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Review

NHC-Catalyzed Reaction of Aldehydes for C(sp^2)–O Bond Formation

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Abstract: In the past few decades, *N*-heterocyclic carbenes (NHCs) have opened the new field of organocatalysis in synthetic organic chemistry. This review highlights the dramatic progress in the field of NHC-catalyzed C–O bond formation based on the activation of aldehyde C(sp^2)–H bonds. The oxidative and redox transformations for the synthesis of various molecules with structural diversity and complexity are summarized. Furthermore, new methods and strategies for NHC catalysis are emerging continuously; thus, cooperative catalysis with Brønsted acid, hydrogen-bonding catalyst, transition-metal catalyst, and photocatalyst are also described.

Keywords: *N*-heterocyclic carbenes; organocatalysis; C–O bond formation; aldehyde; cooperative catalysis

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1. Introduction

N-Heterocyclic carbenes (NHCs) have gained increasing attention as powerful and versatile organocatalysts in organic synthesis since the first isolation of stable carbene in 1991 [1]. The NHC catalysis leads to the novel approach for activating the aldehyde C(sp^2)–H bonds via the formation of the Breslow intermediates. In particular, reversing the reactivity of aldehydes via the "umpolung of aldehydes" opens the new field of organocatalysis [2–9].

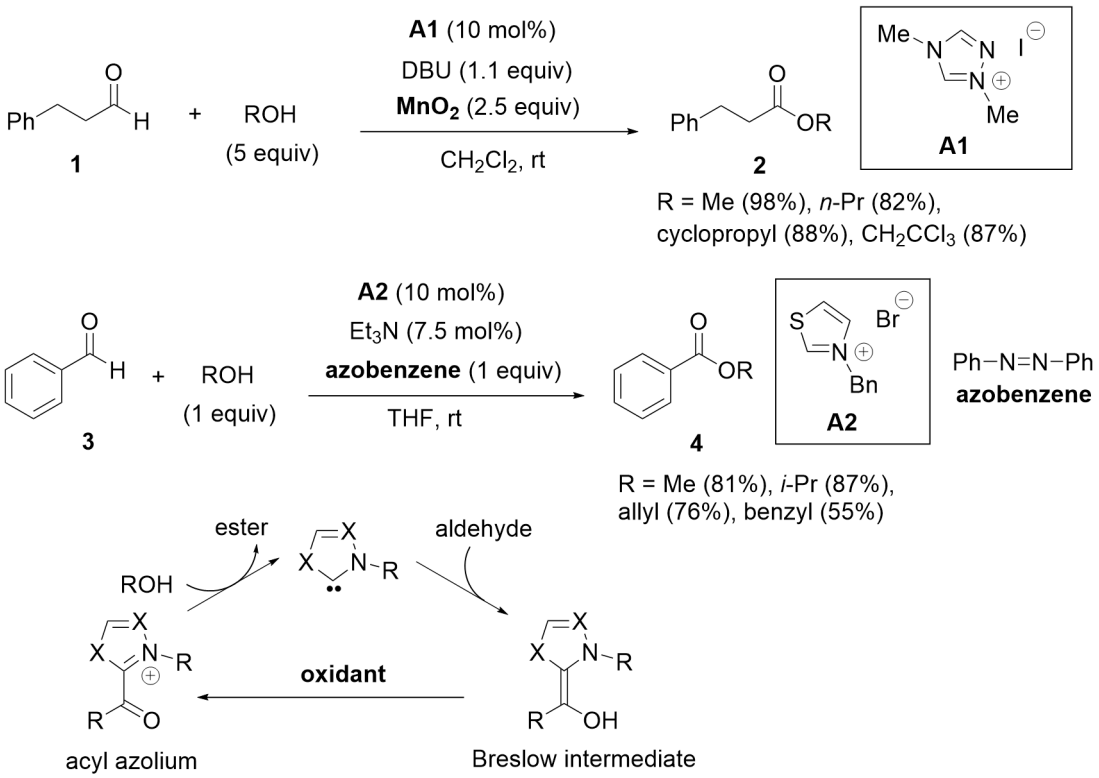
In recent years, the use of chiral NHCs has attracted substantial attention for the enantioselective synthesis of various molecules with structural diversity and complexity [10–22]. Furthermore, new methods and strategies for NHC catalysis are emerging continuously, leading to the remarkable progress in the cooperative catalysis with Lewis acid, Brønsted acid, hydrogen-bonding organocatalyst, and transition-metal catalyst [23–27]. More recently, the NHC catalysis has been expanded by its combination with photocatalysis, as well as radical catalysis [28–33]. In this review article, we overview the progress in the NHC-catalyzed C–O bond formation of aldehydes by showing the representative reactions.

2. Oxidative Esterification of Aldehydes

2.1. Esterification of Aldehydes under Oxidation Conditions

The NHC-catalyzed esterification of aldehydes was widely investigated under the oxidation conditions as an important approach to achieve the dehydrogenative reaction of aldehydes with alcohols [34–43]. Oxidative NHC catalysis was achieved by using MnO_2 or azobenzene as an oxidant (Scheme 1) [34,35]. In the presence of NHC generated from the triazolium-based NHC precursor **A1** (10 mol%) and DBU (1.1 equiv.), the dehydrogenative reaction of aldehyde **1** with alcohols was performed in CH_2Cl_2 at room temperature under the oxidative conditions using MnO_2 [34]. The corresponding ester **2** was obtained in good yields. The oxidative esterification of benzaldehyde **3** using the precursor **A2** and azobenzene as stoichiometric oxidants gave the ester **4** [35]. These transformations are initiated by the formation of the Breslow intermediate, which is oxidized to acyl azolium by an oxidant. Finally, the reaction of acyl azolium with ROH results in the release of free NHC catalyst and the formation of ester. Furthermore, 3,3,5,5-*t*-butyldiphenoqinone

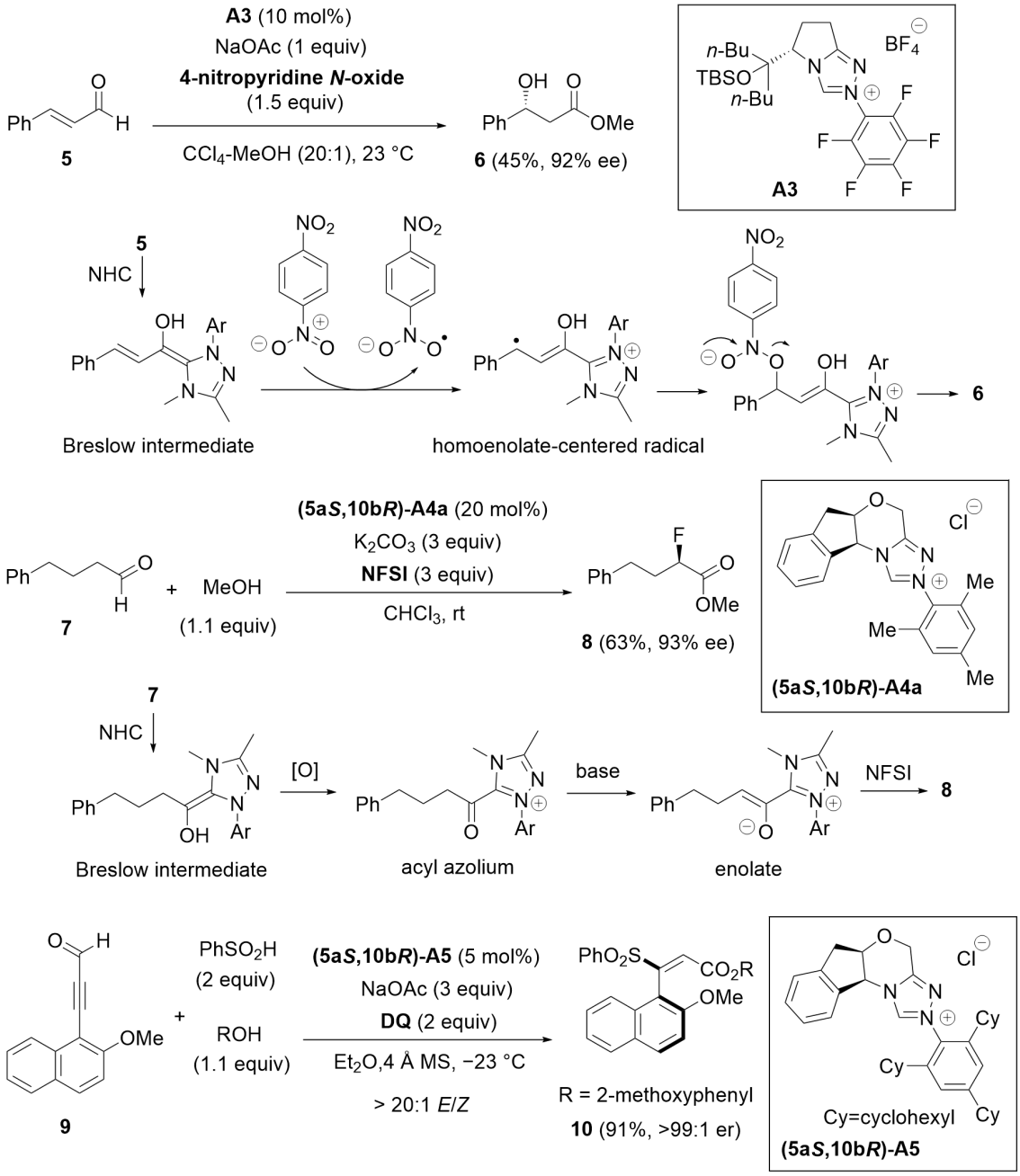
(DQ), phenazine, CCl_3CN, phenazine, and *tert*-butyl hydroperoxide (TBHP) are used as an oxidant for the esterification of aldehydes [36–46]. The aerobic or electrochemical oxidations are also used in conjunction with NHC-catalyzed esterification of aldehydes [47–52]. Additionally, the oxidative esterification of aldehydes has been studied using boronic acids, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and alkyl halides [53–56].



Scheme 1. Dehydrogenative reaction of aldehydes with alcohols.

Chiral NHCs have gained increasing attention as organocatalysts for enantioselective synthesis. The enantioselective synthesis of β-hydroxyl esters from enals was achieved under the oxidation conditions using chiral NHC catalysts (Scheme 2) [57,58]. Employing 4-nitropyridine *N*-oxide as an oxidant with chiral NHC generated from the precursor **A3** (10 mol%) and NaOAc, the β-hydroxylation of cinnamaldehyde **5** took place to generate β-hydroxyl ester **6** in 45% yield with 92% ee [57]. In this reaction, β-hydroxyl group is introduced by the oxygen transfer from nitro group of an oxidant through the radical pathway. The enantioselective synthesis of α-fluoro esters from aldehydes was reported [59]. In the presence of the precursor **(5a*S*,10b*R*)-A4a**, K_2CO_3 and *N*-fluorobenzenesulfonimide (NFSI), the oxidative functionalization of aliphatic aldehyde **7** proceeded to give α-fluoro ester **8** with good enantioselectivity. In this reaction, NFSI serves not only as the electrophilic fluorination reagent but also an oxidant. Chiral NHC catalyst was used for the atroposelective synthesis of axially chiral styrenes [60]. When the precursor **(5a*S*,10b*R*)-A5** with a bulkier *N*-tricyclohexylphenyl substituent was employed under the oxidation conditions using DQ as an oxidant, the reaction of ynal **9** with sulfinic acid and 2-methoxyphenol afforded the styrene **10** bearing a chiral axis in 91% yield with >99:1 er and >20:1 *E*/*Z* selectivity. This transformation proceeds through the 1,4-addition of sulfinic anion to acetylenic acyl azolium intermediate, followed by *E*-selective protonation, to set up the chiral axis. Furthermore, the chiral NHC-catalyzed oxidative coupling of enals with carboxylic acids was developed by employing hypervalent iodine-(III) reagent [61]. Additionally, chiral NHCs were used for the regioselective functionalization of carbohydrates [62,63]. The oxidative esterification of carbohydrates proceeded with excellent regioselectivities when

2,6-dichloro-benzaldehyde or 2-fluoro-6-iodo-benzaldehyde was employed as an acylation precursor [62].

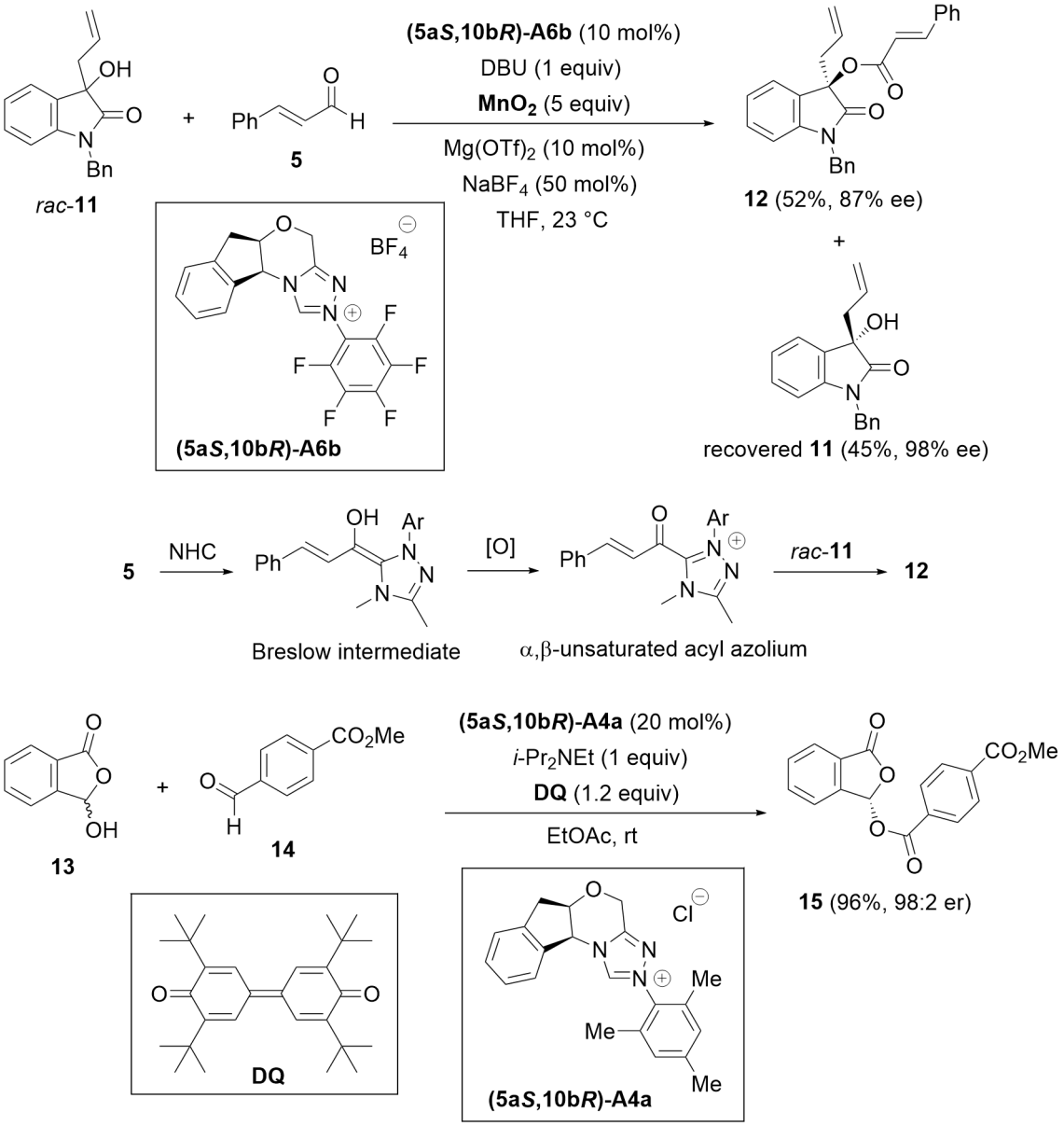


Scheme 2. Enantioselective functionalization of aldehydes.

2.2. Kinetic Resolution

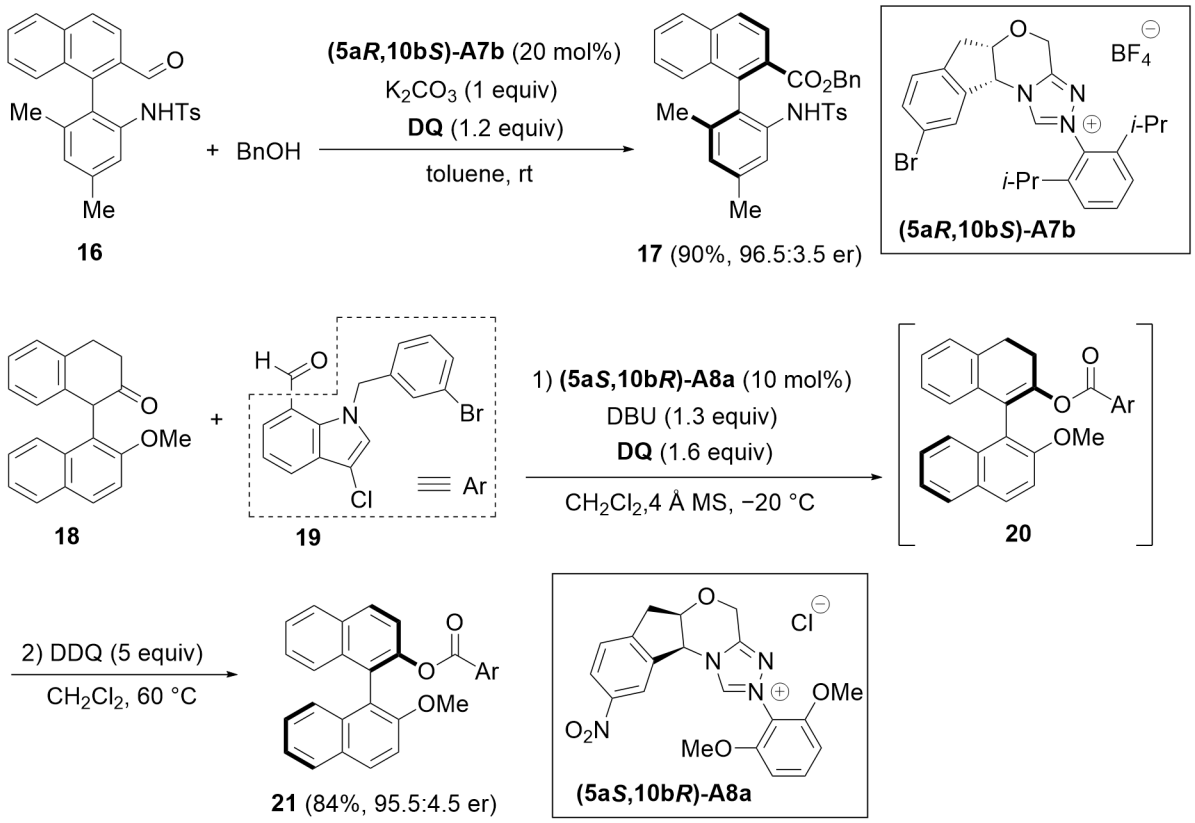
Chiral NHC-catalyzed oxidative esterification has been used for achieving kinetic resolution [64–72]. The kinetic resolution of racemic 3-hydroxy oxindole *rac*-**11** was examined using chiral NHC generated from **(5a*S*,10b*R*)-A6b** (Scheme 3) [64]. In the presence of $Mg(OTf)_2$ and $NaBF_4$, the use of MnO_2 as an external oxidant effectively induced the reaction between *rac*-**11** and cinnamaldehyde **5** to give the ester **12** in 52% yield and 87% ee, accompanied with the recovered **11** in 45% yield and 98% ee. The dynamic kinetic resolution of racemic 3-hydroxyphthalide **13** was achieved via NHC-catalyzed acylation [67]. In the presence of chiral NHC generated from **(5a*S*,10b*R*)-A4a** (20 mol%) and *i*-Pr_2NEt (1 equiv.), the acylation of **13** with aldehyde **14** was performed in EtOAc at room tempera-

ture under oxidative conditions using DQ (1.2 equiv.) as an oxidant. The corresponding ester **15** was obtained in 96% yield with 98:2 er.



Scheme 3. Kinetic resolution via oxidative esterification.

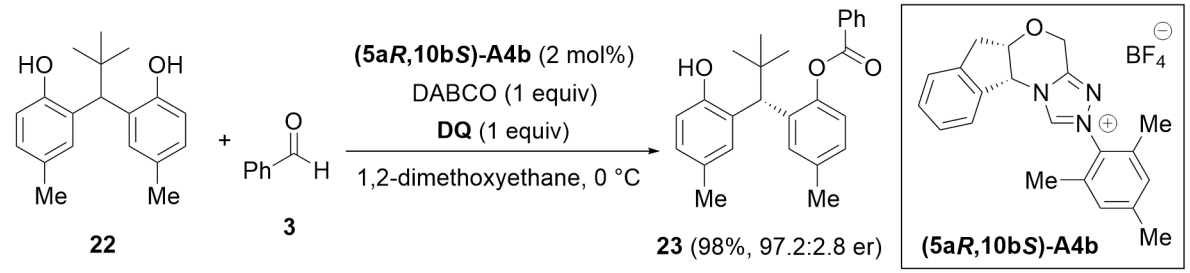
The NHC-catalyzed dynamic kinetic resolution was applied to the synthesis of axially chiral compounds (Scheme 4) [70,71]. The atroposelective dynamic kinetic resolution of racemic biaryl aldehyde **16** was developed using oxidative NHC catalysis [70]. In the presence of NHC, generated from the precursor **(5a*R*,10b*S*)-A7b**, and DQ oxidant, the esterification of aldehyde **16** with benzyl alcohol gave chiral biaryl amino ester **17** in 90% yield with 96.5:3.5 er. The one-pot synthesis of the axially chiral binaphthyl compound **21** from racemic ketone **18** was also developed [71]. Initially, the NHC-catalyzed atroposelective acylation of ketone oxygen atom on **18** with aldehyde **19** gave the enol ester intermediate **20** via dynamic kinetic resolution. The subsequent one-pot oxidation of **20** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant led to the chiral binaphthyl compound **21**.



