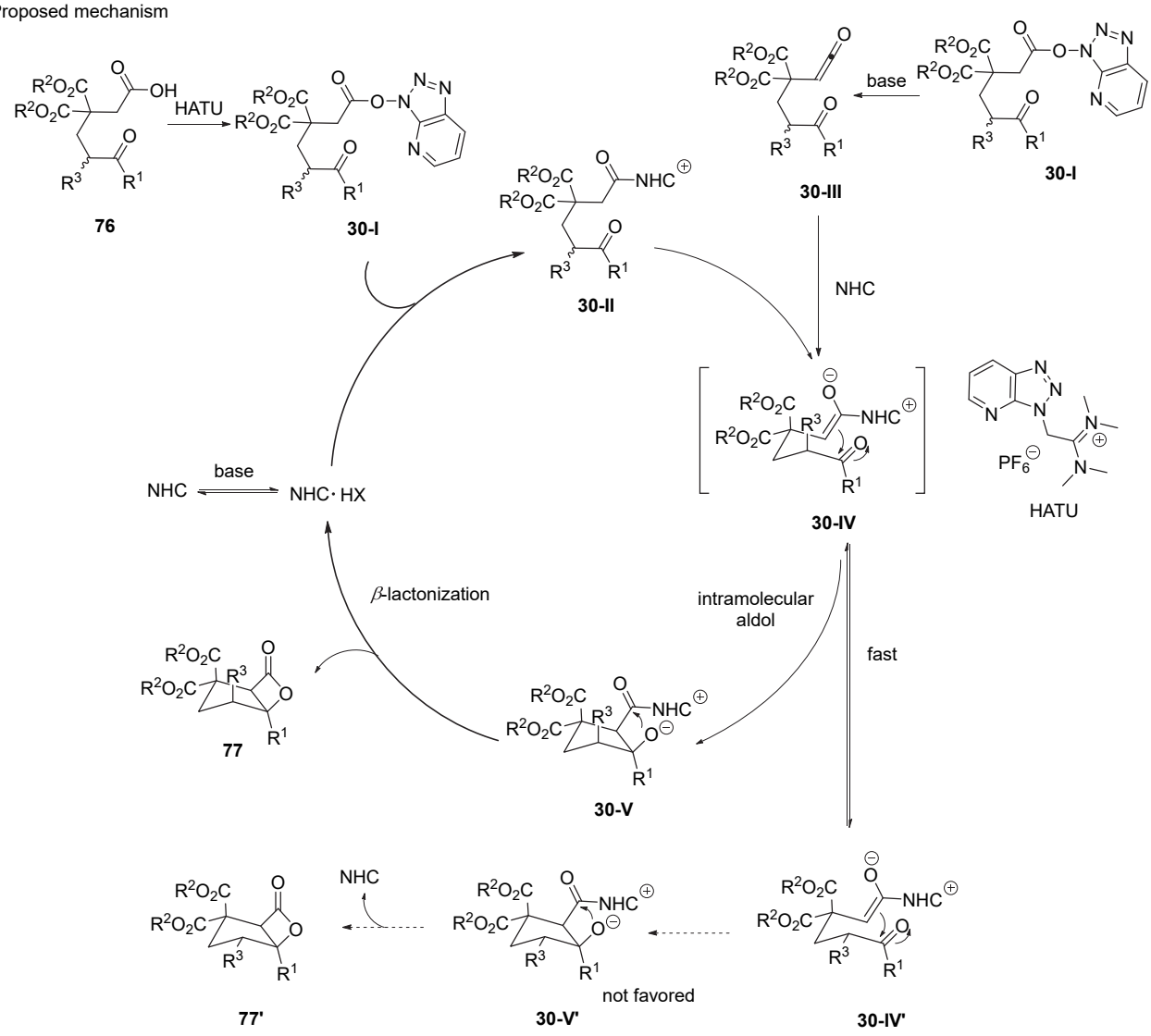
77b, 72% yield
16:1 *dr*, 86% *ee*

77c, 67% yield
> 20:1 *dr*, 84% *ee*

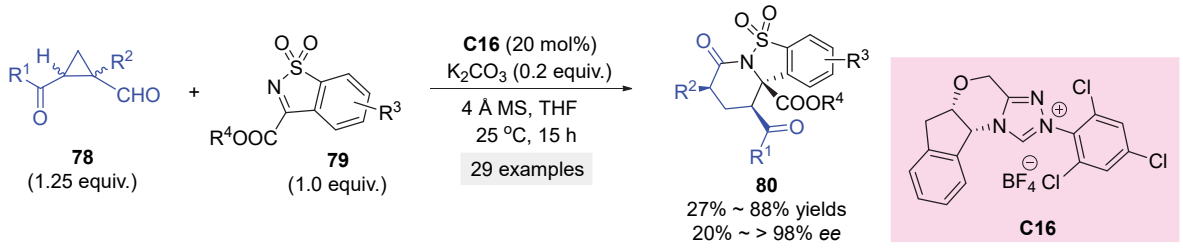
77d, 40% yield
> 20:1 *dr*, 90% *ee*

77e, 75% yield
2:1 *dr*, 88% *ee*

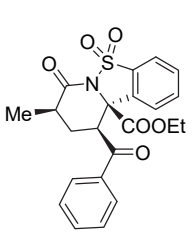
Proposed mechanism



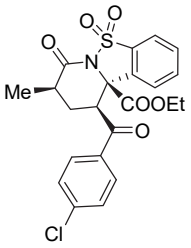
Scheme 30 Dynamic kinetic resolution of acyclic ketoacids