Scheme 4. Atroposelective dynamic kinetic resolution.

2.3. Desymmetrization

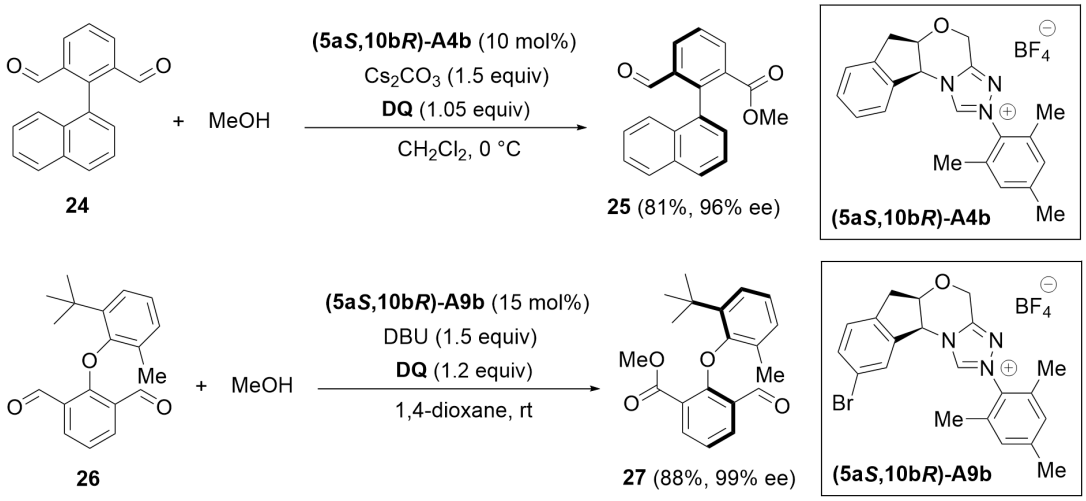
The desymmetrization of diols based on the chiral NHC-catalyzed oxidative esterification of aldehydes was studied [73–75]. The desymmetrization reaction of triarylmethane-bisphenol **22** with benzaldehyde **3** was performed under the conditions using the precursor **(5a*R*,10b*S*)-A4b**, 1,4-diazobicyclo(2.2.2)octane (DABCO, and DQ) as oxidants in 1,2-dimethoxyethane at 0 °C (Scheme 5) [74]. The desymmetrization product **23** was obtained at a 98% yield with 97.2:2.8 er.



Scheme 5. Desymmetrization of diols via oxidative esterification.

The chiral NHC-catalyzed oxidative esterification of dialdehydes was studied [76–80]. The NHC-catalyzed atroposelective esterification of biaryl dialdehyde **24** was reported (Scheme 6) [77]. In the presence of the precursor **(5a*S*,10b*R*)-A4b**, Cs_2CO_3 and DQ, the selective esterification of **24** proceeded to give the axially chiral ester **25** at a 81% yield with 96% ee. The mechanistic studies indicate that the highly enantioselective transformation is achieved through the NHC-catalyzed desymmetrization of dialdehyde **24** and the further kinetic resolution via the second esterification of the undesired enantiomer of ester **25**. The atroposelective esterification of dialdehyde **26** was also studied [79,80]. The NHC-catalyzed desymmetrization of prochiral dialdehyde **26** gave the axially chiral diaryl ether **27** with the

excellent enantioselectivity. The enantioselectivity of **27** was also improved by the kinetic resolution leading to diether.

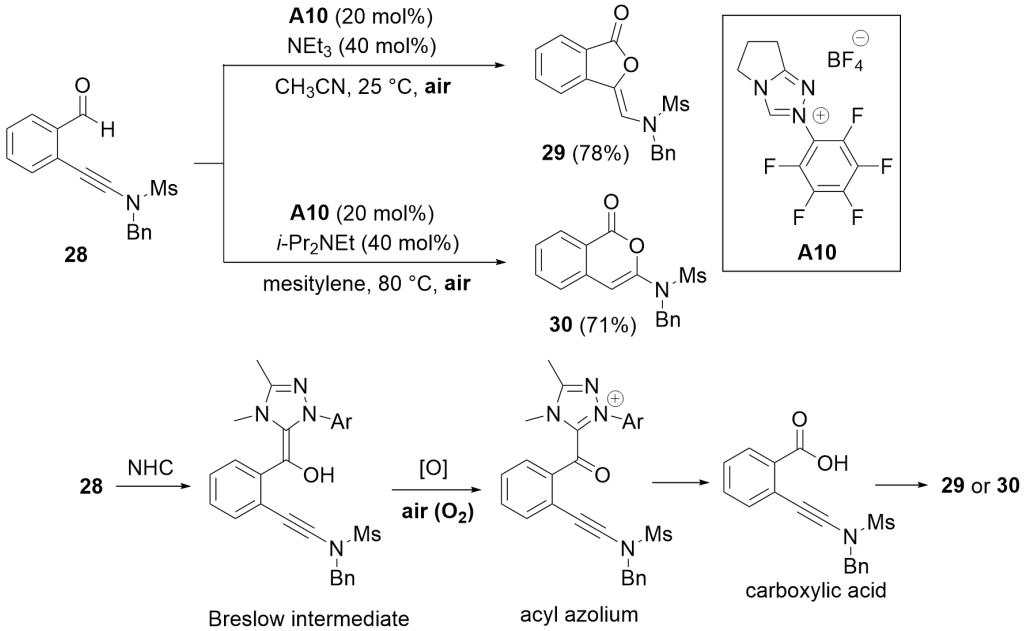


Scheme 6. Desymmetrization of dialdehydes.

3. Oxidative Cyclization and Annulation

3.1. Cyclization

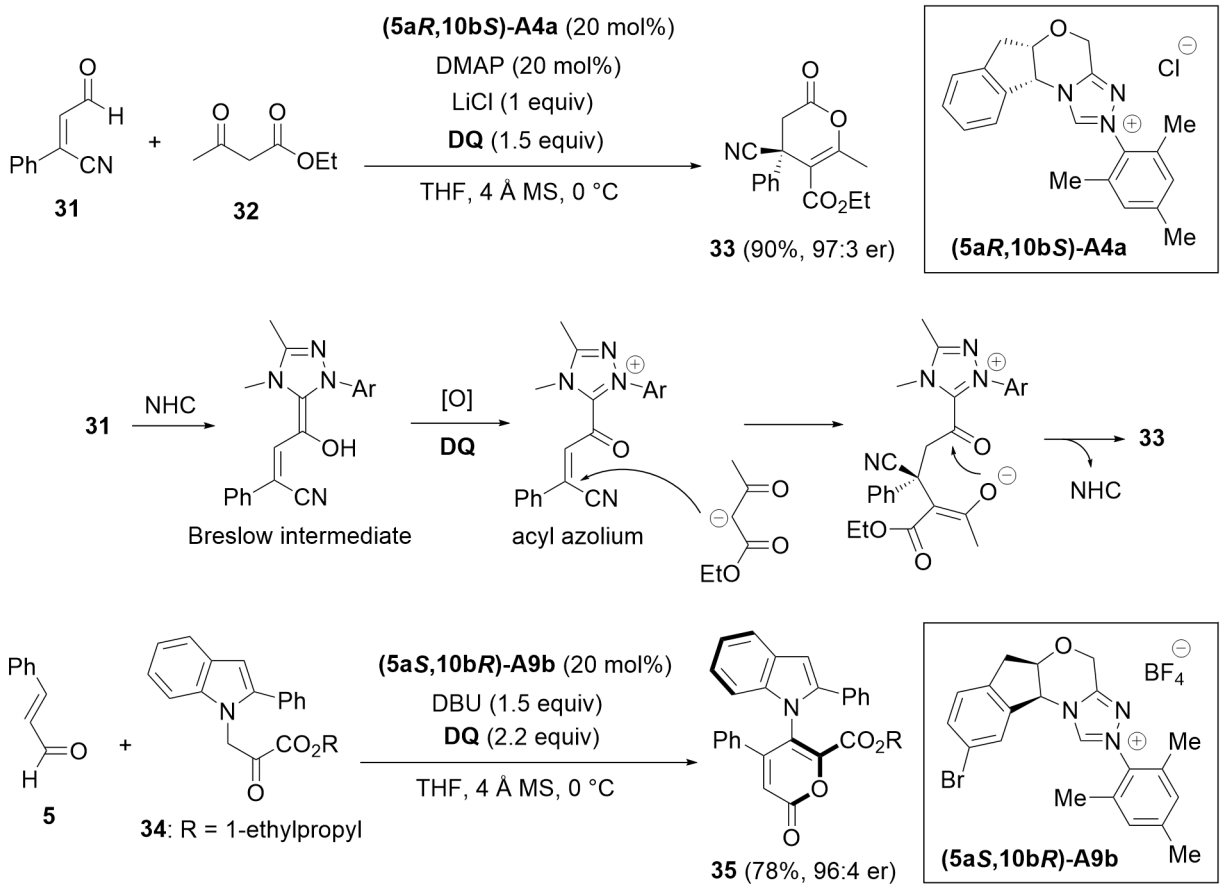
Several examples of oxidative cyclization were reported [81–85]. The NHC-catalyzed aerobic oxidation of ynamide-tethered benzaldehyde **28** was studied (Scheme 7) [84]. The regioselective synthesis of (*Z*)-3-aminomethylenephthalide **29** was achieved by using NEt_3 as a base, whereas the use of *i*-Pr_2NEt led to the 6-*end* cyclization giving 3-aminoisocoumarin **30**. Initially, the carboxylic acid intermediate was generated through the aerobic oxidation of the Breslow intermediate. Next, the base-promoted regioselective cyclization of carboxylic acid toward the ynamide moiety afforded **29** or **30**. Furthermore, chiral NHC-catalyzed macrocyclization was developed for the atroposelective synthesis of planar-chiral indoles [85].



Scheme 7. Regioselective oxidative cyclization.

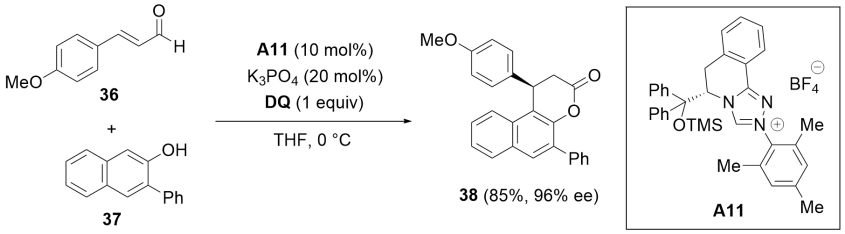
3.2. [3 + 3] Annulation

In the NHC catalysis, the α,β-unsaturated acyl azoliums are Michael acceptors acting as a C3 synthon for [3 + 3] annulation [86–98]. The oxidative reactions of β-cyano-substituted α, β-unsaturated aldehyde **31** and ethyl acetoacetate **32** were studied (Scheme 8) [90]. Under the optimized conditions using the precursor **(5a*R*,10b*S*)-A4a** (20 mol%), DMAP (20 mol%), LiCl (1 equiv.) and DQ (1.5 equiv.) as oxidants, dihydropyran-4-carbonitrile **33** bearing a quaternary carbon center was obtained at a 90% yield with 97:3 er. In this reaction, both the reaction efficiency and stereoselectivity were improved by the use of LiCl as an additive. This annulation was initiated by the generation of a Breslow intermediate, which was oxidated into the α,β-unsaturated acyl azolium. Next, the Michael addition of **32** to acyl azolium intermediate and the subsequent lactonization provide the annulation product **33**, accompanied by the liberation of the NHC catalyst. The asymmetric synthesis of axially chiral molecules was achieved via oxidative [3 + 3] annulation [97]. The chiral NHC-catalyzed oxidative annulation of cinnamaldehyde **5** and indole-1-pyruvate ester **34** gave the *N*-arylindole **35** with a C–N chiral axis.



Scheme 8. Oxidative [3 + 3] annulation.

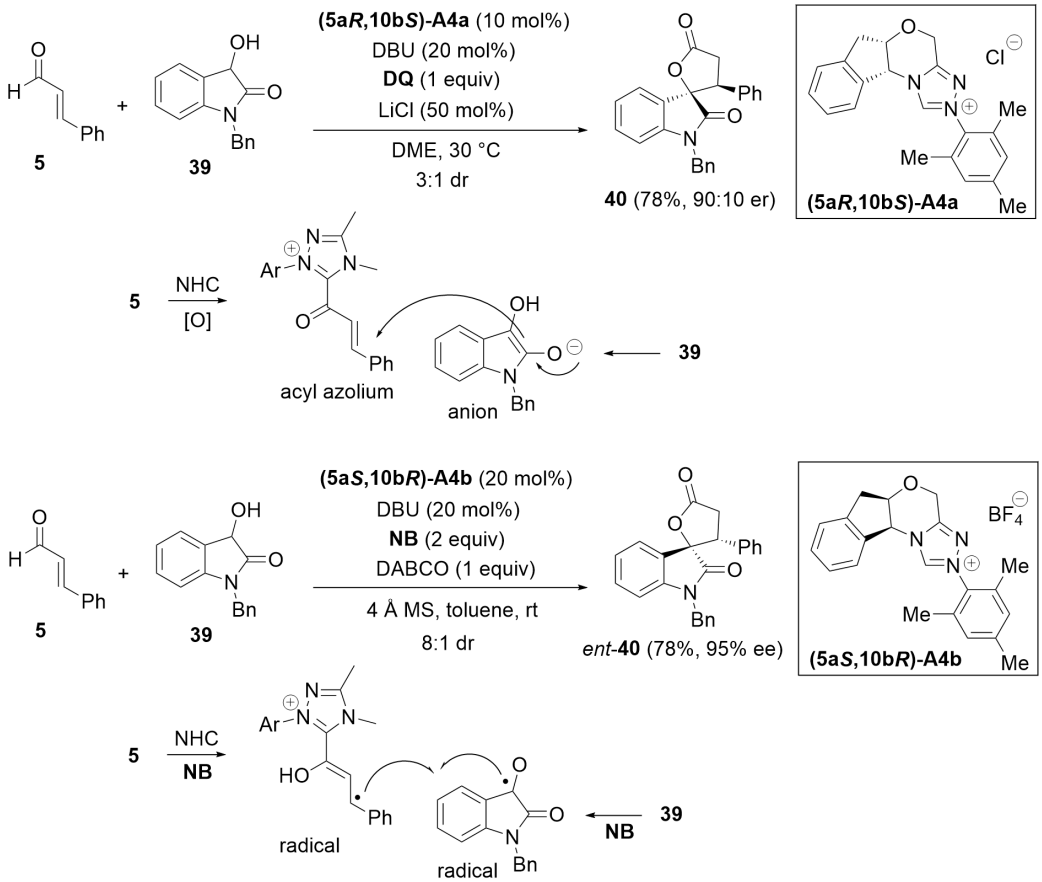
The NHC-catalyzed oxidative esterification of α,β-unsaturated aldehydes with 2-naphthols was applied to the enantioselective [3 + 3] annulation reaction via merging with Claisen rearrangement (Scheme 9) [99]. The chiral NHC-catalyzed annulation reaction of α,β-unsaturated aldehyde **36** and 3-phenyl 2-naphthol **37** gave the enantioenriched product **38** via the route involving oxidative esterification and the subsequent Claisen rearrangement.



Scheme 9. NHC-catalyzed annulation via Claisen rearrangement.

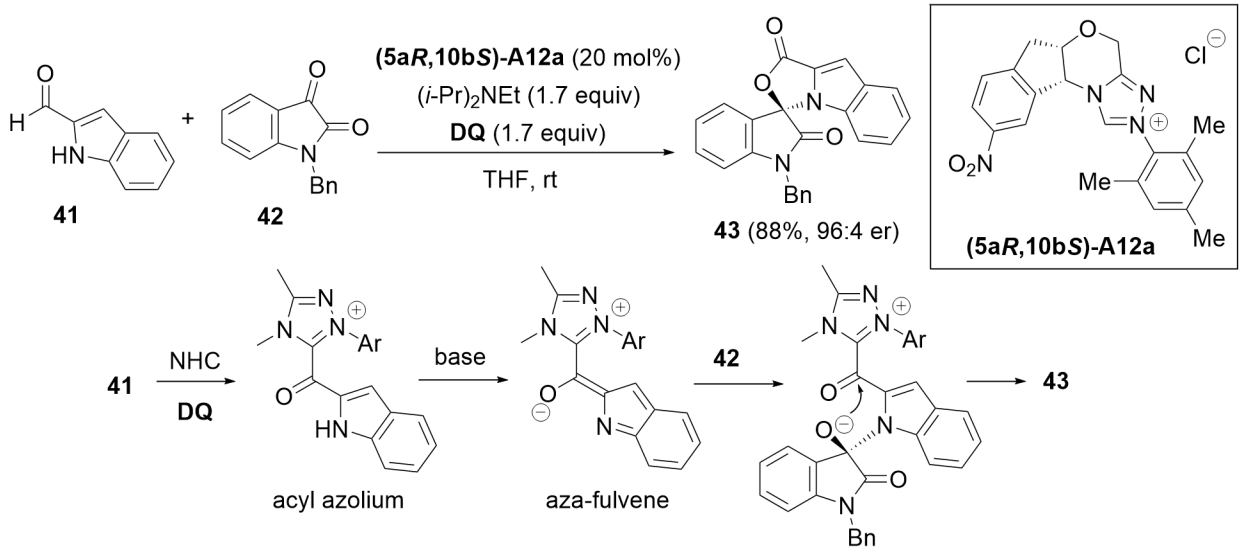
3.3. [3 + 2] Annulation

Oxidative [3 + 2] annulation between cinnamaldehyde **5** and 4-hydroxy oxindole **39** was reported by Biju's and Ye's groups, respectively (Scheme 10) [100–102]. In the presence of the precursor **(5a*R*,10b*S*)-A4a** (10 mol%), DBU (20 mol%), LiCl (50 mol%) and DQ (1 equiv.) as oxidants, the reaction of aldehyde **5** with oxindole **39** was carried out in DME, affording spirooxindole-γ-lactone **40** at a 78% yield with 90:10 er [100]. In this reaction, the α,β-unsaturated acyl azolium is the Michael acceptor acting as a C3 synthon for [3 + 2] annulation; thus, the enolate, generated from **39** under basic conditions, added to α,β-unsaturated acyl azolium in a 1,4 fashion. When aldehyde **5** and oxindole **39** were treated with the precursor **(5a*S*,10b*R*)-A4b** (20 mol%), DBU (20 mol%), DABCO (1 equiv.) and nitrobenzene (NB, 2 equiv.) as a single electron oxidant in toluene, the annulation product *ent*-**40** was obtained in 78% yield with 95% ee [101]. Since both radicals from enolate and homoenolate were observed via EPR spectra. a radical/radical cross-coupling pathway is proposed as a possible reaction mechanism. The reaction of homoenolate radical generated from **5** with the radical generated from **39** leads to the cross-coupling intermediate, which is further converted to the final product *ent*-**40** via tautomerization and lactonization.



Scheme 10. Oxidative [3 + 2] annulation.

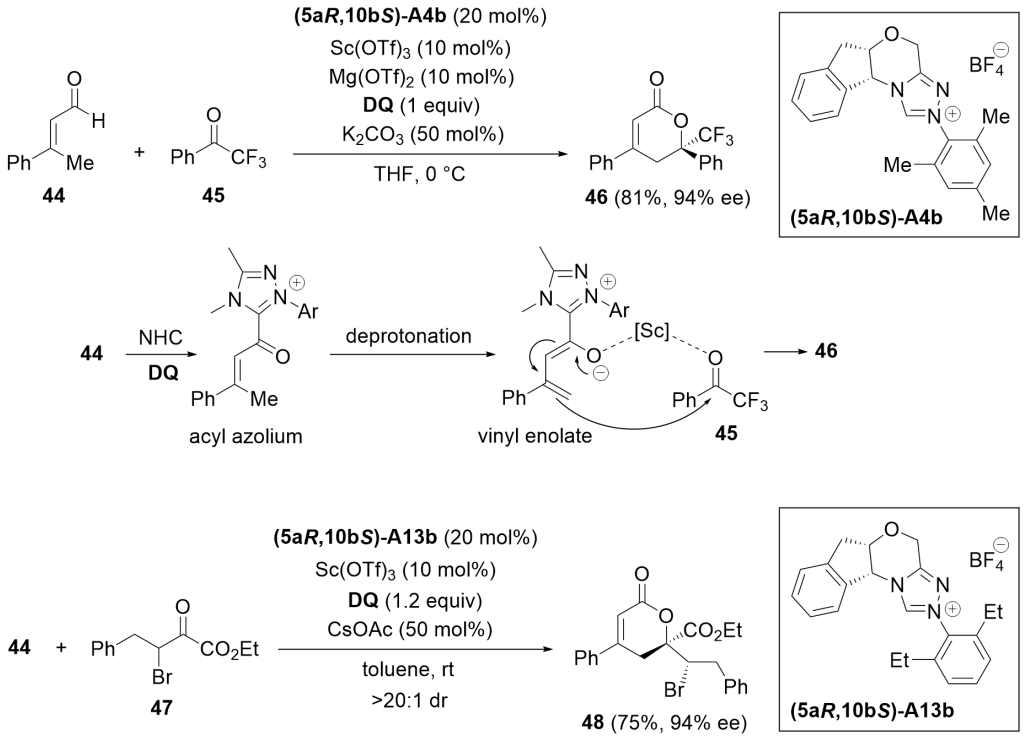
Oxidative [3 + 2] annulation reactions involving the activation of the nitrogen atoms of the aromatic π-rings were investigated [103–105]. In the presence of chiral NHC generated from the precursor **(5a*R*,10b*S*)-A12a** and DQ, the annulation between indole aldehyde **41** and isatin **42** proceeded smoothly to give the cyclic product **43** (Scheme 11) [103]. In this catalytic cycle, a key step was the formation of aza-fulvene intermediate from acyl azolium under the basic conditions. The nucleophilic addition of nitrogen atom on aza-fulvene to isatin **42**, followed by the intramolecular ester formation, would lead the annulation product **43**.