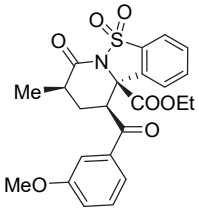
Selected examples



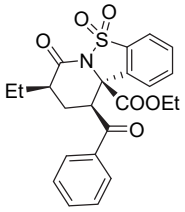
80a, 83% yield
96% *ee*, 7:1 *dr*



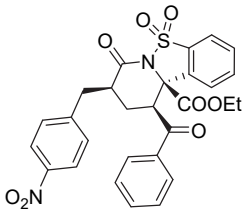
80b, 83% yield
96% *ee*, 5:1 *dr*



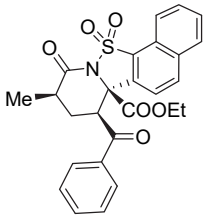
80c, 75% yield
98% *ee*, 4:1 *dr*



80d, 71% yield
94% *ee*, 5:1 *dr*

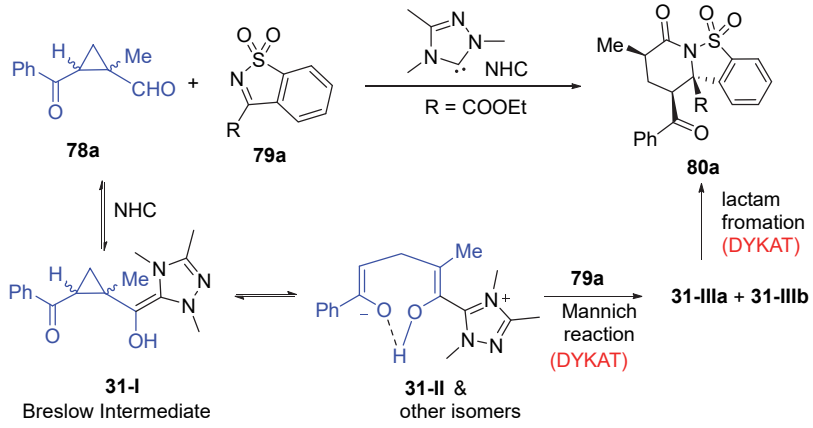


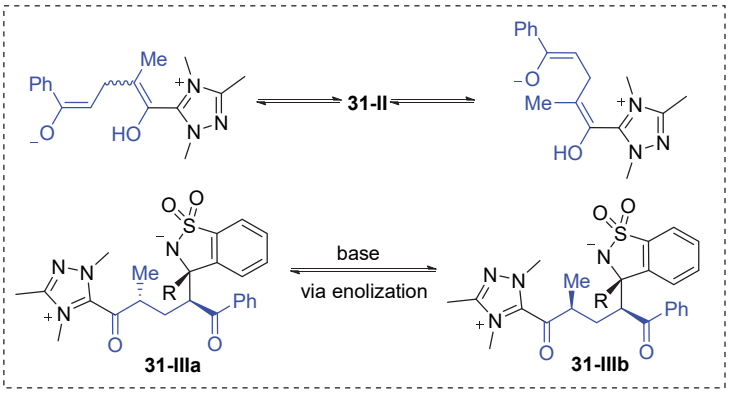
80e, 60% yield
80% *ee*, 5:1 *dr*



80f, 76% yield
96% *ee*, 3:1 *dr*

Proposed mechanism





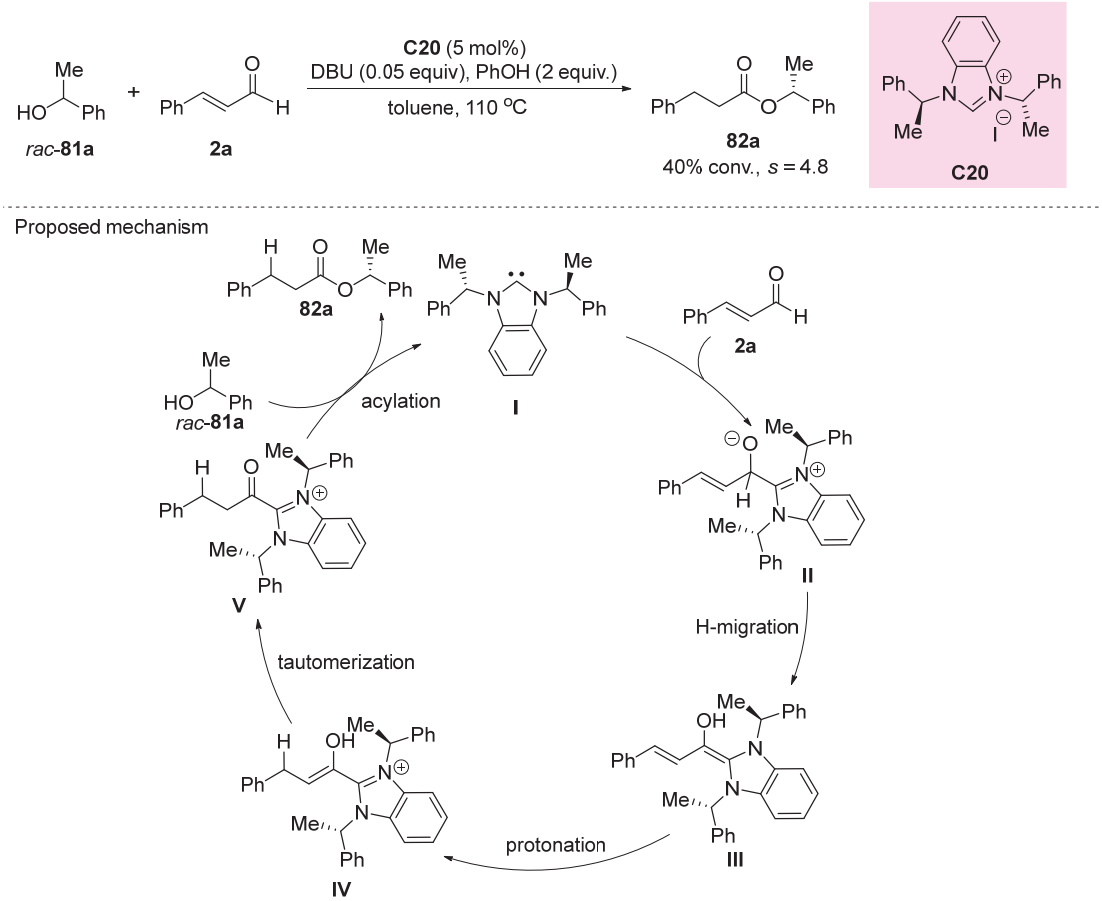
Scheme 31 Dynamic kinetic asymmetric transformation of cyclopropylcarbaldehydes