Scheme 11. Oxidative [3 + 2] annulation using acyl azolium.

3.4. [4 + 2] Annulation

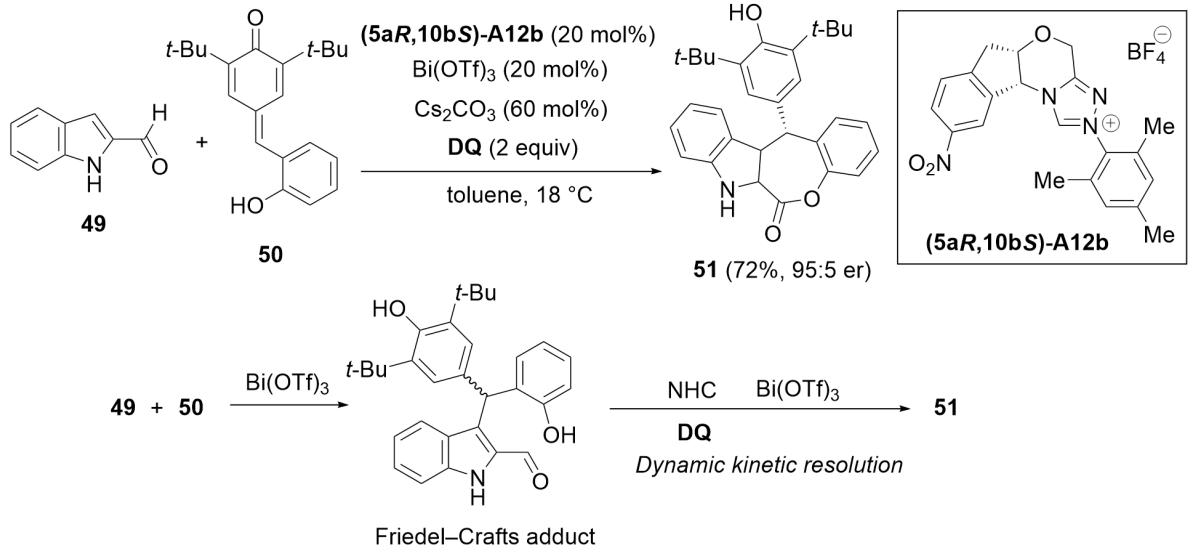
The NHC-linked vinyl enolates (dienolates) act as a C4 synthon for [4 + 2] annulation (Scheme 12) [106–110]. The oxidative γ-functionalization of α,β-unsaturated aldehydes with trifluoroacetophenone **45** was studied under NHC catalysis [106]. The high enantioselectivities were achieved via the NHC- and Sc/Mg-based Lewis acid cooperative catalysis. In the presence of the precursor **(5a*R*,10b*S*)-A4b**, $Sc(OTf)_3$, $Mg(OTf)_2$, K_2CO_3 and DQ as oxidants, α,β-unsaturated aldehyde **44** reacted with ketone **45** to give δ-lactone **46** at a 81% yield with 94% ee. In this reaction, a key step was the activation of γ-carbon of α,β-unsaturated acyl azolium. The γ-CH deprotonation of α,β-unsaturated acyl azolium led to the NHC-linked vinyl enolate bearing a nucleophilic γ-carbon, which added to ketone **45** by coordinating of scandium Lewis acid with the reaction partners. Similarly, treatment of aldehyde **44** with ketoester **47** in the presence of the precursor **(5a*R*,10b*S*)-A13b**, $Sc(OTf)_3$, CsOAc and DQ led to the formation of δ-lactone **48** in 75% yield with 94% ee [107]. As the relative examples, the [4 + 2] annulation reactions via NHC-linked *ortho*-quinine methide intermediate or the formal [10+2] cycloaddition reaction via NHC-linked 12π species were reported [111–114]. Additionally, the [4 + 2] annulation using azolium enolate as a C2 synthon was also developed [115,116].



Scheme 12. Oxidative [4 + 2] annulation using NHC-linked vinyl enolates.

3.5. [4 + 3] Annulation

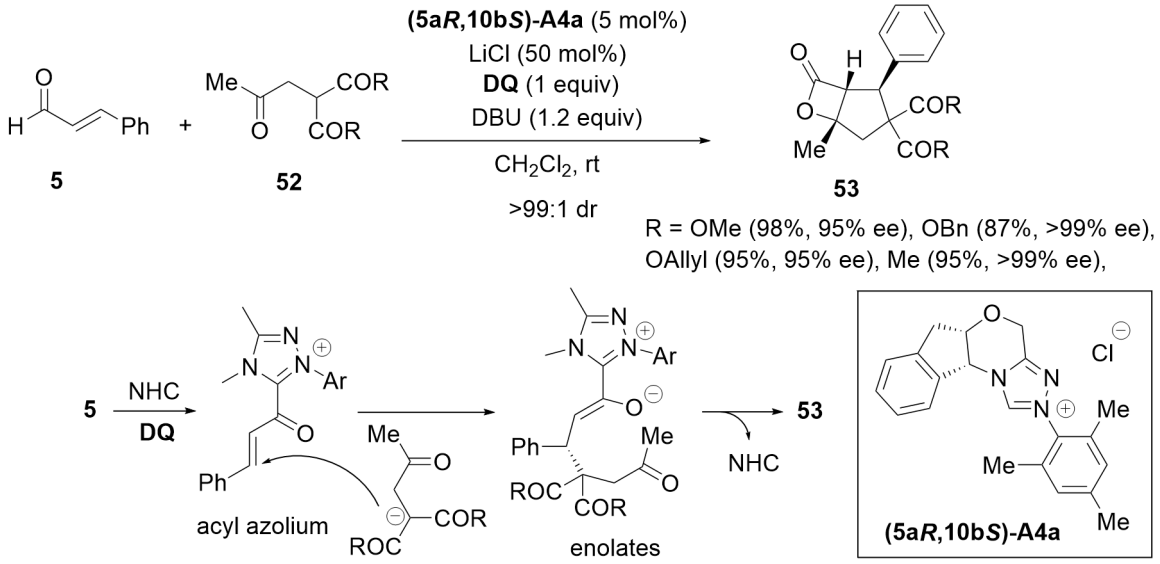
The NHC–Lewis acid cooperatively catalyzed formal [4 + 3] annulation was developed (Scheme 13) [117]. In the presence of the precursor **(5a*R*,10b*S*)-A12ba**, $Bi(OTf)_3$, Cs_2CO_3 and DQ, the reaction of indole-2-carboxaldehyde **49** with 2-hydroxy phenyl *p*-quinone methide **50** was carried out in toluene, affording tetracyclic ε-lactone **50** in 72% yield with 95:5 er. Initially, the Lewis acidic $Bi(OTf)_3$ promotes the addition of indole-2-carboxaldehyde **49** to *p*-quinone methide **50**, in situ generating the Friedel–Crafts adduct as a racemic intermediate. Subsequently, chiral NHC and $Bi(OTf)_3$ catalyzed the oxidative lactonization of the racemic Friedel–Crafts adduct with good enantioselectivity via the dynamic kinetic resolution process.



Scheme 13. NHC–Lewis acid cooperative-catalyzed [4 + 3] annulation.

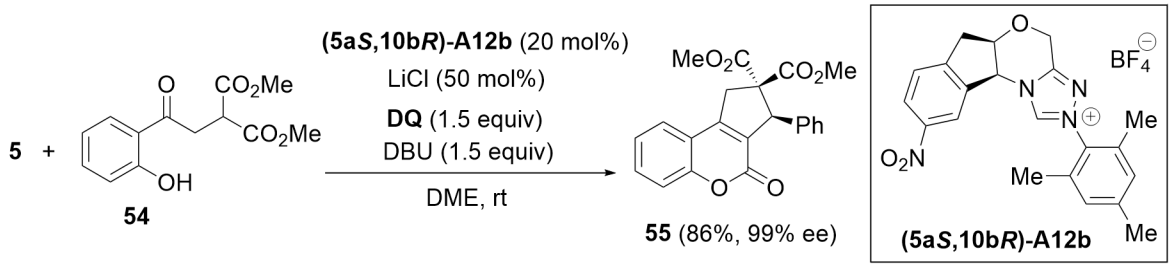
3.6. Cascade Annulation

Cascade annulation reactions using chiral NHC catalyst have been studied [118–123]. The enantioselective cascade reaction of cinnamaldehyde **5** with malonates or β-diketone **52** was developed (Scheme 14) [118]. Under the optimized conditions using the precursor **(5a*R*,10b*S*)-A4a** (5 mol%), LiCl (50 mol%), DQ (1 equiv.) and DBU (1.2 equiv.), the lactones **53** were obtained with excellent diastereo- and enantioselectivities. In NHC catalysis, the Michael addition of anions, generated from **52**, to α,β-unsaturated acyl azolium led to intermediate enolates. The lactones **53** were formed from enolates via the concerted, asynchronous formal [2 + 2] aldol lactonization process or the two-step sequence involving an intramolecular aldol reaction and subsequent intramolecular lactonization.



Scheme 14. Cascade annulation through oxidative NHC catalysis.

Employing the precursor **(5a*S*,10b*R*)-A12b**, LiCl, DQ and DBU for the reaction of cinnamaldehyde **5** with malonate **54**, the bicyclic product **55** was obtained at a 86% yield with 99% ee (Scheme 15) [121]. This cascade annulation is also initiated via the oxidation of the Breslow intermediate to α,β-unsaturated acyl azolium. The bicyclic product **55** is formed via the Michael addition of malonate **54** to α,β-unsaturated acyl azolium, the subsequent intermolecular aldol reaction and the final lactonization step.



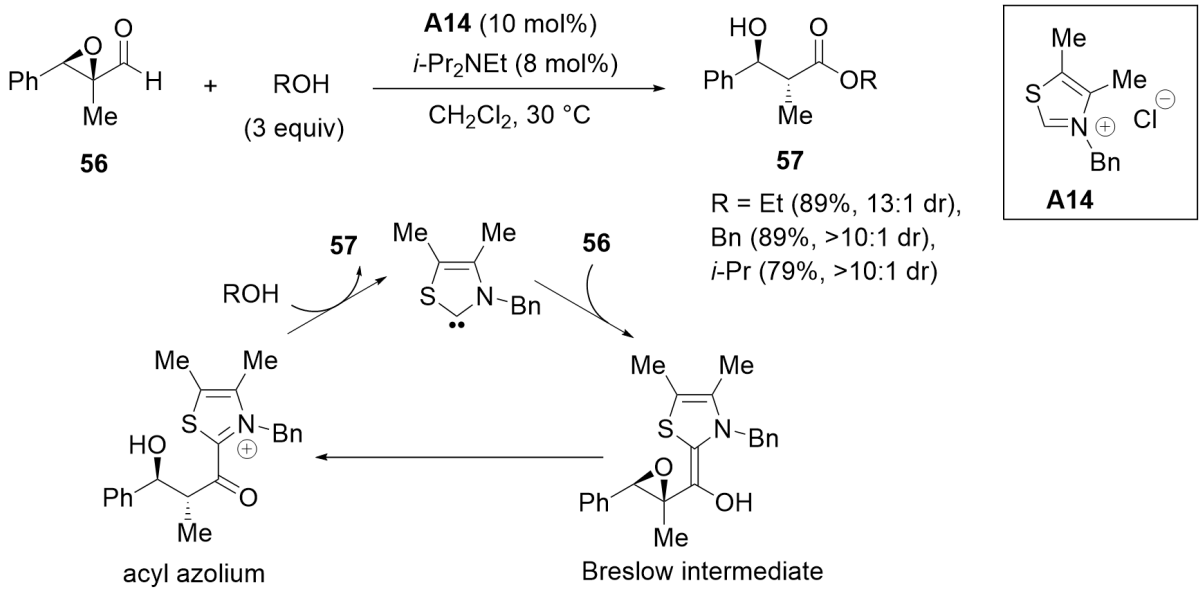
Scheme 15. Oxidative cascade annulation.

4. External Oxidant-Free Redox Esterification

4.1. Esterification of Aldehydes under Redox Conditions

Redox esterification can be achieved via the incorporation of a reducible functionality into aldehyde substrates. In the absence of oxidants, the esterification of α,β-epoxy aldehydes or α-haloaldehydes takes place due to the simultaneous reduction of epoxy moiety or halogen substituent on substrate [124–130].

The NHC-catalyzed external oxidant-free esterification of α,β-epoxy aldehyde **56** led to the formation of β-hydroxy ester **57** in good yields (Scheme 16) [124]. This transformation proceeded via the formation of the Breslow intermediate, followed by the epoxide-opening step, leading to acyl azolium. The subsequent reaction with alcohols provides ester **57**, accompanied by the regeneration of NHC catalyst.

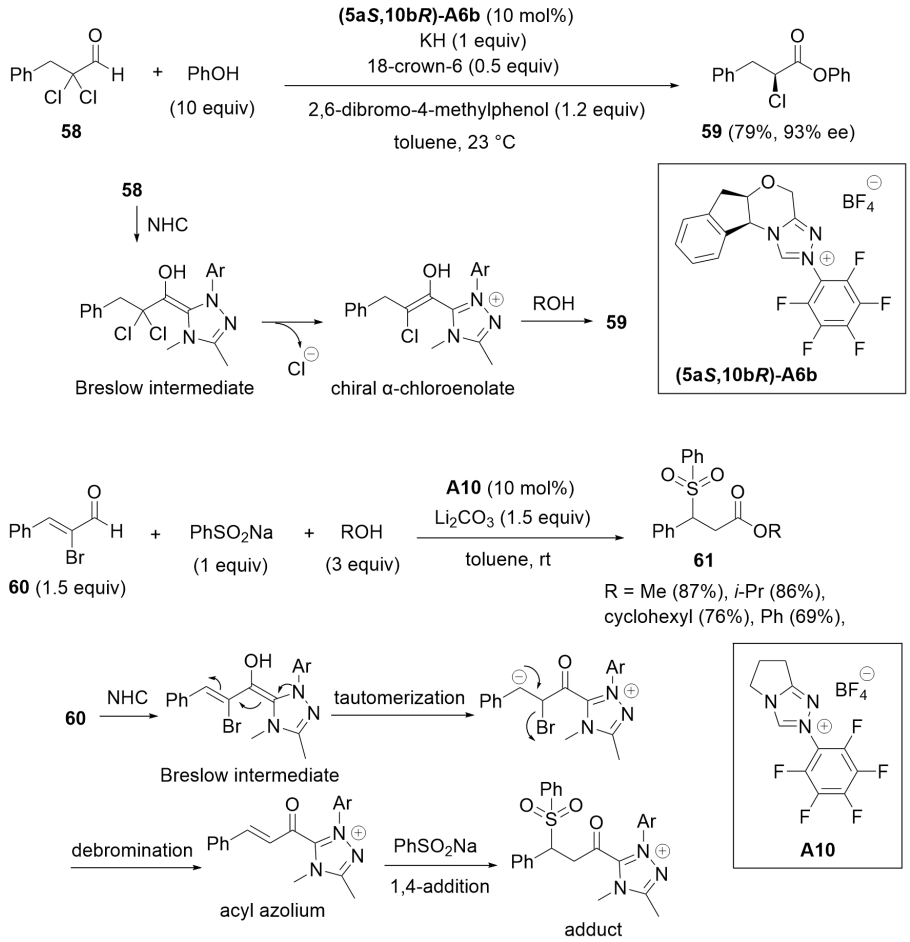


Scheme 16. Redox esterification of α,β-epoxy aldehyde.

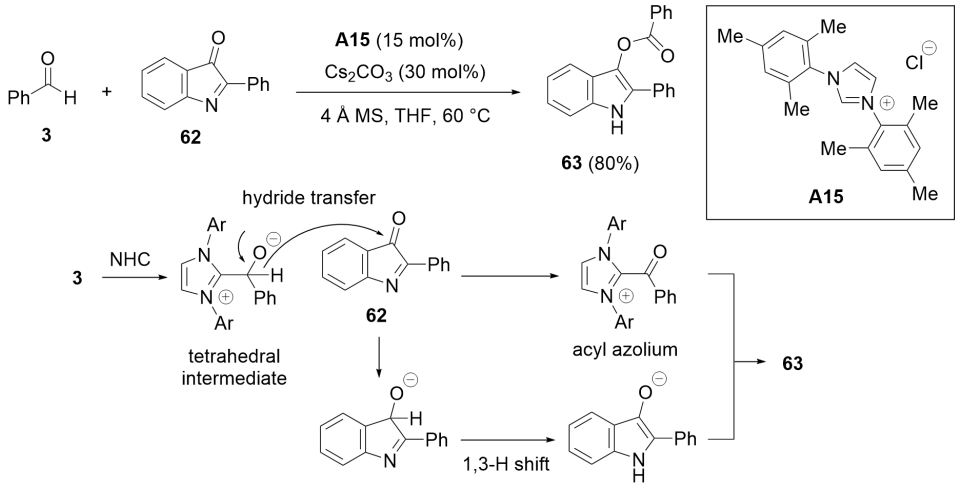
The enantioselective oxidant-free esterification of α,α-dichloroaldehydes was studied using the chiral NHC catalyst (Scheme 17) [126]. Employing the chiral NHC precursor **(5a*S*,10b*R*)-A6b**, the reaction of α,α-dichloroaldehyde **58** with phenol gave α-chloroester **59** at a 79% yield with 93% ee. Initially, aldehyde **58** reacts with NHC catalyst to give the Breslow intermediate. The subsequent dehalogenation and stereoselective α-protonation of chiral α-chloroenolate led to chiral α-chloroester **59**. The oxidant-free esterification of α-bromoenals proceeds because α-bromoenals react with NHC catalyst to afford α,β-unsaturated acyl azoliums in the absence of oxidants via debromination [129,130]. The NHC-catalyzed three-component tandem β-sulfonylation/esterification of α-bromoenals was developed [129]. Under the optimized conditions and using the precursor **A10**, the three-component reaction of α-bromoenal **60** with sodium sulfinate and alcohols gave sulfone ester **61**. The addition of NHC to α-bromoenal **60** led to the formation of the Breslow intermediate, which is transformed into α,β-unsaturated acyl azolium through tautomerization and debromination. The proposed reaction mechanism involves the 1,4-addition of sodium sulfinate to α,β-unsaturated acyl azolium. Additionally, redox esterification was also achieved by using the aldehydes with cyclopropyl moiety or leaving the group as a reducible functionality [131–133].

The α,β-unsaturated aldehydes are widely used as reducible substrates for oxidant-free esterification [134–140]. In the absence of an oxidant, the NHC catalysis of α,β-unsaturated aldehydes leads to redox esterification accompanying the reduction of the C=C bond to a C–C bond or the C≡C bond to a C=C bond.

Interestingly, the combined use of 2-phenyl-indol-3-one **62** as a reducible substrate with simple aldehydes led to the oxidant-free redox esterification (Scheme 18) [141]. In the presence of the precursor **A15** and Cs_2CO_3, the hydroacylation of **62** with benzaldehyde **3** proceeded effectively to give 1*H*-indol-3-yl ester **63** at a yield of 80%. The proposed reaction mechanism involves a reductive hydride transfer from an NHC-linked tetrahedral intermediate to the carbonyl of **62**.



Scheme 17. Redox esterification of α-haloaldehydes.

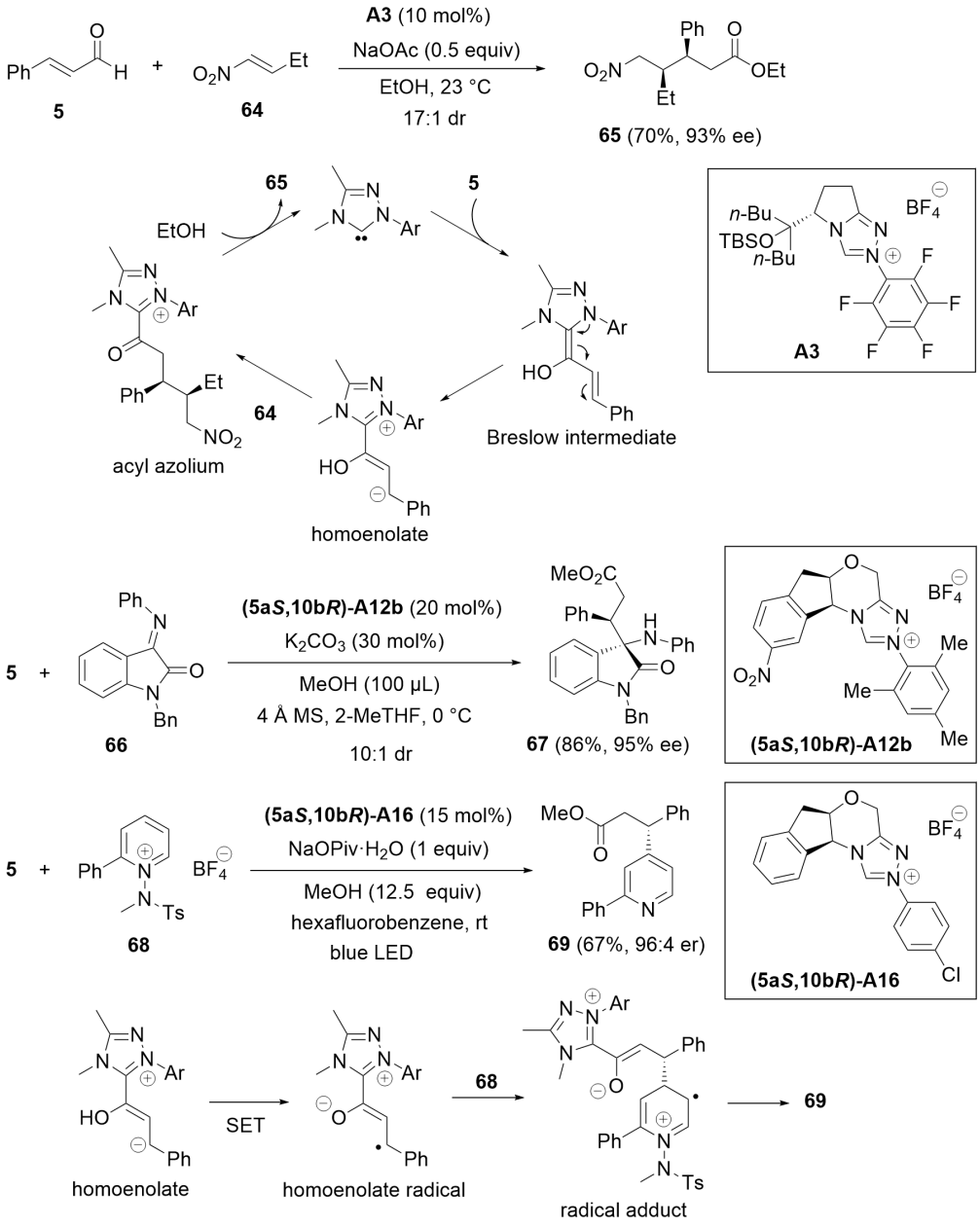


Scheme 18. Redox esterification involving the hydride transfer process.

4.2. Cascade Redox Esterification of Aldehydes

The cascade oxidant-free esterification of enals was achieved via the pathway involving the reaction of NHC-linked homoenolate intermediates with electrophiles [142–149]. In the presence of chiral NHC generated from the precursor **A3**, the reaction of cinnamaldehyde **5** with (*E*)-1-nitrobut-1-ene **64** was performed in EtOH at 23 °C to generate δ-nitroester **65** in 70% yield with 93% ee (Scheme 19) [143]. This transformation was initiated by the formation of the NHC-linked homoenolate from cinnamaldehyde **5**. Next, the 1,4-addition

of homoenolate to nitroalkene **64** generated the acyl azolium. Finally, δ-nitroester **65** was obtained via the esterification of acyl azolium with EtOH. Ender's group developed the cascade reaction using isatin-derived ketimines as an electrophile toward NHC-linked homoenolate intermediates [144]. The chiral NHC-catalyzed reaction of cinnamaldehyde **5** with isatin ketimine **66** gave the highly functionalized oxindole-γ-amino ester **67** at a 86% yield with 95% ee. Recently, the NHC-catalyzed reactions involving radical intermediates were developed [150,151]. The asymmetric β-pyridylation of cinnamaldehyde **5** with pyridinium salt **68** was reported [151]. In the presence of the chiral precursor **(5aS,10bR)-A16**, β-pyridylation of **5** proceeded effectively under the irradiation of visible light using blue LED to give the adduct **68** in 67% yield with 96:4 er. In this reaction, the use of hexafluorobenzene as a solvent was the key to achieving excellent enantioselectivity. The proposed mechanism involved the formation of homoenolate radical from NHC-linked homoenolate via single-electron transfer (SET). The final product **69** was obtained via the addition of homoenolate radical to the C4 position of pyridinium salt **68**.

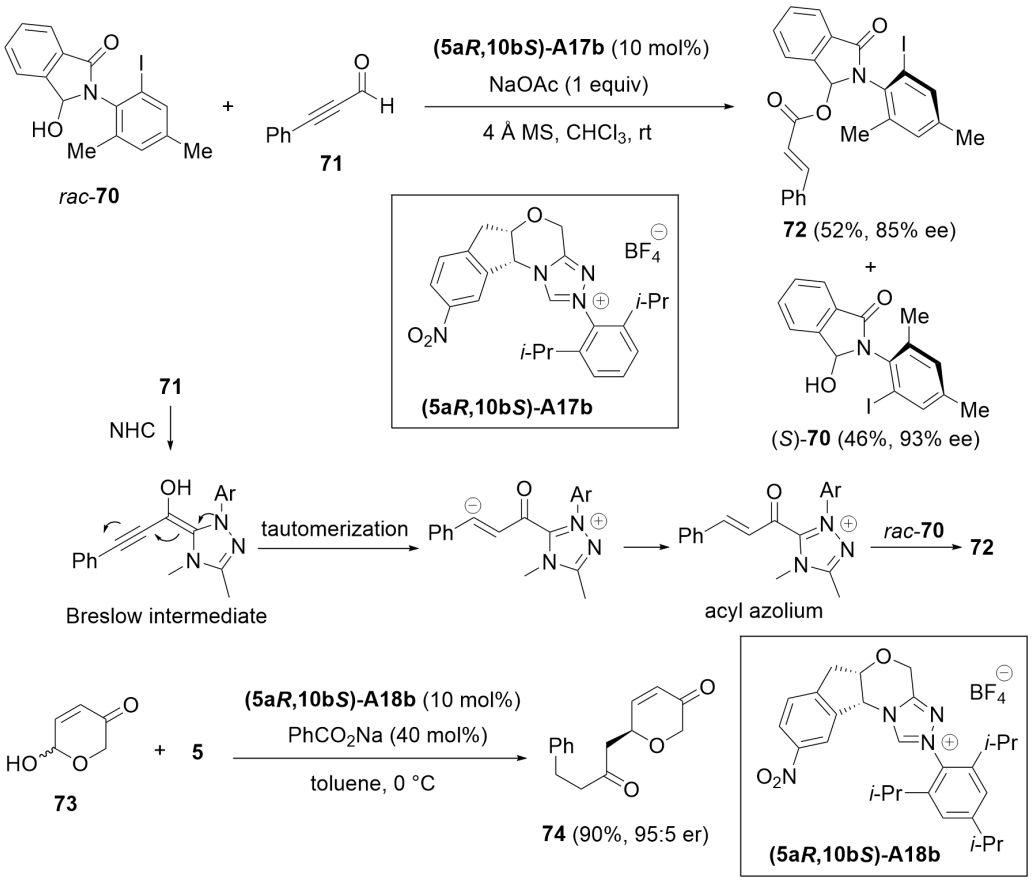


Scheme 19. Cascade redox esterification via NHC-linked homoenolate intermediates.

Furthermore, cascade oxidant-free redox esterification reactions were developed using NHC-linked dienolates (vinylogous NHC-linked enolates) [152], NHC-linked enolate [153], and NHC-linked *p*-quinodimethane [154].

4.3. Kinetic Resolution

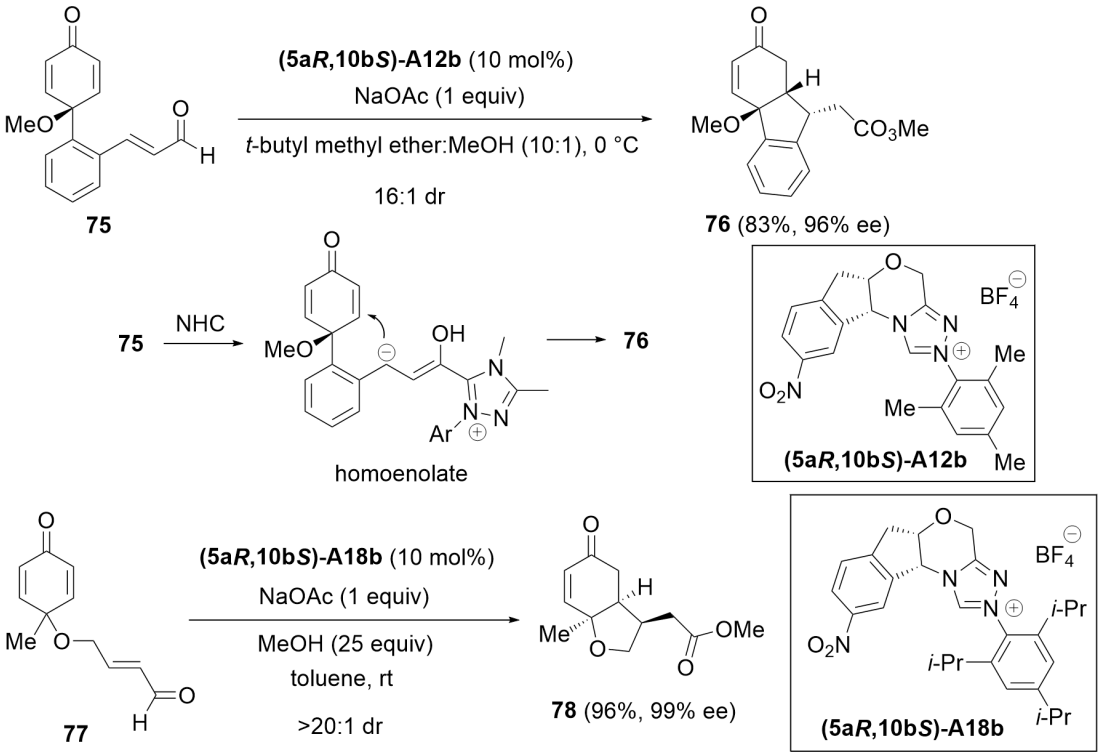
The kinetic resolution has been studied via chiral NHC-catalyzed oxidant-free redox esterification [155–160]. The kinetic resolution of racemic anilide *rac*-**70** was achieved via redox esterification using alkynal **71** as a reducible substrate (Scheme 20) [155]. In the presence of **(5a*R*,10b*S*)-A17b** and NaOAc, the enantioselective acylation of *rac*-**70** gave the ester **72** in 52% yield with 85% ee, accompanied with the enantioenriched (*S*)-**70** in 46% yield with 93% ee. Chiral NHC-catalyzed redox esterification was used for achieving the dynamic kinetic resolution of racemic pyranones [156]. The acylation of **73** with cinnamaldehyde **5** was performed in toluene at 0 °C under optimized conditions using **(5a*S*,10b*R*)-A18b** (10 mol%) and $PhCO_2Na$ (40 mol%). The corresponding ester **74** was obtained at a 90% yield with 95:5 er.



Scheme 20. Kinetic resolution via redox esterification.

4.4. Desymmetrization

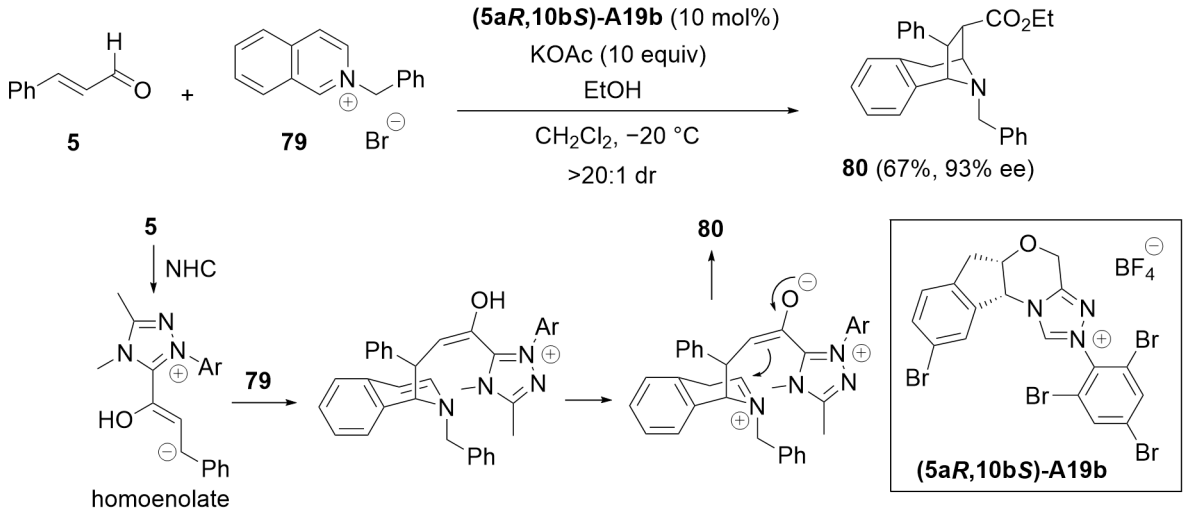
The chiral NHC-catalyzed desymmetrization of the cyclohexadienone-tethered enals was studied (Scheme 21) [161,162]. The oxidant-free cyclization of enal-tethered cyclohexadienone **75** was achieved via the esterification of the formyl group [161]. The treatment of **75** with the precursor **(5a*R*,10b*S*)-A12b** (10 mol%) and NaOAc (1 equiv.) in *t*-butyl methyl ether/MeOH (10:1, *v*/*v*) at 0 °C led to the cyclized product **76** at a 83% yield with 96% ee. This transformation involves the asymmetric Michael addition of NHC-linked homoenolate intermediate to the prochiral cyclohexadienone moiety. Similarly, the asymmetric desymmetrization of the cyclohexadienone-tethered enal **77** was achieved [162].



Scheme 21. Desymmetrization using redox esterification.

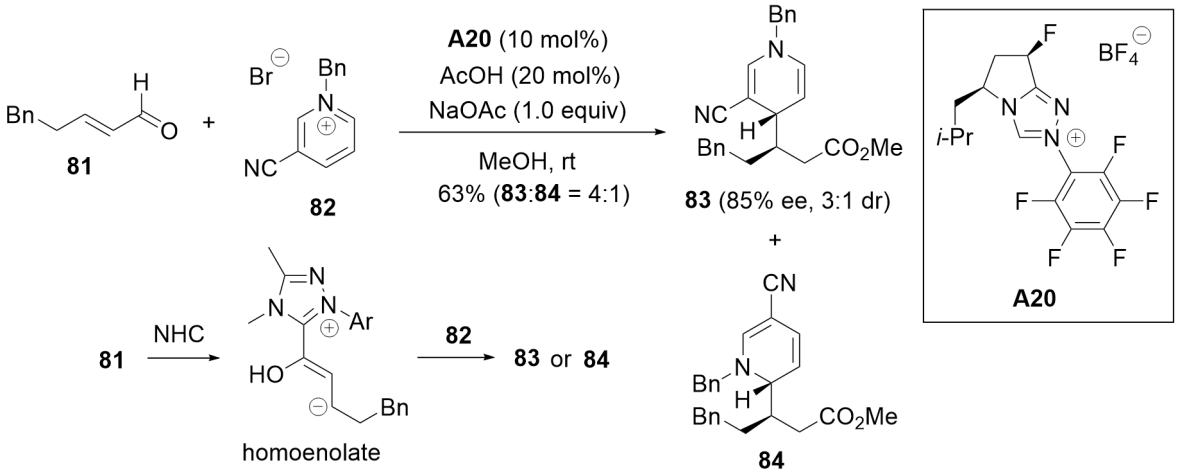
4.5. Dearomatization

The chiral NHC-catalyzed dearomatization of prochiral aromatic compounds is the powerful strategy for preparing the chiral compounds. The dearomatizing annulation of isoquinolinium bromide **79** with cinnamaldehyde **5** was developed (Scheme 22) [163]. The employment of the precursor **(5a*R*,10b*S*)-A19b**, KOAc and EtOH in CH_2Cl_2 allowed for the asymmetric dearomatization of **79** to give the substituted tropane derivative **80** with four contiguous stereocenters at a 67% yield with 93% ee. The reaction was initiated by the catalytical generation of NHC-linked homoenolate from the Breslow intermediate. The subsequent double Mannich addition of homoenolate to **79** led to the formation of tropane derivative **80**.



Scheme 22. NHC-catalyzed dearomatizing annulation reaction.

Asymmetric induction into the prochiral alkyl pyridinium **82** was achieved via chiral NHC-catalyzed dearomatization based on the addition of NHC-linked homoenolate (Scheme 23) [164]. Under the optimized conditions using the precursor **A20**, the dearomatization of pyridinium **82** with enal **81** gave 1,4-dihydropyridine **83** with 85% ee as a major product, accompanied with 1,4-dihydropyridine **84** as a regioisomer.

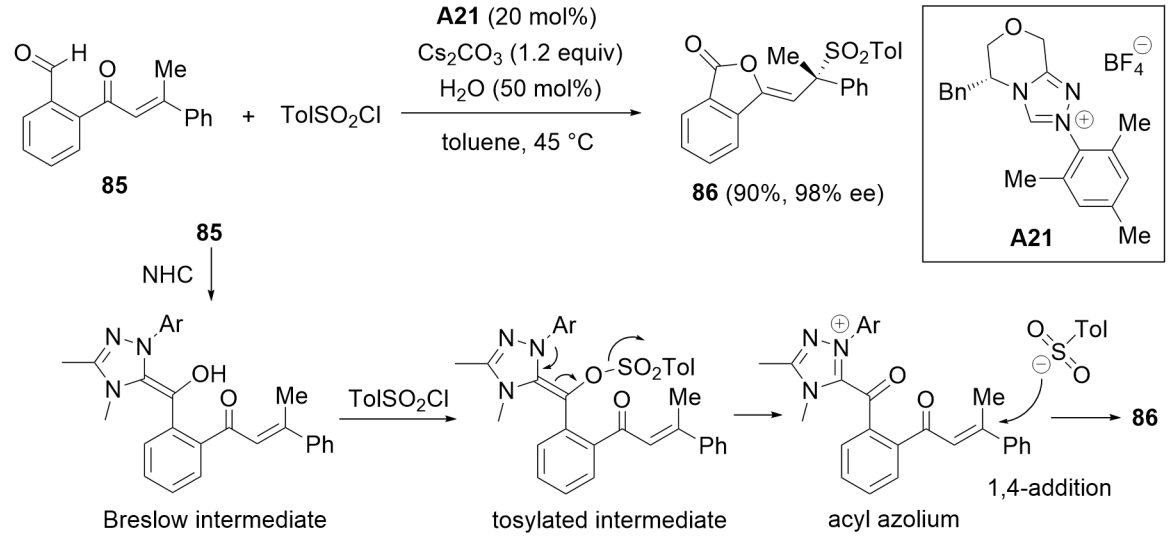


Scheme 23. Dearomatizing reaction of prochiral aromatic nitrogen-heterocycle.

5. Redox Cyclization and Annulation

5.1. Cyclization

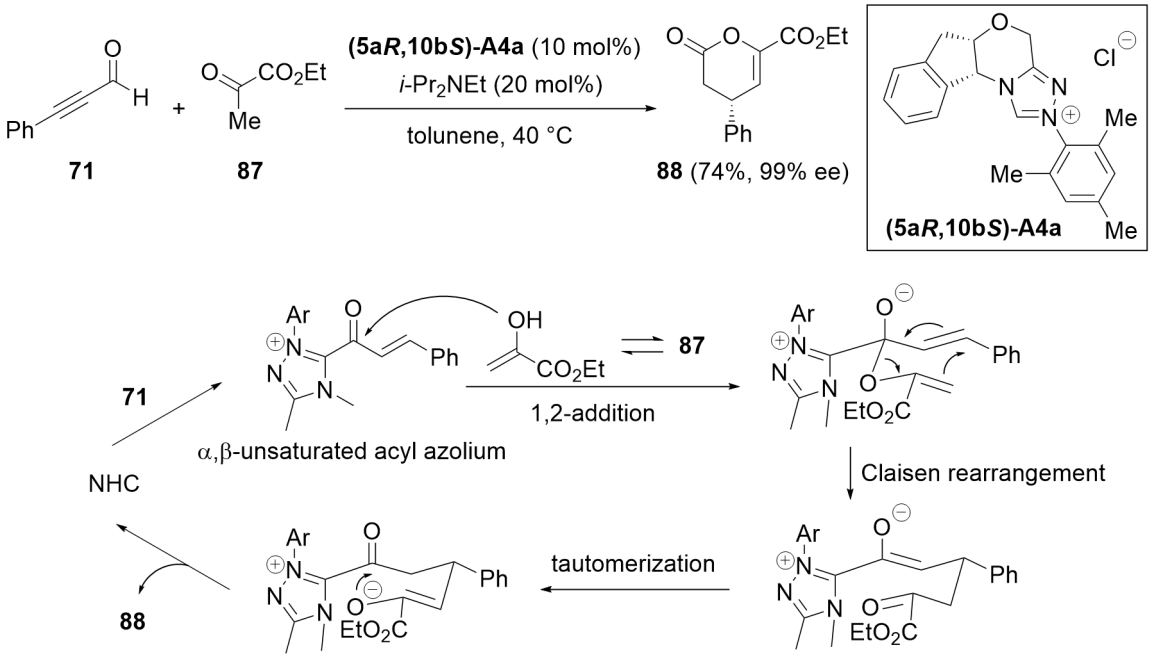
Several redox cyclization reactions were reported [151–153,165]. In the presence of the precursor **A21**, Cs_2CO_3 and H_2O, the treatment of **85** with tosyl chloride in toluene at 45 °C gave the cyclized product **86** at a 90% yield with 98% ee (Scheme 24) [165]. As a proposed reaction mechanism, this transformation involves the oxidation of the Breslow intermediate by tosyl chloride, leading to the formation of tosylated intermediate. Next, the tosylated intermediate was converted into acyl azolium and tosyl anion. Finally, the enantioselective 1,4-addition of tosyl anion, followed by lactonization, affords the product **86**. Since the overall reaction is a redox-neutral process, we classified this reaction as redox cyclization. However, tosyl chloride behaves not only as a nucleophile but also as an oxidant; thus, this reaction may also be considered one of oxidative cyclization.