6 Kinetic resolutions mediated by NHC-bound homoenolates

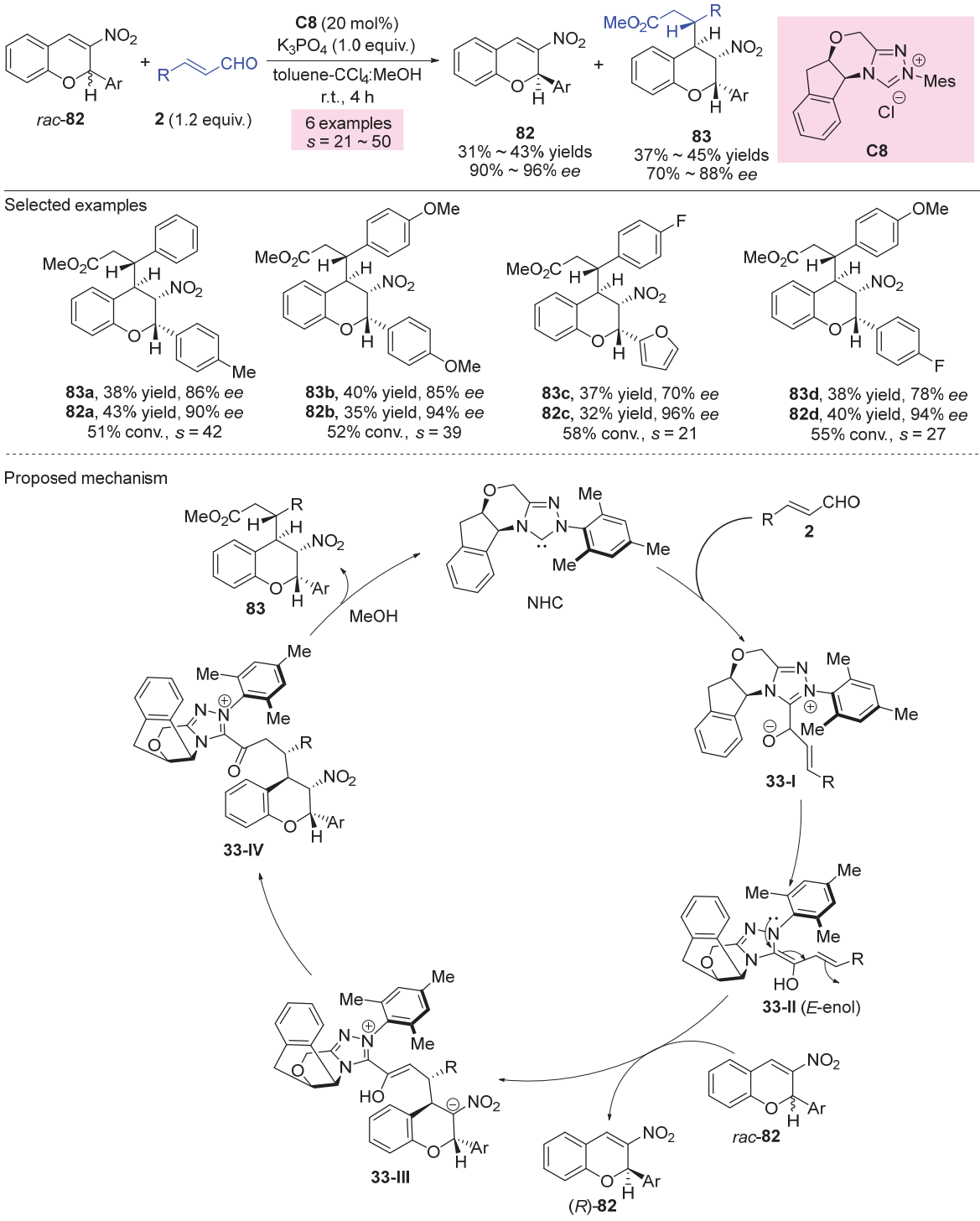
In this section, the kinetic resolutions involving NHC-bound homoenolate intermediates are described. These intermediates are also nucleophilic and featured by cascade annulations or protonation-esterification. Scheidt *et al.*[38] transformed unsaturated aldehydes into saturated esters using an NHC-catalyzed homoenolate process (Scheme 32). The reaction could also be used to the kinetic resolution of secondary alcohols with the *s* of 4.8. The addition of carbene to enal generates **32-II**, which undergo subsequent proton transfer to afford homoenolate. Then the protonation and tautomerization of homoenolate generate acyl azolium **32-V**, which can be esterificated by alcohol to produce the final product. Phenol is involved in the protonation process.