Scheme 24. Redox cyclization of enal-tethered cyclohexadienone.

5.2. [3 + 3] Annulation

In the NHC-catalyzed oxidant-free redox [3 + 3] annulation, the α,β-unsaturated acyl azoliums are the Michael acceptors acting as C3 synthons [166–169]. In the absence of an oxidant, the [3 + 3] annulation of ynals proceeds via the formation of α,β-unsaturated acyl azolium intermediates (Scheme 25) [166]. The ynal **71** is used as a reducible substrate for redox transformation. Under the optimized conditions using the precursor **(5a*R*,10b*S*)-A4a**, the reaction of ynal **71** with ethyl pyruvate **87** gave the annulation product **88**. As a possible mechanism, the pathway involving the Claisen rearrangement was proposed. This catalysis was initiated via the formation of α,β-unsaturated acyl azolium from ynal **71** and NHC. Next, pyruvic ester **87** isomerizes to enol, which undergoes the 1,2-addition to α,β-unsaturated acyl azolium. The [3 + 3] product **88** is formed through the Claisen rearrangement, tautomerization, and lactamization.



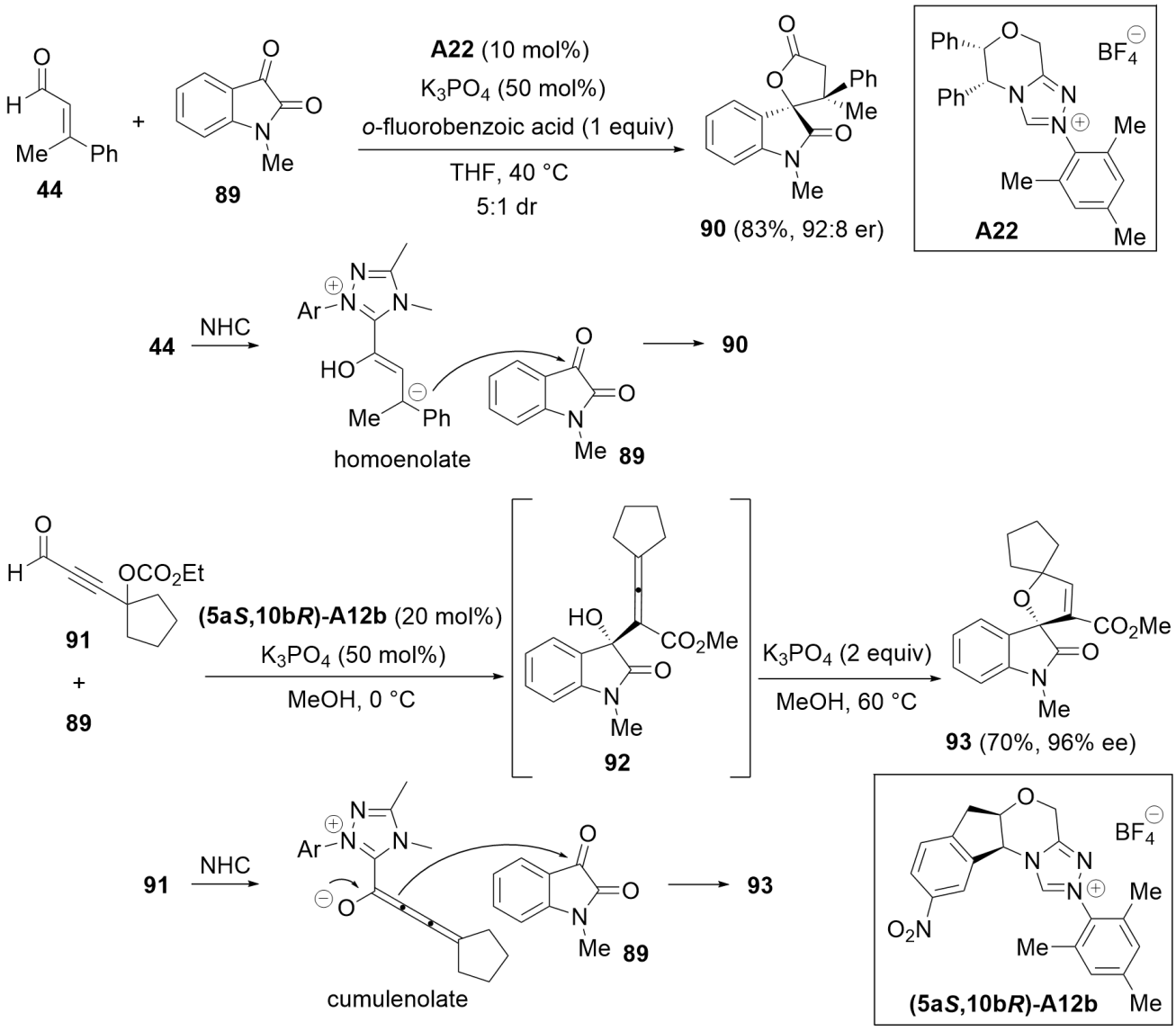
Scheme 25. NHC-catalyzed redox [3 + 3] annulation.

Furthermore, redox [3 + 3] annulation using α-bromoenals was developed because α-bromoenals react with the NHC catalyst to afford α,β-unsaturated acyl azoliums in the absence of an oxidant via debromination [167–169].

5.3. [3 + 2] Annulation

For oxidant-free redox [3 + 2] annulation, the reducible aldehydes are employed [170–180]. The NHC-linked homoenolate derivatives act as a C3 synthon for [3 + 2] annulation [170–178]. The NHC-linked homoenolate, generated from α,β-unsaturated aldehyde **44** and NHC catalyst, reacts as a C3 synthon (Scheme 26) [170]. Employing the precursor **A22** (10 mol%), K_3PO_4 (50 mol%) and *o*-fluorobenzoic acid (one equiv.) as the Brønsted acid, the [3 + 2] annulation of aldehyde **44** with *N*-methyl isatin **89** led to the formation of spirooxindole **90** at a 83% yield with 92:8 er. The reactivity and diastereo- and enantioselectivity were dependent on the acid cocatalyst; thus, the Brønsted acid would promote the addition of homoenolate to isatin **89** by hydrogen bonds. The [3 + 2] annulation reaction between alkynal **91** and isatin **89** was developed [179]. In the presence of the precursor **(5a*S*,10b*R*)-A12b** (20 mol%) and K_3PO_4 (50 mol%), the reaction of alkynal **91** with isatin **89** was performed in MeOH at 0 °C, leading to the allene product **92**. The allene product **92** could be converted to spirooxindole **93** via the treatment of the reaction mixture with K_3PO_4 (two equiv.) as an additional base at 60 °C. This transformation is initiated by the formation of azolium cumulenolate intermediate from

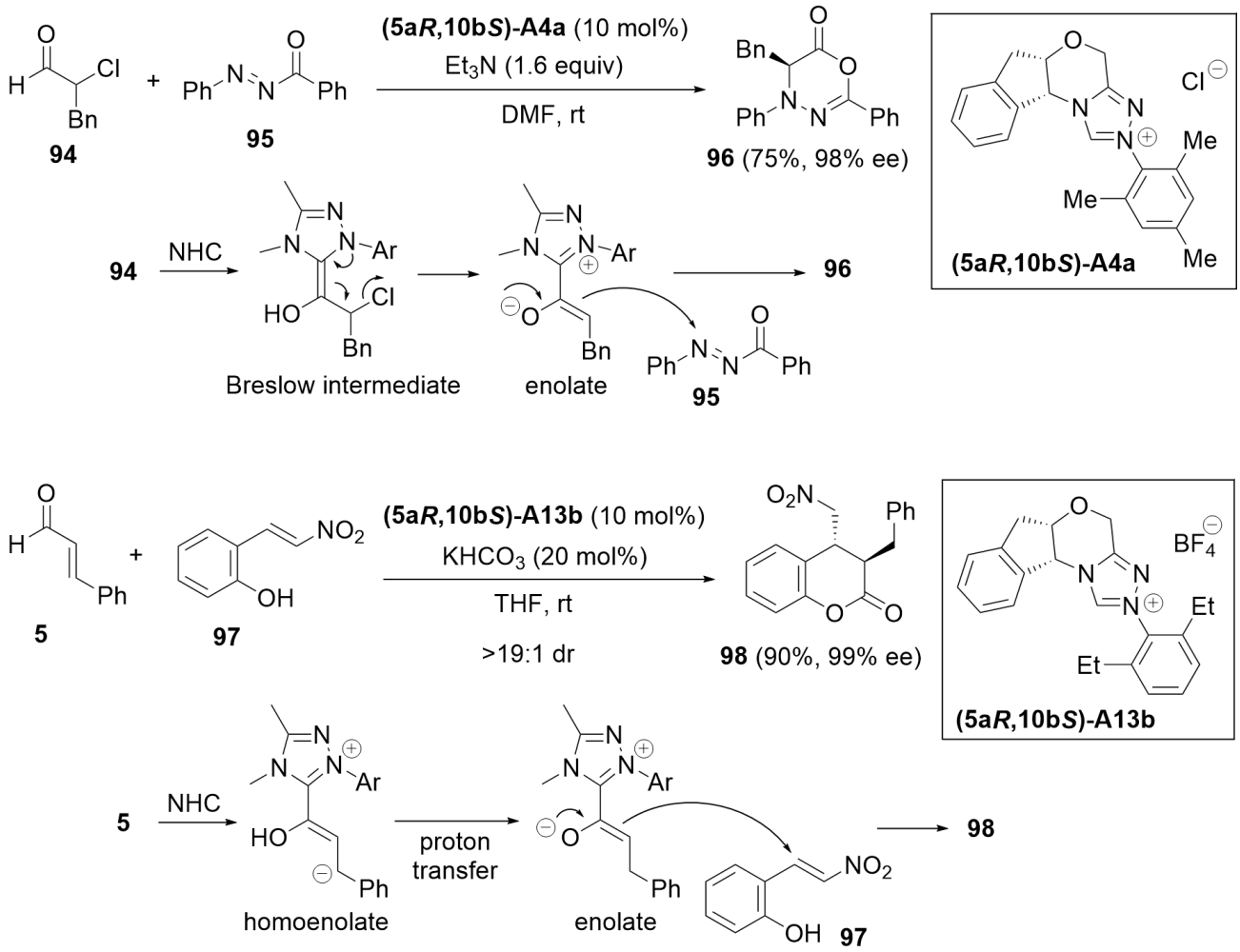
alkynal **91**. The subsequent addition of the α-carbon on cumulenolate to isatin **89** affords the allene product **92**. Additionally, the NHC-linked enolate was used as a C2 synthon for [3 + 2] annulation [180].



Scheme 26. NHC-catalyzed redox [3 + 2] annulation reactions.

5.4. [4 + 2] Annulation

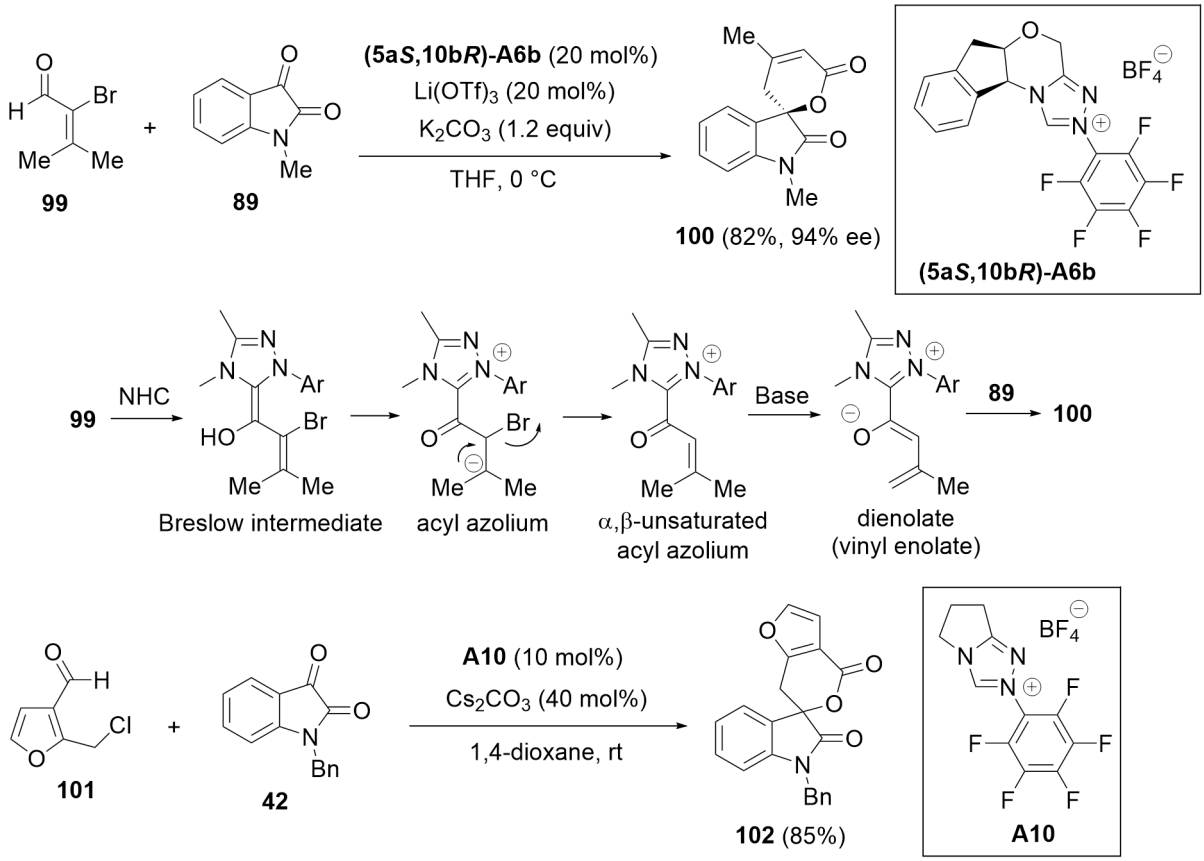
The NHC-linked enolates act as a C2 synthon for oxidant-free redox [4 + 2] annulation [181–193]. In the presence of the precursor **(5a*R*,10b*S*)-A4a** (10 mol%) and Et_3N (1.6 equiv.), the [4 + 2] annulation reaction of α-chloroaldehyde **94** with *N*-phenyl-*N*′-benzoyl-diazene **95** proceeded effectively to give 1,3,4-oxadiazin-6-one **96** at a 75% yield with 98% ee via the generation of the NHC-linked enolate from α-chloroaldehyde **94** (Scheme 27) [181]. The [4 + 2] annulation of cinnamaldehyde **5** with nitroalkene **97** was studied [182]. Under the optimized reaction conditions using the precursor **(5a*R*,10b*S*)-A13b**, the desired dihydrocoumarin **98** was obtained at a 90% yield with 99% ee. The reaction was initiated via the formation of homoenolate, which was converted to azolium enolate via proton transfer. This NHC-linked enolate reacted as a C2 synthon with nitroalkene **97** to give the annulation product **98**.



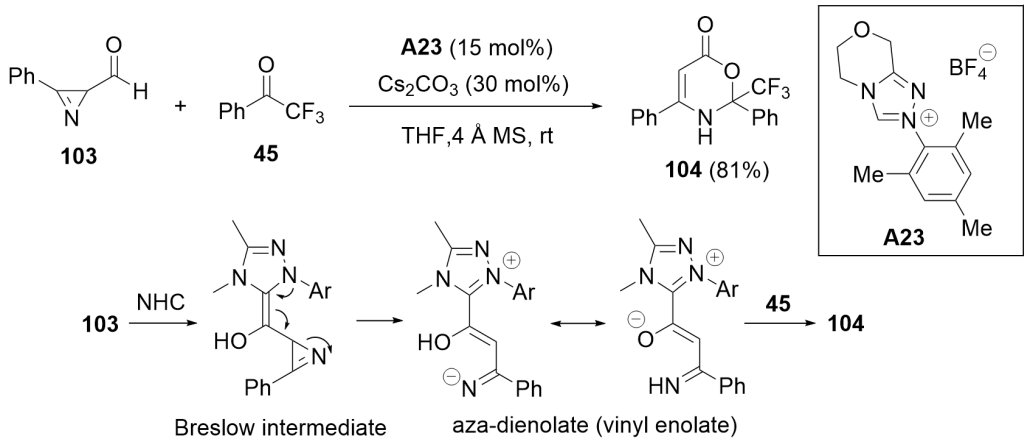
Scheme 27. Redox [4 + 2] annulation reactions using NHC-linked enolate.

The oxidant-free redox [4 + 2] annulation using the NHC-linked dienolate (vinyl enolate) as a C4 synthon was developed (Scheme 28) [194]. In the presence of chiral NHC catalyst generated from the precursor **(5a*S*,10b*R*)-A6b**, 2-bromo-2-enal **99** reacted with *N*-methylisatin **89** to give the [4 + 2] annulation product **100**. Initially, the Breslow intermediate was formed by the addition of NHC to enal **99**. The Breslow intermediate was transformed to α,β-unsaturated acyl azolium via debromination. The subsequent deprotonation at γ-H on α,β-unsaturated acyl azolium led to the NHC-linked dienolate (vinyl enolate), which undergoes nucleophilic addition to *N*-methylisatin **89**. Similarly, [4 + 2] annulation between 2-(chloromethyl)furan-3-carbaldehyde **101** and *N*-benzylisatin **42** gave the cycloadduct **102** via the formation of the NHC-linked dienolate via the dearomative 1,4-elimination of HCl [195].

Annulation using the NHC-linked aza-dienolate as a C4 synthon was reported (Scheme 29) [196,197]. In the presence of the precursor **A23** and Cs_2CO_3, the treatment of 2*H*-azirine-2-carbaldehyde **103** with ketone **45** in THF gave the cyclized product **104** at a 81% yield [196]. This transformation involves the formation of NHC-linked aza-dienolate from the Breslow intermediate of aldehyde **103**.



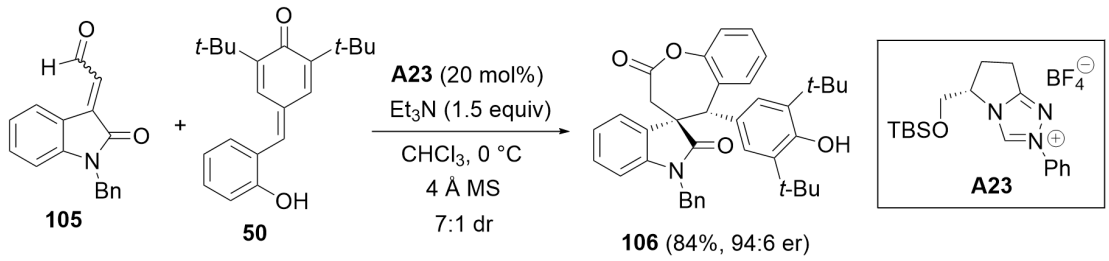
Scheme 28. Redox [4 + 2] annulation using NHC-linked dienolate.



Scheme 29. Annulation using NHC-linked aza-dienolate.

5.5. [4 + 3] Annulation

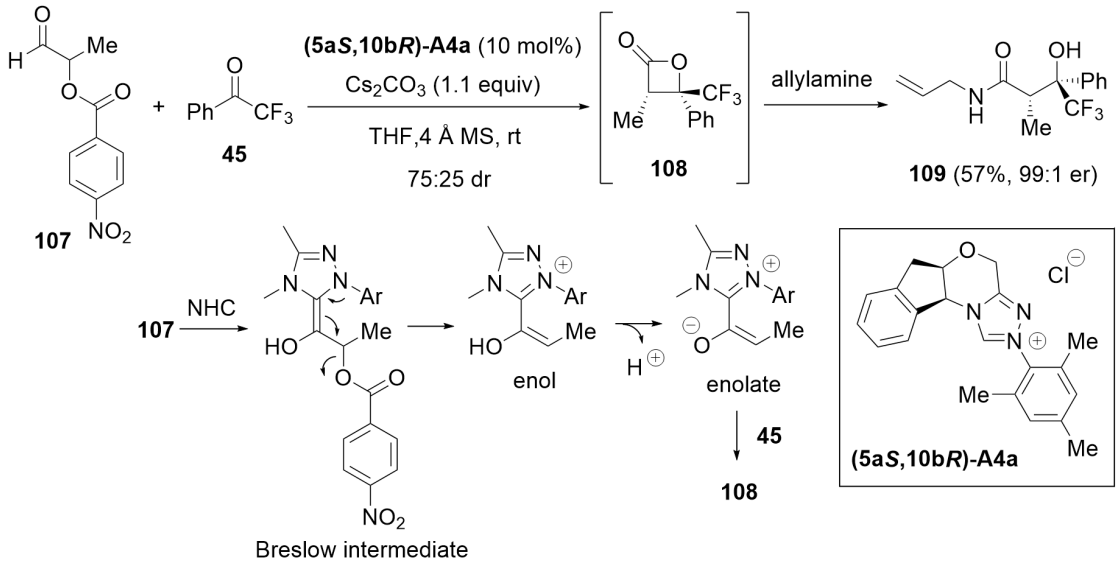
The NHC-linked homoenolate intermediates are used as a C3 synthon for oxidant-free redox [4 + 3] annulation [198–204]. The enantioselective reaction of isatin-derived enal **105** with *o*-hydroxyphenyl-substituted *p*-quinone methide **50** was reported (Scheme 30) [202]. In the presence of the precursor **A23** (20 mol%) and Et_3N (1.5 equiv.), the treatment of enal **105** with *p*-quinone methide **50** in $CHCl_3$ at 0 °C gave the oxindole-ε-lactone **106** at a 84% yield with 94:6 er. This annulation proceeded via the 1,6-addition of NHC-linked homoenolate, generated from enal **105**, to the hydroxy donor–1,6-Michael acceptor **50**, followed by lactonization, leading to ε-lactone **106**.