NHC-catalyzed kinetic resolution through Michael addition by homoenolate intermediate has been less explored. Due to the widespread synthetic applications of chromane and 2*H*-chromene, in 2019, Maji *et al.*[39] developed an efficient NHC-catalyzed kinetic resolution to synthesize highly functionalized 2-aryl-3-nitro-2*H*-chromanes and its derivatives with high diastereo- and stereoselectivities (Scheme 33). An NHC-bound homoenolate pathway was proposed for the kinetic resolution. The reactive carbene is generated in the presence of K_3PO_4 and produces homoenolate intermediate **33-II** using the same method as before. Then the addition of the homoenolate intermediate **33-II** to the more kinetically favored (*S*)-enantiomer affords the intermediate **33-III**. The less kinetically favored (*R*)-**82** is recovered. Although the stereocenter of 2-aryl-3-nitro-2*H*-chromene was remote from the homoenolate intermediate, the kinetic resolution also happened successfully.

Recently, Gong and Song *et al.*[40] developed a unique process in which NHC can regulate the catalytic activity of the copper complex to switch the chemoselection between kinetic resolution and dynamic kinetic resolution by binding reversibly to the copper catalyst (Schemes 34-1, 34-2). Highly enantioenriched *N*-tosylaziridine derivatives and various substituted spirooxindole derivatives was synthesized with high stereoselectivities via [3＋3] annulation of racemic *N*-tosylaziridines with isatin-derived enals. Mechanistic studies suggest that highly efficient kinetic resolution and dynamic kinetic resolution of racemic *N*-tosylaziridines are achieved by the cooperative catalysis of chiral NHC and copper complex. The NHC catalyst in this process plays dual roles of Lewis base organocatalyst and ligand coordinating to the copper complex regulate the catalytic activity. The chemoselection between the kinetic resolution and dynamic kinetic resolution is switchable by changing the ratio of the chiral NHC and Cu complex of diphosphine.



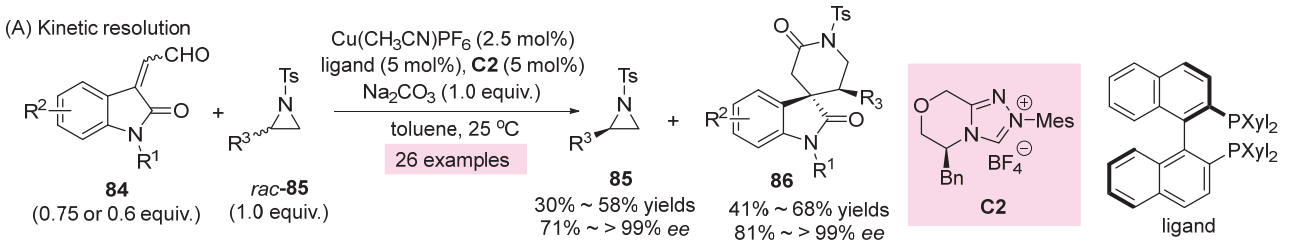
Scheme 32 Kinetic resolution of secondary alcohols



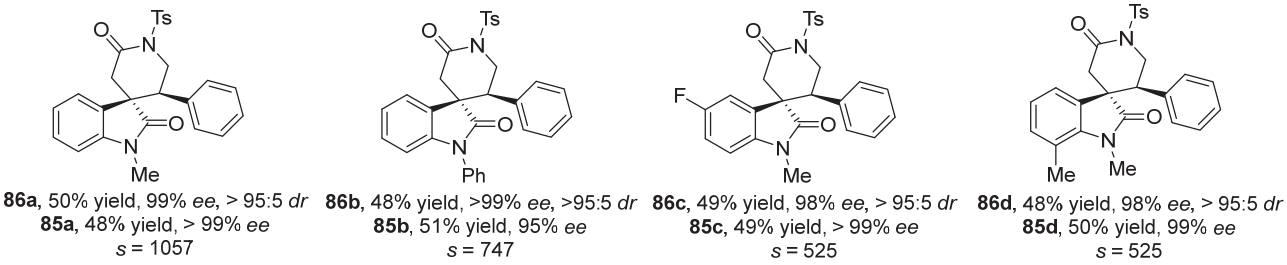
Scheme 33 Synthesis of 2-aryl-3-nitro-2*H*-chromanes and its derivatives