Scheme 30. Redox [4 + 3] annulation using NHC-linked homoenolate.

5.6. [2 + 2] Annulation

The NHC-linked enolate was used as a C2 synthon for oxidant-free redox [2 + 2] annulation (Scheme 31) [205]. The chiral NHC-catalyzed formal [2 + 2] cycloaddition between α-aroyloxyaldehyde **107** and ketone **45** afforded the unstable β-lactone product **108**. Thus, β-trifluoromethyl-β-hydroxyamide **109** was isolated as a stable product after ring opening with allylamine. The elimination of *p*-nitrobenzoate from the Breslow intermediate led to azolium enol. Subsequent deprotonation gave enolate, which underwent formal [2 + 2] cycloaddition with ketone **45**. Additionally, similar oxidative [2 + 2] annulation was reported [115].

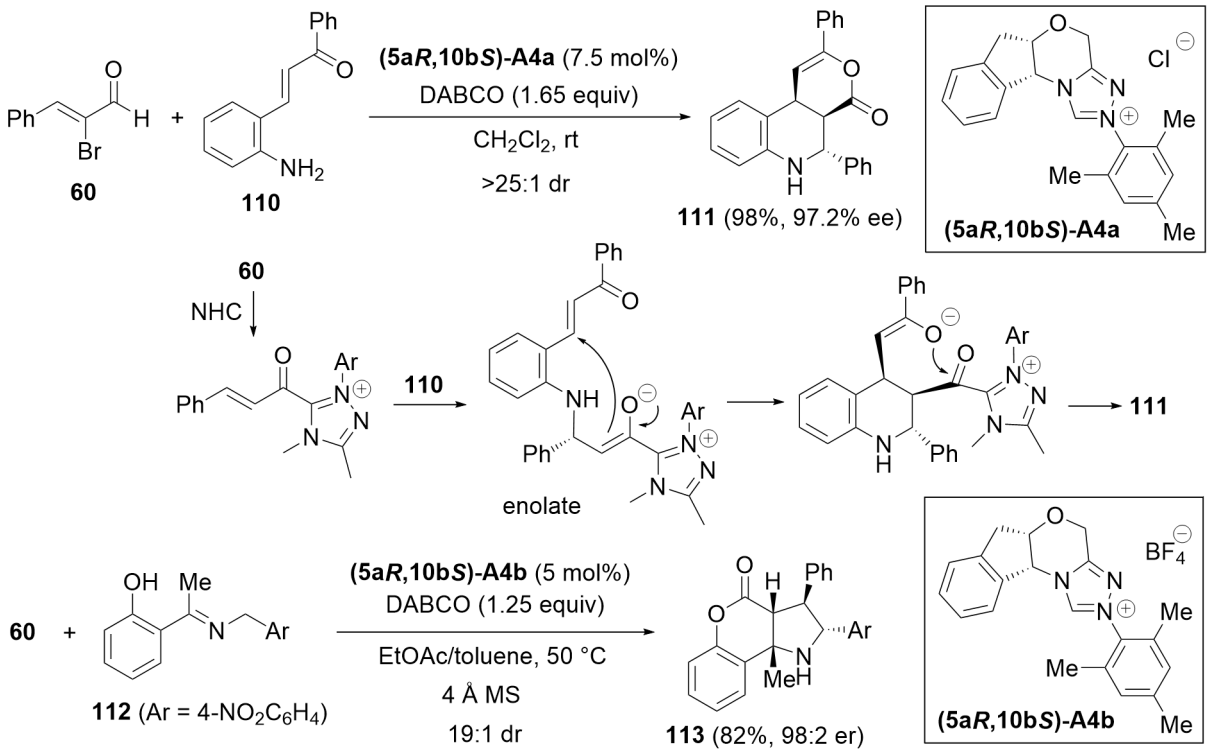


Scheme 31. Formal [2 + 2] cycloaddition using NHC-linked enolate.

5.7. Cascade Annulation

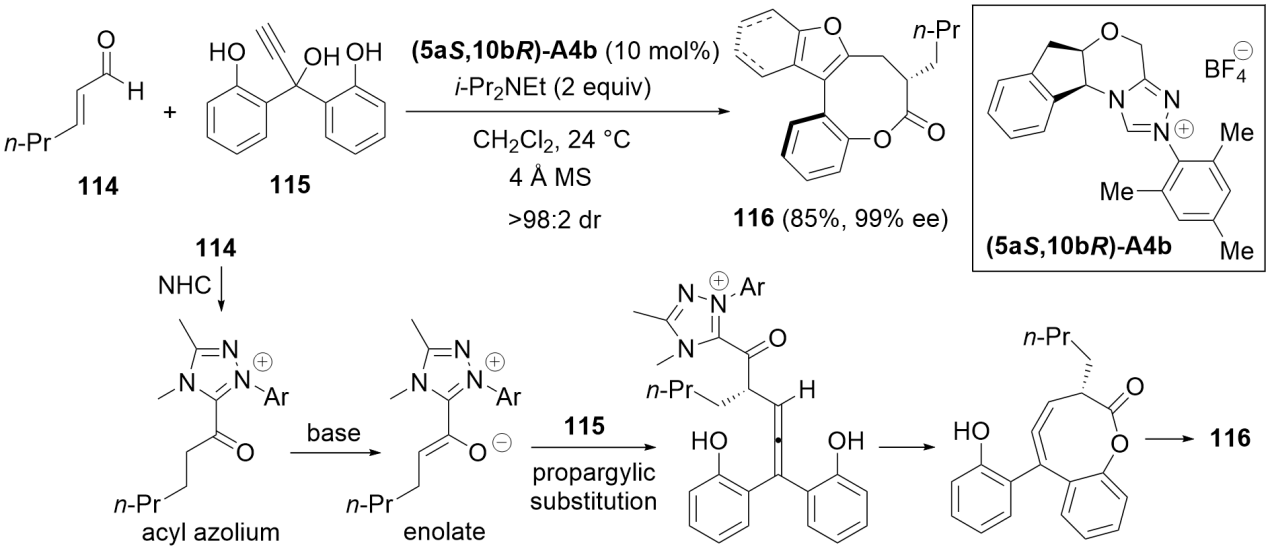
The NHC-catalyzed cascade reactions were widely investigated under the redox conditions [206–217]. The α,β-unsaturated acyl azoliums were Michael acceptors acting as a C2 synthon for the cascade annulation reactions [206–211]. Under the optimized conditions using the precursor **(5a*R*,10b*S*)-A4a** (7.5 mol%) and DABCO (1.65 equiv.), the cascade reaction of α-bromocinnamaldehyde **60** with 2-aminophenylenone**110** gave the cyclized product **111** at a 98% yield with 97.2% ee (Scheme 32) [207]. In these reactions, α,β-unsaturated acyl azolium was initially formed from the Breslow intermediate via bromide elimination. The subsequent aza-Michael addition of **110** to α,β-unsaturated acyl azolium provided enolate, which underwent intramolecular Michael addition. Finally, the cyclized product **111** was obtained via lactonization. The cascade reaction between α-bromocinnamaldehyde **60** and imine **112** with the benzylic carbon of 4-nitrobenyl group was achieved [208]. The tetrahydrochromeno [4,3-*b*]pyrrole derivative **113** was obtained at a 82% yield with 98:2 er under redox catalysis using the precursor **(5a*R*,10b*S*)-A4b** and

DABCO. The cyclized product **113** was obtained through the Michael addition of anion of imine **112** to α,β-unsaturated acyl azolium.



Scheme 32. Cascade reactions using α,β-unsaturated acyl azoliums as a Michael acceptor.

The atropo-enantioselective synthesis of bridged biaryls was achieved via the NHC-catalyzed cascade reaction (Scheme 33) [212]. Employing the precursor **(5aS,10bR)-A4b** and *i*-Pr_2Net, the cascade reaction of α,β-unsaturated aldehyde **114** with triol **115** led to the formation of bridged biaryl **116** with an eight-membered lactone at a 85% yield with 99% ee. This NHC-catalyzed transformation proceeded through the propargylic substitution of propargylic alcohol **115** with NHC-linked enolate. Furthermore, redox cascade reactions using NHC-linked homoenolates were also developed [213–216].



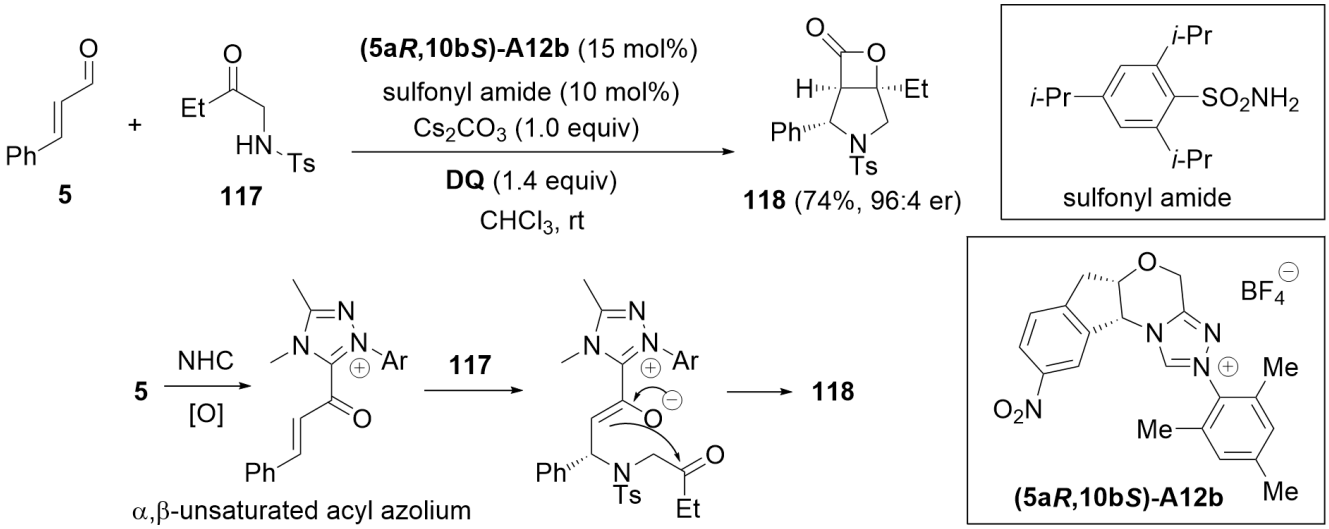
Scheme 33. Cascade reaction using NHC-linked enolate.

6. Cooperative Catalysis with Brønsted Acid and a Hydrogen-Bonding Catalyst

6.1. Cooperative Catalysis Using Brønsted Acid

Since Rovis's group reported cooperative NHC catalysis using the Brønsted acid [218], the use of the Brønsted acid has widely been demonstrated in the NHC-catalyzed activation of aldehyde C(sp^2)–H bonds for C–O bond formation [170,219–223].

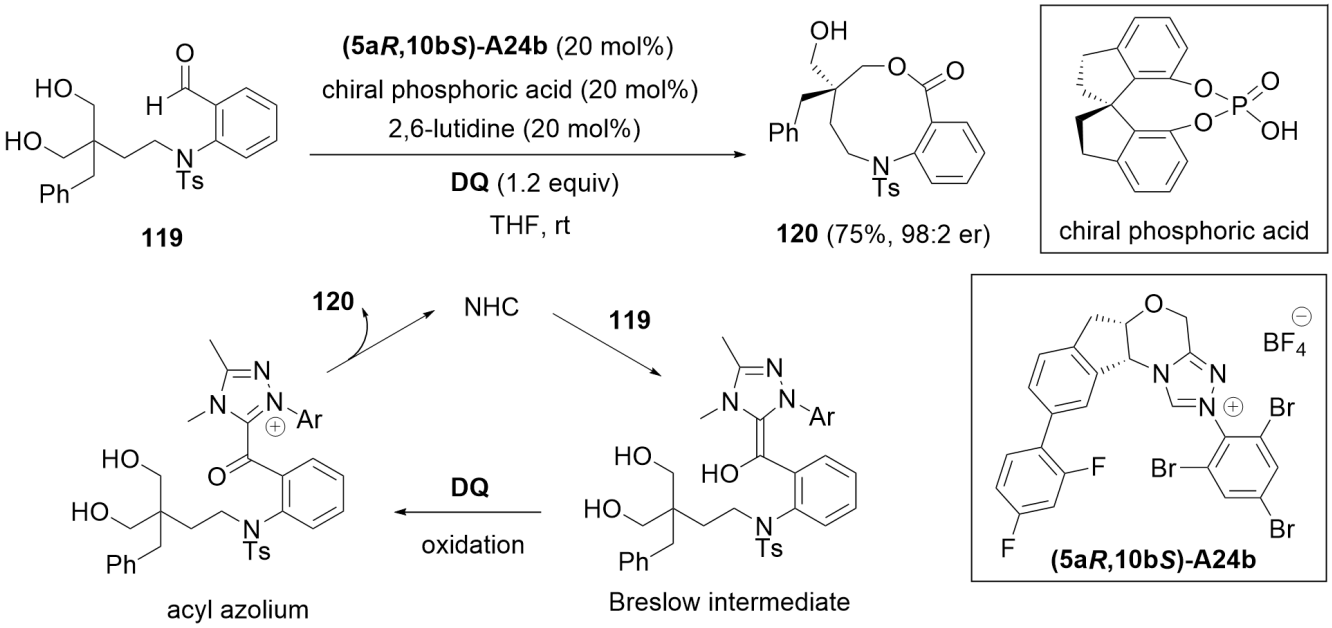
In the presence of the NHC precursor **(5a*R*,10b*S*)-A12b** (15 mol%), Cs_2CO_3 (1.0 equiv.) and DQ (1.4 equiv.), the oxidative [3 + 2] annulation of cinnamaldehyde **5** with the *N*-T amino ketone **117** gave the cyclized product **118** with β-lactone moiety at a 74% yield with 96:4 er (Scheme 34) [220]. The enantioselectivity of this transformation was improved by employing sulfonyl amide (10 mol%) as an additive. In this reaction, α,β-unsaturated acyl azolium is a Michael acceptor acting as C3 synthon.



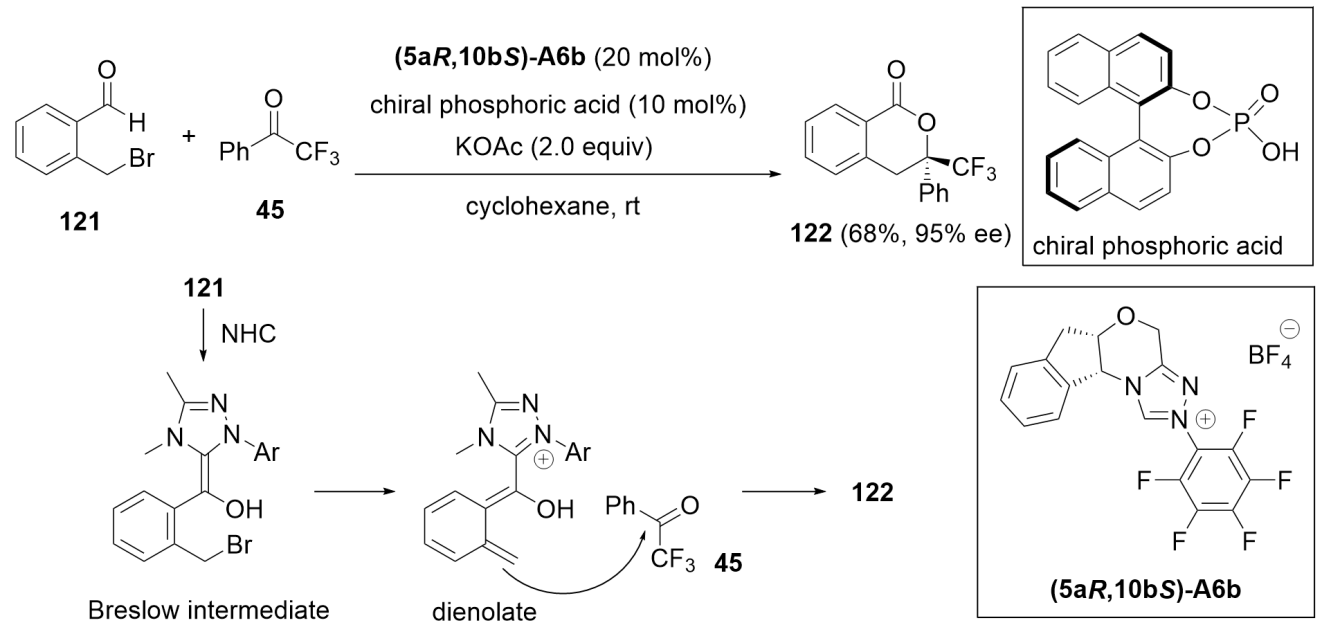
Scheme 34. Oxidative [3 + 2] annulation using acyl azoliums.

The combined use of the chiral Brønsted acid in NHC catalysis has gained increasing attention as a novel method to improve enantioselectivity. The NHC-catalyzed enantioselective synthesis of medium-ring lactones was developed [221]. The desymmetrization of prochiral 1,3-diol **119** was studied under oxidative conditions using DQ (1.2 equiv.) as an oxidant (Scheme 35). In the presence of the precursor **(5a*R*,10b*S*)-A24b** (20 mol%), 2,6-lutidine (20 mol%) and chiral phosphoric acid (20 mol%), the reaction of **119** was carried out to give the nine-membered-ring lactone **120** at a 75% yield with 98:2 er. In this reaction, chiral spiro-phosphoric acid was employed as a cocatalyst to enhance the enantioselectivity and catalytic performance. This NHC-catalyzed macrolactonization proceeded via the oxidation of the Breslow intermediate to acyl azolium.

Glorius's group developed [4 + 2] the annulation of ketone **45** with 2-(bromomethyl)-benzaldehyde **121** as a substrate with a leaving group at the *ortho*-benzylic position (Scheme 36) [222]. However, the use of chiral NHC led to only moderate enantioselectivity for product **122**. Later, Rovis's group achieved the highly enantioselective [4 + 2] annulation of identical starting materials by using chiral phosphoric acid and chiral NHC [223]. In the presence of the precursor **(5a*R*,10b*S*)-A6b** (20 mol%), KOAc (2.0 equiv.) and chiral phosphoric acid (10 mol%), the reaction of **121** with **45** gave the product **122** at a 68% yield with 95% ee. In this reaction, the extrusion of the bromide within the Breslow intermediate led to dienolate, which underwent [4 + 2] annulation with ketone **45**.



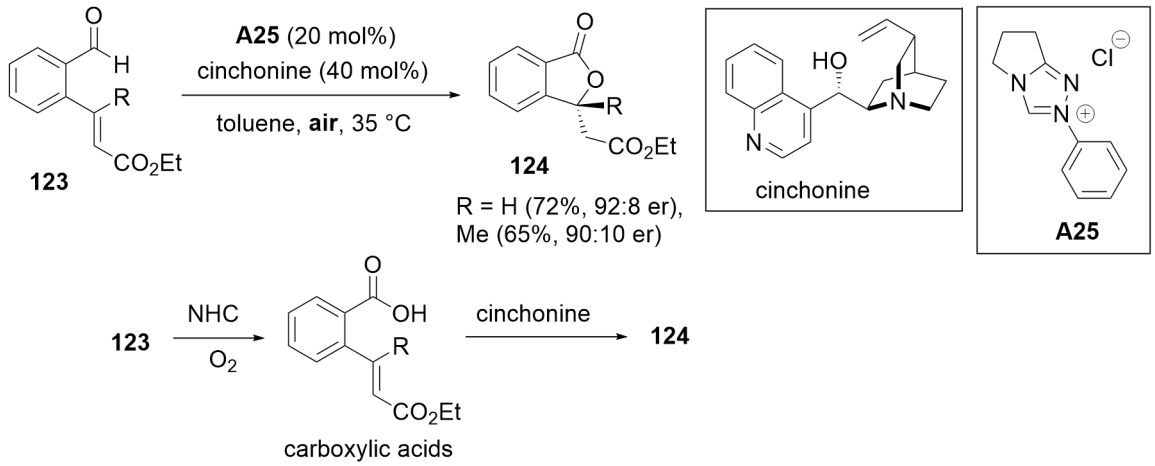
Scheme 35. Medium-ring lactone synthesis via desymmetrization of 1,3-diol.



Scheme 36. [4 + 2] Annulation using chiral phosphoric acid.

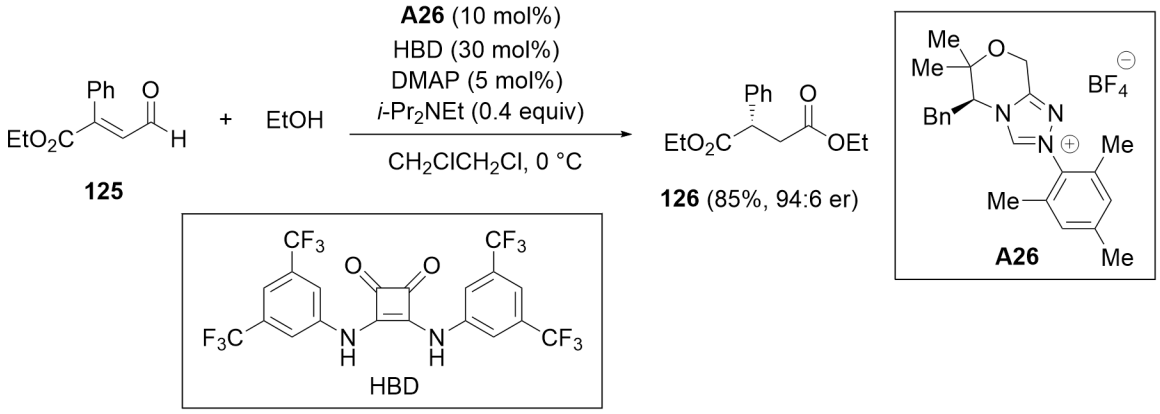
6.2. Cooperative Catalysis Using a Hydrogen-Bonding Catalyst

The dual catalysis using NHC and a hydrogen-bonding catalyst was developed [224]. The cooperative catalysis using cinchonine as chiral bifunctional organocatalyst with achiral NHC catalyst was reported [225]. In the presence of the achiral NHC precursor **A25** (20 mol%) and cinchonine (40 mol%), the domino oxidation/oxa–Michael addition reaction of aldehydes **123** proceeded without an additional base to give the phthalides **124** with good enantioselectivities (Scheme 37). This reaction was initiated via the NHC-catalyzed oxidation reaction of aldehydes **123**, leading to carboxylic acids as a key intermediate. Next, the intramolecular oxa–Michael addition reaction of carboxylic acids was promoted by cinchonine to give the products **124** in an enantioselective manner. In this process, the hydrogen bond donor (OH) and tertiary amine (quinuclidine) of cinchonine would activate and orient the nucleophile and electrophile, respectively.



Scheme 37. Use of cinchonine as chiral hydrogen-bonding catalyst.

The cooperative catalysis using the chiral NHC catalyst and H-bond doner catalyst (HBD) was reported to achieve the enantioselective β-protonation in the oxidant-free esterification of α,β-unsaturated aldehydes (Scheme 38) [226]. In the presence of the precursor **A26** (10 mol%), H-bond doner catalyst (HBD, 30 mol%), DMAP (5 mol%) and *i*-Pr_2NEt (0.4 equiv.), the reaction of β-ethyl ester **125** with ethanol was performed at 0 °C. The saturated bis-ester **126** was obtained at a 85% yield with 94:6 er. The coordination of HBD to the β-ethyl ester group would enhance enantioselectivity via the steric interactions near the β-position of **125**.

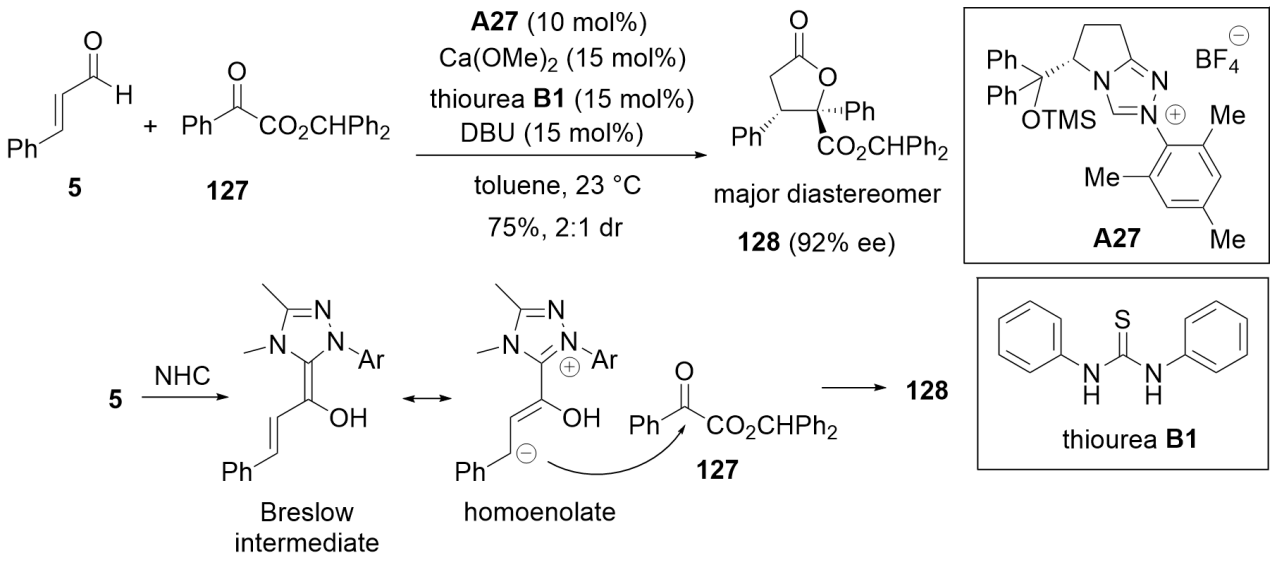


Scheme 38. Reaction catalysis using chiral NHC catalyst and H-bond doner catalyst.

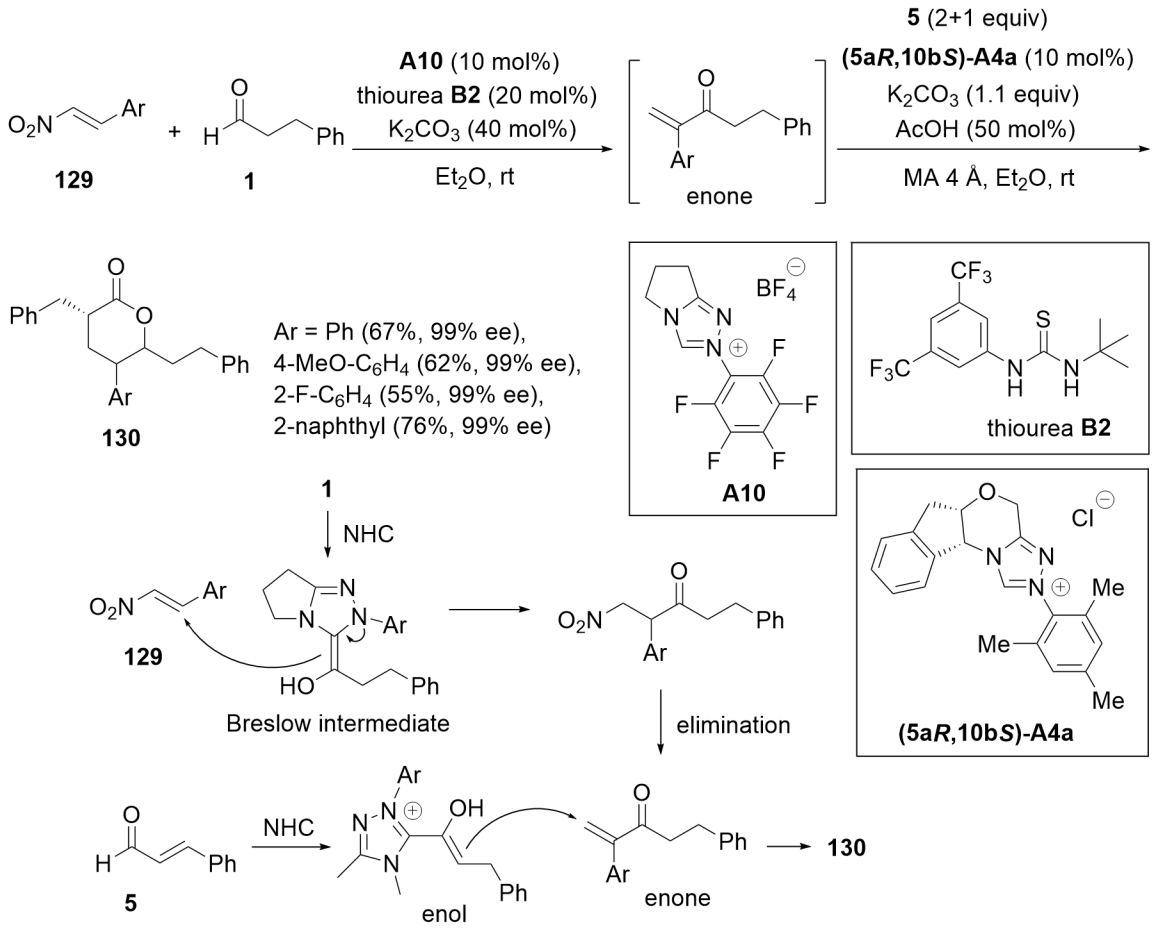
Thiourea catalysts have been used in NHC catalysis for the C–O bond formation of aldehydes [227–230]. The NHC-catalyzed annulation of enals and α-ketoesters was studied (Scheme 39) [227]. In this reaction, the combined use of $Ca(OMe)_2$ as a Lewis acid and thiourea **B1** as a H-bond doner catalyst enhanced the enantioselectivities and yields of products. Under the optimized conditions using the chiral precursor **A27**, the annulation between cinnamaldehyde **5** and α-ketoester **127** proceeded with the modest diastereoselectivity (2:1 dr) to give the major diastereomer **128** with 92% ee. This reaction promoted the addition of homoenolate, generated from **5** and NHC, to α-ketoester **127**.

The sequential three-component reaction of nitroalkene **129**, 3-phenylpropanal **1**, and cinnamaldehyde **5** was achieved via a one-pot procedure (Scheme 40) [228]. The use of two different NHC catalysts, generated from the achiral precursor **A10** and the chiral precursor **(5a*R*,10b*S*)-A4a**, led to the enantioselective formation of dihydropyranones **130**. In the presence of presence of **A10**, thiourea **B2** and K_2CO_3, the reaction of nitroalkene **129** and aldehyde **1** led to the in situ generation of enone intermediates via

the nitro-Stetter/elimination sequence [229]. Next, the chiral presence **(5a*R*,10b*S*)-A4a** and cinnamaldehyde **5** (2+1 equiv.) were employed with K_2CO_3, acetic acid and 4 Å molecular sieves for annulation. The dihydropyranone **130** was obtained via the Michael addition of chiral NHC-linked enol to β-unsubstituted enones, followed by lactonization.



Scheme 39. Reactions using the thiourea catalyst and Lewis acid.

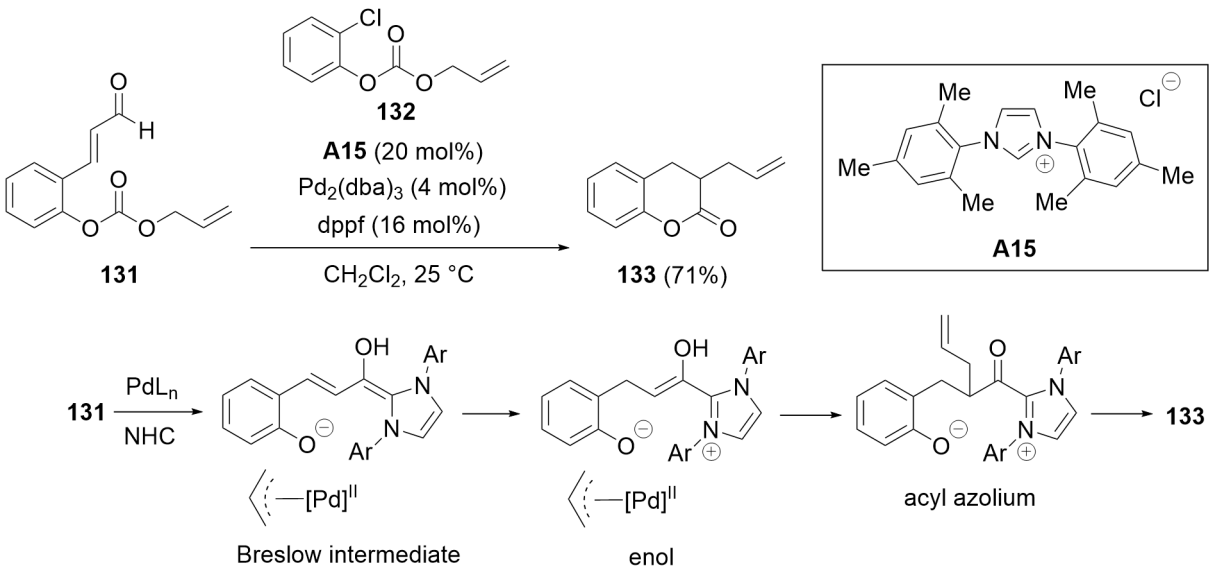


Scheme 40. Sequential NHC-catalyzed reaction.

7. Cooperative Catalysis with Transition-Metal Catalyst

7.1. Cooperative Catalysis Using a Palladium Catalyst

Scheidt's group reported the cooperative catalysis involving the simultaneous activation of substrates using the NHC catalyst and palladium catalyst (Scheme 41) [231]. In the presence of the NHC precursor **A15** and palladium catalyst, generated from $Pd_2(dba)_3$ and dppf ligand, the carbonate **131** was converted to the allylated dihydrocoumarin **133**. To improve the chemical yield, allyl carbonate **132** was used as an additive for increasing the concentration of the π-allyl palladium intermediate. The substrate **131** reacted with the NHC catalyst and palladium catalyst to give the Breslow intermediate and π-allyl palladium. This cooperative transformation was based on the addition of enol, generated from the Breslow intermediate, into the π-allyl palladium intermediate.



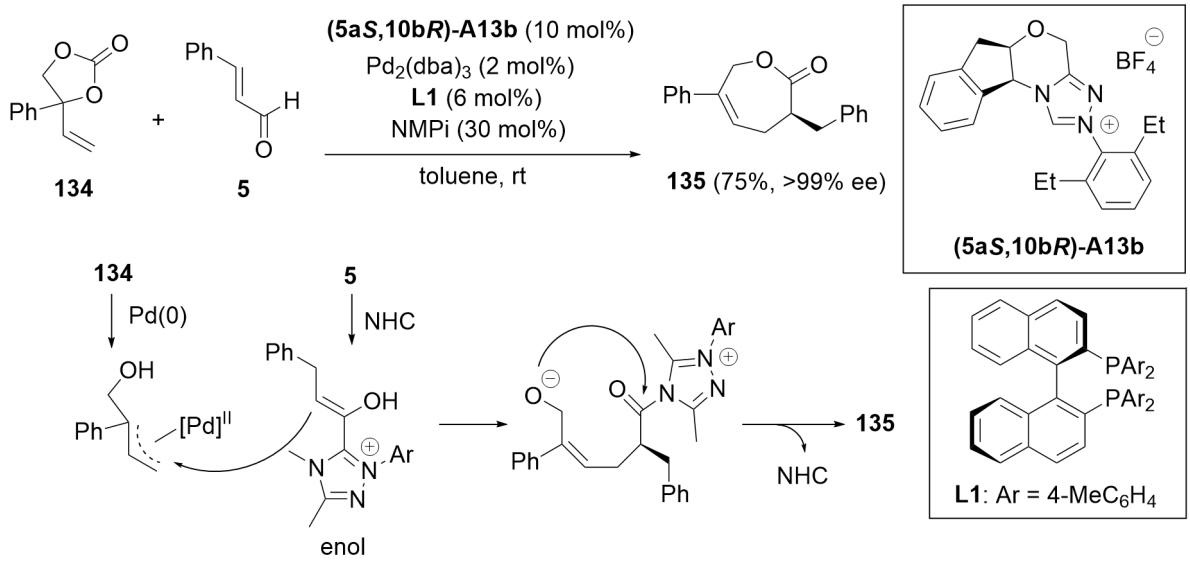
Scheme 41. Cooperation between NHC and palladium catalyst.

The palladium-catalyzed allylic substitution was applied to the enantioselective cooperative catalysis by using chiral NHC catalyst [232–238]. Glorius's group reported enantioselective catalysis using the combination of chiral NHC, generated from the precursor **(5a*S*,10b*R*)-A13b**, and chiral palladium catalyst, generated from $Pd_2(dba)_3$ and ligand **L1** (Scheme 42) [234]. Under the optimized conditions, the [5 + 2] annulation reaction between phenyl vinylethylene carbonate **134** and cinnamaldehyde **5** gave the annulation product **135** with excellent enantioselectivity. NHCs are known to act as a ligand for transition-metals; thus, the use of a bidentate phosphine ligand **L1** is crucial to prevent the coordination of NHC to the active Pd catalyst. The proposed catalytic cycle involves the NHC-catalyzed activation of cinnamaldehyde **5**, followed by Pd-catalyzed allylic substitution. Initially, the palladium-catalyzed decarboxylation of **134** gives the π-allyl palladium(II) complex, which reacts with enol generated from **5** and NHC. The subsequent cyclization provides the cyclized product **135** accompanied by the regeneration of the NHC catalyst.

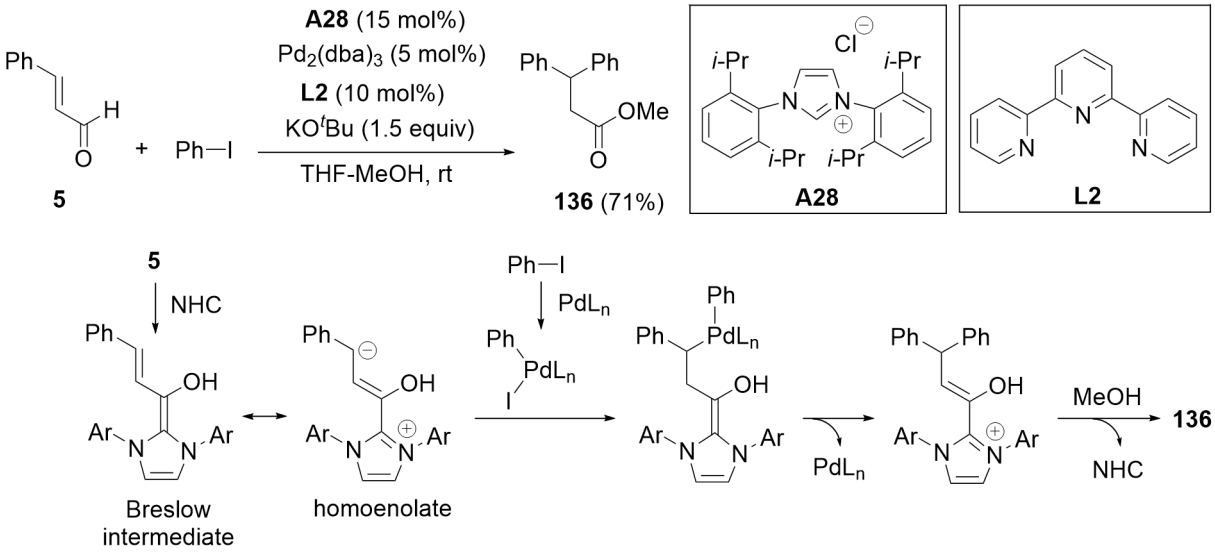
Recently, the [3 + 2] annulation reaction for the synthesis of enantioenriched α,β-disubstituted γ-butyrolactones was reported by using chiral NHC and chiral iridium catalysts [235,236]. Furthermore, the umpolung allylic and propargylic substitution reactions of enals were achieved by using chiral NHC and nickel catalysts [237,238].

The umpolung 1,4-addition of aryl iodides or vinyl bromides to enals was carried out under the cooperative NHC/palladium reaction conditions [239,240]. The 1,4-addition of iodobenzene to cinnamaldehyde **5** was promoted via the combination of NHC, generated from the precursor **A28**, and palladium catalyst, generated from $Pd_2(dba)_3$ and ligand **L2**, to give methyl β,β-diphenyl propanoate **136** at a 71% yield (Scheme 43) [239]. Initially, the homoenolate equivalent was generated from cinnamaldehyde **5** and NHC. Next, the

nucleophilic homoenolate reacted with the activated PhPdI(L_n), which was generated via the oxidative addition of the palladium catalyst to iodobenzene. The subsequent reductive elimination provided the NHC-bonding intermediate, which reacted with MeOH to afford methyl β,β-diphenyl propanoate **136**. Additionally, 1,4-addition of vinyl bromides to enals was studied under similar reaction conditions [240].



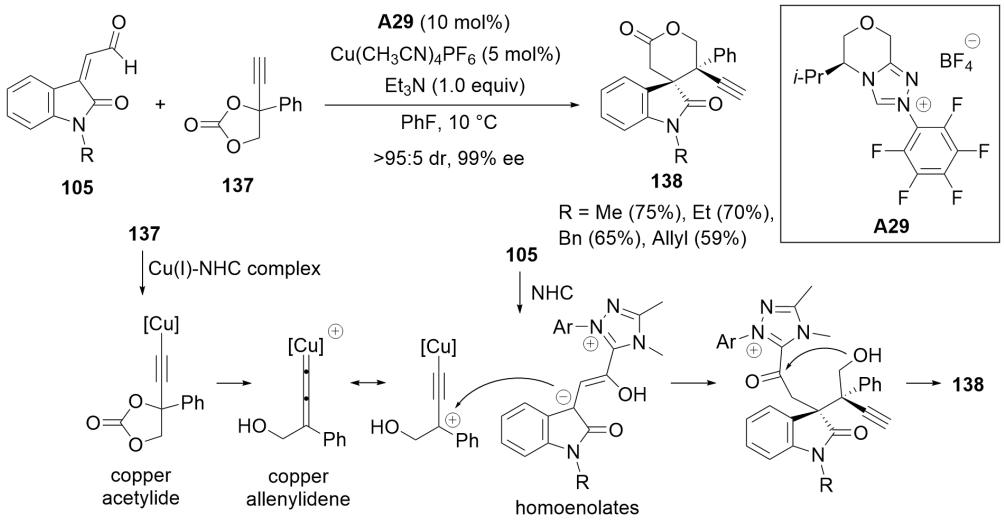
Scheme 42. Enantioselective cooperative catalysis.