7 Kinetic resolutions mediated by *β*-azolium ylide

In this section the kinetic resolution involving *β*-azolium ylide intermediate is described. *β*-Azolium ylide was firstly reported by Fu *et al.*[41] in NHC-catalyzed *β*- alkylations of a variety of *α*,*β*-unsaturated esters, amides, and nitriles bearing leaving groups. While reactions of acyl anion and related intermediate continue to draw extensive attention, there are few studies about *β*-azolium ylides. Lupton *et al.*[42] realized the dynamic kinetic resolution of a benzyl 1,5-diene via *β*-azolium ylide intermediate (Scheme 35). A chiral cyclopentene with two stereocenters was synthesized with 78% *ee*. Although the diastereoselectivity of the reaction was moderate, this work opened up a new direction in NHC-catalyzed kinetic resolution. They also proposed



Selected examples

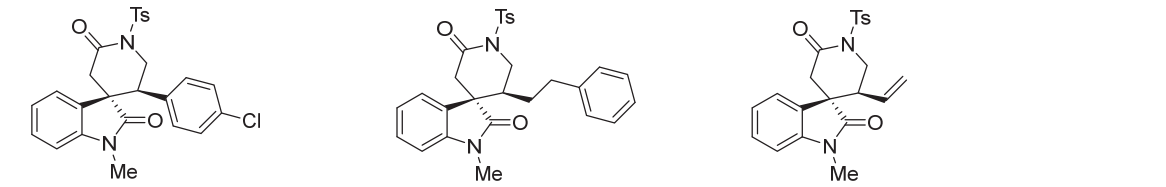


86a, 50% yield, 99% *ee*, > 95:5 *dr*
85a, 48% yield, > 99% *ee*
s = 1057

86b, 48% yield, >99% *ee*, >95:5 *dr*
85b, 51% yield, 95% *ee*
s = 747

86c, 49% yield, 98% *ee*, > 95:5 *dr*
85c, 49% yield, > 99% *ee*
s = 525

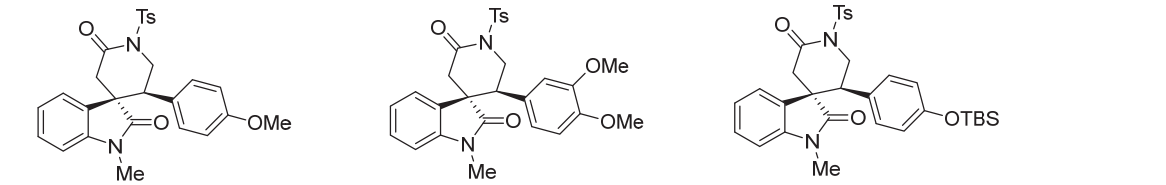
86d, 48% yield, 98% *ee*, > 95:5 *dr*
85d, 50% yield, 99% *ee*
s = 525



86e, 47% yield, 97% *ee*, > 95:5 *dr*
85e, 46% yield, > 99% *ee*
s = 348

86f, 55% yield, 88% *ee*, 85:15 *dr*
85f, 42% yield, > 99% *ee*
s = 82

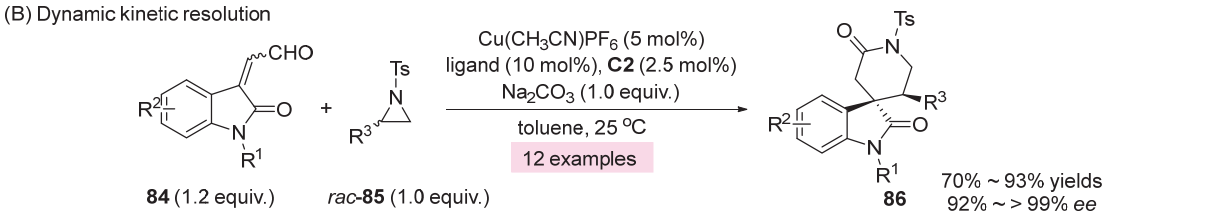
86g, 49% yield, 97% *ee*, 91:9 *dr*
85g, 46% yield, > 99% *ee*
s = 348



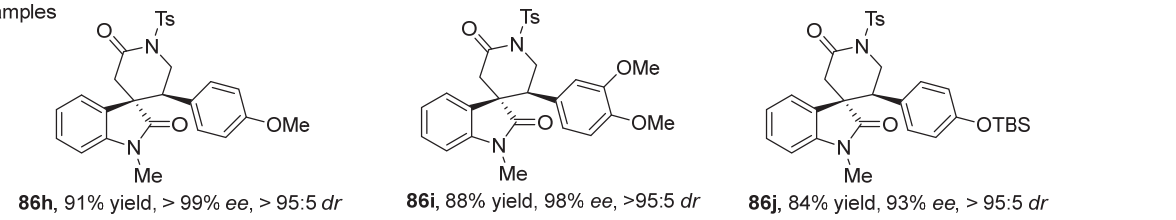
86h, 48% yield, 94% *ee*, > 95:5 *dr*
85h, 47% yield, 96% *ee*
s = 127

86i, 54% yield, 94% *ee*, 94:6 *dr*
85i, 42% yield, 92% *ee*
s = 106

86j, 48% yield, 93% *ee*, 85:15 *dr*
85j, 47% yield, >99% *ee*
s = 145



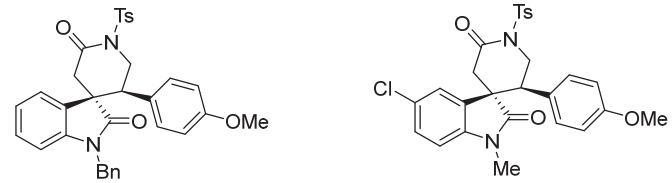
Selected examples



86h, 91% yield, > 99% *ee*, > 95:5 *dr*

86i, 88% yield, 98% *ee*, >95:5 *dr*

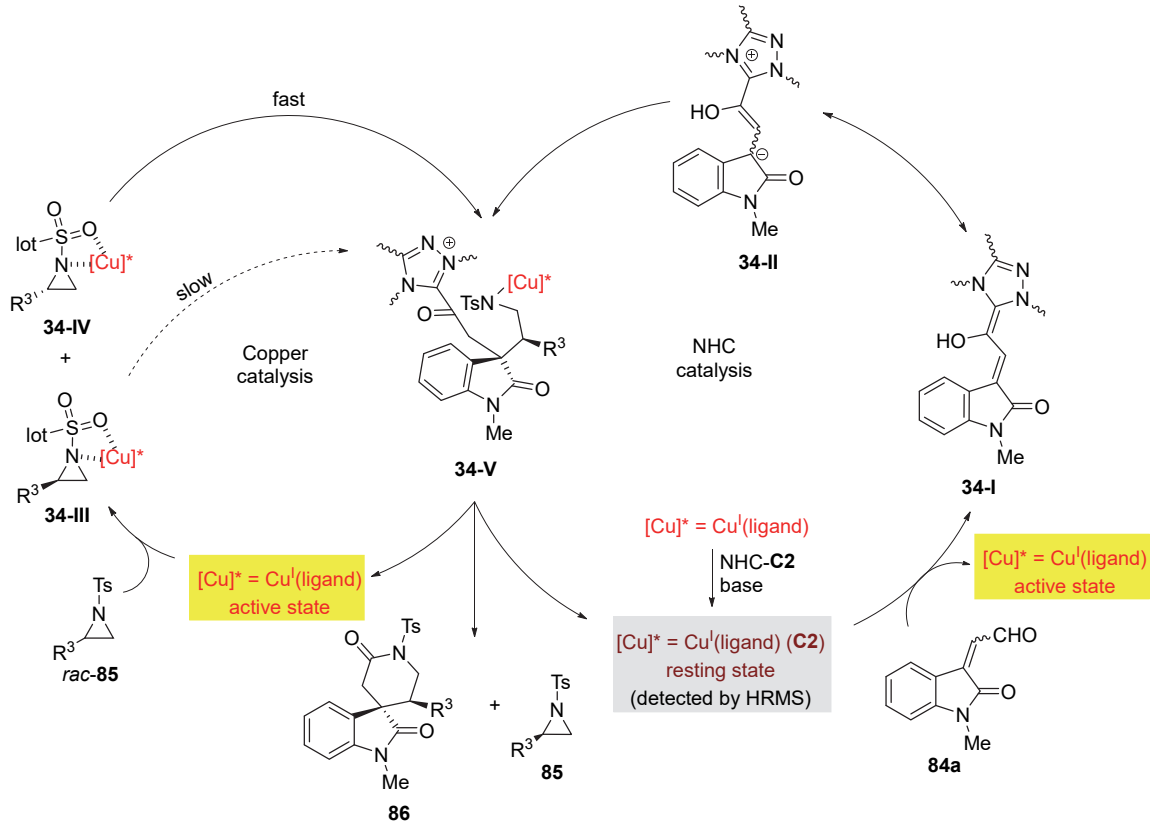
86j, 84% yield, 93% *ee*, > 95:5 *dr*



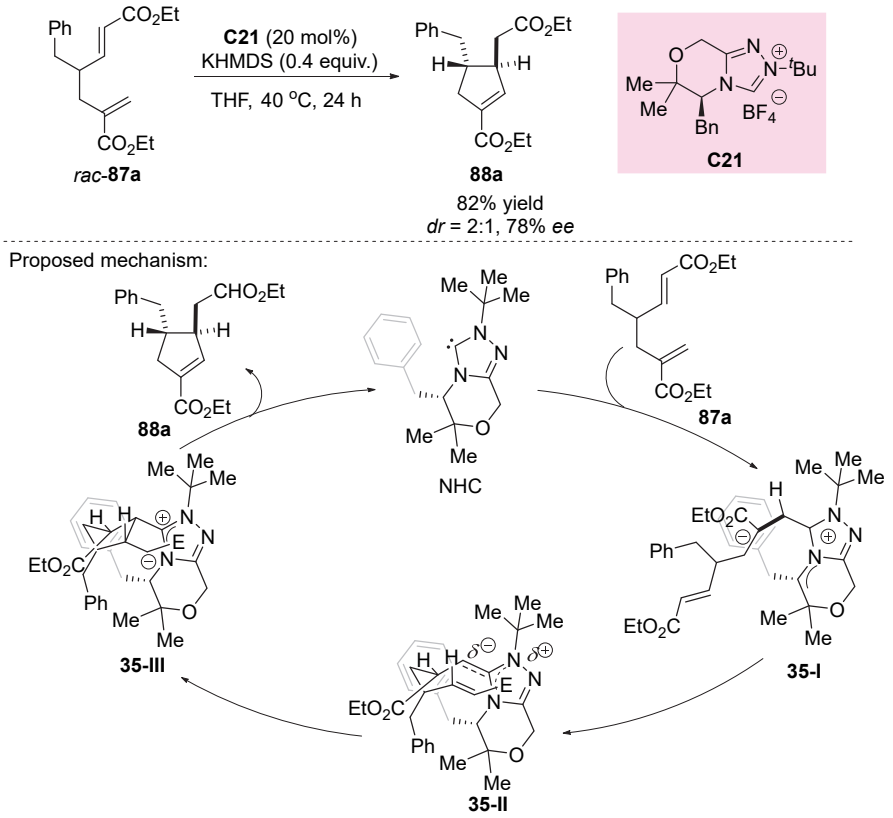
86k, 93% yield, > 99% *ee*, > 95:5 *dr*

86l, 90% yield, 96% *ee*, 93:7 *dr*

Scheme 34-1 Kinetic resolution and dynamic kinetic resolution of racemic *N*-tosylaziridines



Scheme 34-2 Proposed mechanism for the kinetic resolution and dynamic kinetic resolution of racemic *N*-tosylaziridines



Scheme 35 *β*-Azolium ylide-participated kinetic resolution by Lupton *et al*.

mechanism for the reaction. First, the 1,4-addition of NHC to **87a** affords the enolate **35-I**, which undergoes protonation and deprotonation to give the *β*-azolium ylide **35-II**. Diastereo- and enantioselective cyclization of **35-II** allows the access to **35-III**. Finally, protonation of **35-III** and elimination of the catalyst give cyclopentene **88a**.

8 Conclusions

In the past six years, NHC catalysis has achieved a rapid development in kinetic resolutions. Various NHC-bound intermediates have been successfully used in the resolutions of a diverse set of molecules, such as acyl azolium, *α*,*β*-unsaturated acyl azolium, Breslow intermediate, azolium enolate, NHC-bound homoenolate, and *β*-azolium ylide. However, a statistical analysis shows that the acyl azolium is still the most widely used intermediate for the related kinetic resolutions, and the Breslow intermediate and conjugated acyl azolium are the second. In contrast, other intermediates such as azolium enolate, homoenolate, and *β*-azolium ylide remain underdeveloped and need to be further exploited. Furthermore, NHC-bound allenoates and radical intermediates have been not successfully used in kinetic resolutions. Nevertheless, we believe that this field will continue to draw the attention of synthetic chemists, and new protocols employing NHC-bound intermediates will be developed to allow access to enantioenriched molecules that cannot be easily obtained using known methods.

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