Scheme 43. Cooperative catalysis for umpolung 1,4-addition to cinnamaldehyde.

7.2. Cooperative Catalysis Using a Copper Catalyst

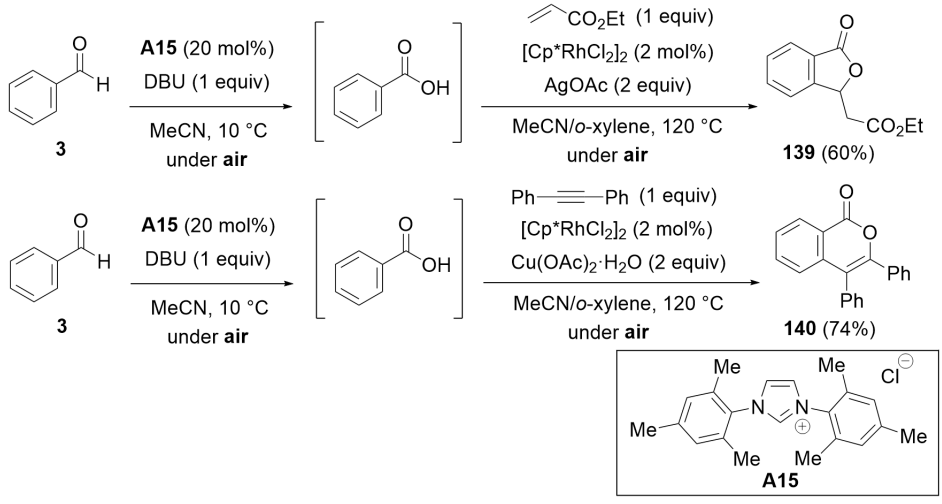
The copper catalysts were used for the cooperative NHC catalysis [241,242]. In the presence of the precursor **A29** (10 mol%), $Cu(CH_3CN)_4PF_6$ (5 mol%) and Et_3N (one equiv.), [3 + 3] annulation between the isatin-derived enal **105** and ethynylethylene carbonate **137** led to the formation of the spirooxindole δ-lactones **138** with >95:5 dr and 99% ee (Scheme 44) [242]. Initially, copper acetylide was generated from **137** under basic conditions. The decarboxylation of copper acetylide leads to copper allenylidene. Subsequently, enals **105** react with NHC to form homoenolates, which undergo formal [3 + 3] cycloaddition with copper allenylidene to afford δ-lactones **138**. Since NHC serves as a ligand of copper, the chiral Cu(I)–NHC complex would participate in the control of stereochemistry, together with the chiral NHC catalyst.



Scheme 44. Cooperative catalysis with copper catalyst.

7.3. Cooperative Catalysis Using a Rhodium Catalyst

The one-pot reactions involving NHC catalysis and rhodium(III) catalysis were reported, although these sequential reactions cannot be strictly classified as types of cooperative catalysis (Scheme 45) [243]. Initially, the aerobic oxidation of benzaldehyde **3** proceeded smoothly under the conditions using NHC generated from the precursor **A15** and DBU to give benzoic acid intermediate. The subsequent addition of ethyl acrylate, $[Cp^*RhCl_2]_2$ and AgOAc to the reaction mixture induced the rhodium(III)-catalyzed oxidative coupling/annulation of benzoic acid with ethyl acrylate. The phthalide **139** was obtained at a 60% yield. When 1,2-diphenylethyne was used for the second step, the isocoumarin **140** was obtained at a 74% yield. In this case, $Cu(OAc)_2 \cdot H_2O$ performed better than AgOAc as an oxidant in rhodium(III) catalysis. More recently, NHC/Rh cooperative catalysis for the asymmetric [3 + 3] annulation of oxabicyclic alkenes with enals was developed [244].

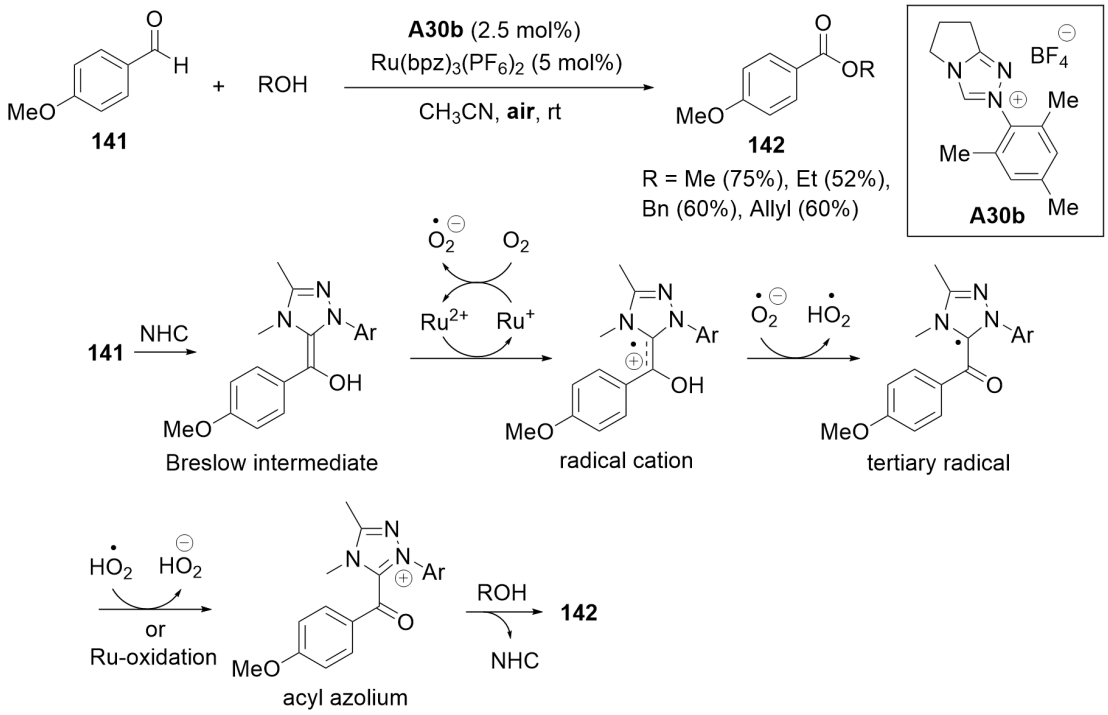


Scheme 45. Sequential reactions via NHC catalysis and rhodium(III) catalysis.

7.4. Cooperative Catalysis Using a Ruthenium Catalyst

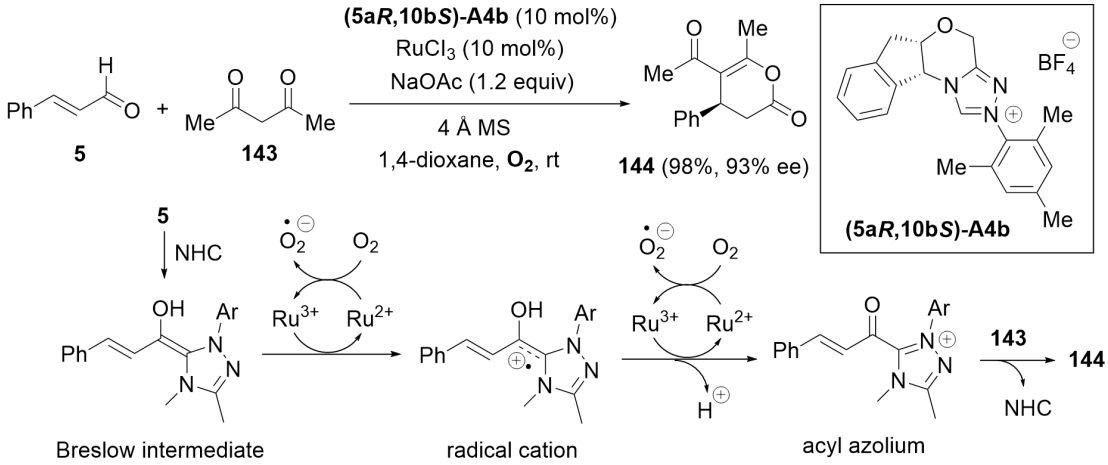
The combination of NHC catalysis and ruthenium redox catalysis was investigated [245–247]. The oxidative esterification of aldehydes was achieved by using the NHC precursor **A30b** and $Ru(bpz)_3(PF_6)_2$ (bpz=2,2′-bipyrazine) as a ruthenium(II) redox catalyst under the mild aerobic conditions (Scheme 46) [245]. The catalytic ruthenium cycle involved the oxidation of the Ru(I) complex to Ru(II) complex by molecular

oxygen to give the superoxide radical anion. Initially, the Ru(I)-catalyzed oxidation of the Breslow intermediate generated from aldehyde **141** led to the radical cation, which would be further oxidized to the acyl azolium via the tertiary radical.



Scheme 46. Cooperative catalysis with ruthenium catalyst.

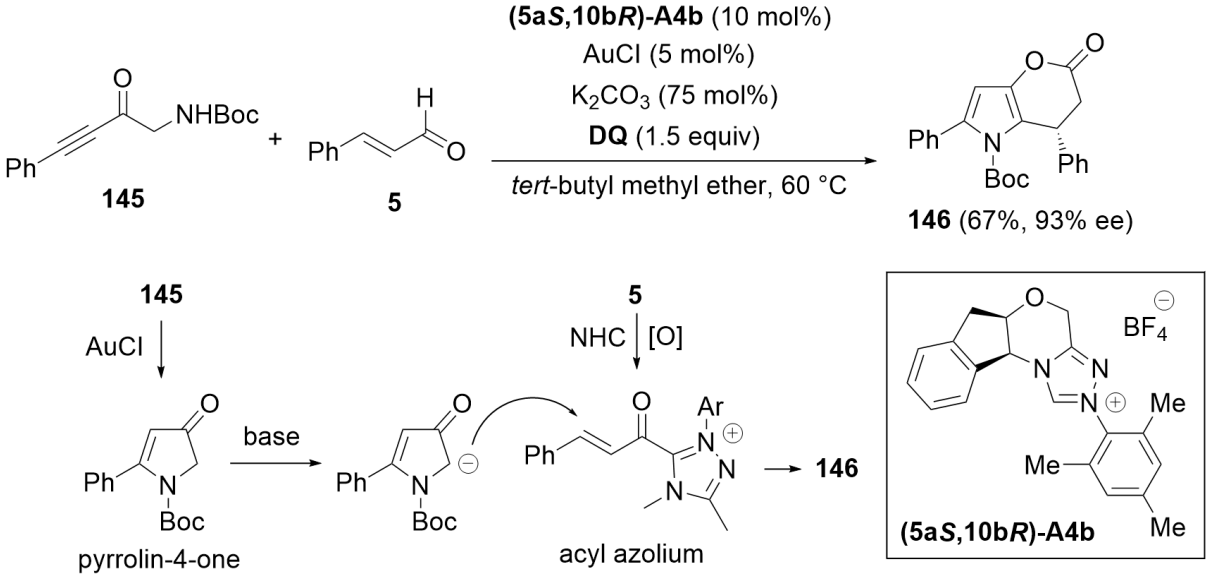
Cooperative NHC/ruthenium redox catalysis was used for oxidative [3 + 3] annulation (Scheme 47) [246]. The oxidation of the Breslow intermediate led to the formation of α,β-unsaturated acyl azolium acting as a C3 synthon. In the presence of chiral NHC generated from the precursor **(5a*R*,10b*S*)-A4b**, $RuCl_3$ and O_2, the oxidative reaction of cinnamaldehyde **5** with 2,4-pentanedione **143** was performed in 1,4-dioxane, affording lactone **144** at a 98% yield with 93% ee. The proposed reaction mechanism involved the oxidation of the Breslow intermediate, generated from NHC and enal **5**, by SET from $RuCl_3$. A second oxidation of radical cation intermediate by $RuCl_3$ gave α,β-unsaturated acyl azolium, which underwent [3 + 3] annulation with 2,4-pentanedione **143**. In this catalysis, Ru(III) was regenerated through the oxidation of Ru(II) by molecular oxygen.



Scheme 47. Oxidative [3 + 3] annulation using ruthenium catalyst.

7.5. Cooperative Catalysis Using a Gold Catalyst

The enantioselective gold and NHC relay catalysis was reported (Scheme 48) [248]. The cascade annulation between α-amino-ynone **145** and cinnamaldehyde **5** was performed under oxidative conditions using DQ as an oxidant. Initially, pyrrolin-4-one intermediate was obtained via gold catalysis. The anion of pyrrolin-4-one added to α,β-unsaturated acyl azolium to produce pyrrole-fused lactone **146** with excellent enantioselectivity.

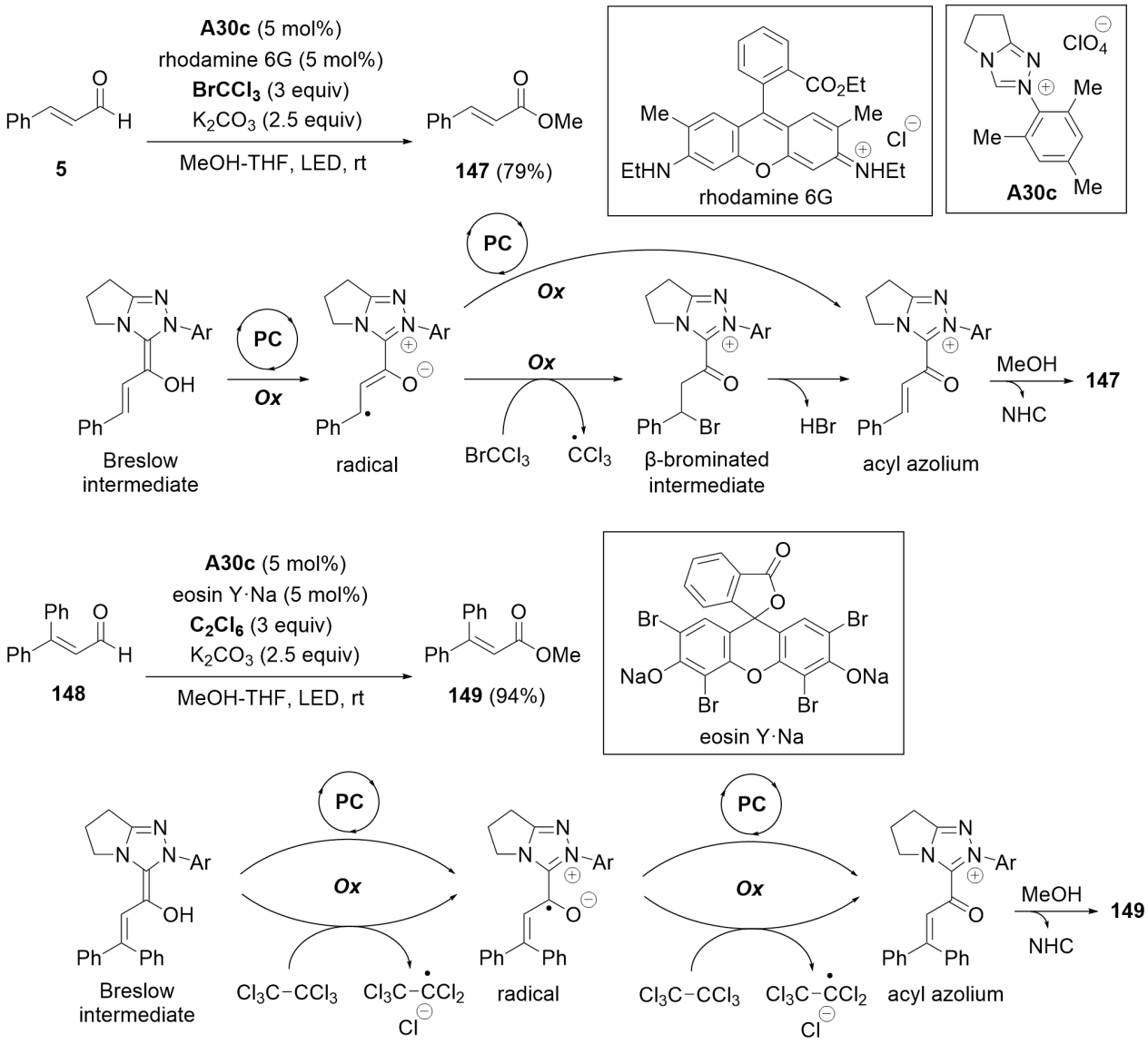


Scheme 48. Relay catalysis with gold catalyst.

8. Cooperative Catalysis with Photocatalysts

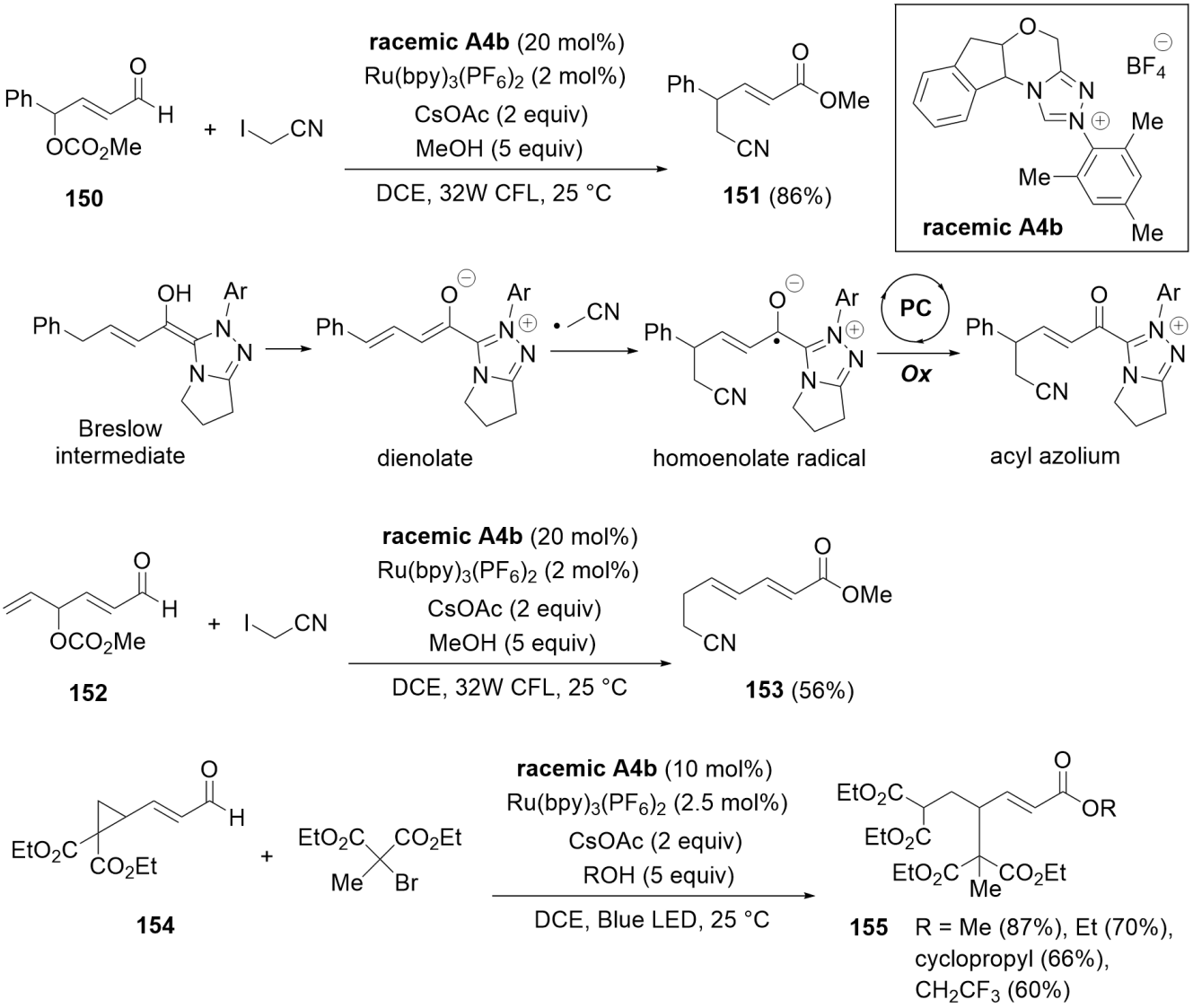
In 2012, DiRocco and Rovis reported the first reaction involving NHC catalysis and photoredox Ru catalysis [249]. In recent years, cooperative NHC catalysis with photocatalyst has gained increasing attention as a novel form of redox catalysis [28–31].

The combined use of NHC and photocatalyst was applied to the oxidative transformation of aldehydes to the corresponding esters [250–257]. The oxidative esterification of aldehydes through the oxidation of the Breslow intermediates was achieved via dual organocatalysis based on the cooperation between NHC and an organophotocatalyst such as rhodamine 6G or eosin Y·Na (Scheme 49) [250,251]. In the presence of the triazolium precursor **A30c** (5 mol%) and rhodamine 6G (5 mol%), the use of $BrCCl_3$ (three equiv.) as a co-oxidant promoted the reaction of cinnamaldehyde **5** to give ester **147** at a 79% yield [250]. Initially, it was assumed that the electron-rich Breslow intermediate was photocatalytically oxidized to acyl azolium via the radical intermediate, whereas co-oxidant $BrCCl_3$ would act as a quencher toward the activated photocatalyst species with the reduction property to turn the catalytic photoredox cycle. After the detailed research conducted in [251], it was shown that $BrCCl_3$ promotes the second oxidation as a brominating reagent toward the radical intermediate to give the β-brominated intermediate. The acyl azolium was formed via the elimination of HBr from the β-brominated intermediate. The use of C_2Cl_6 as a co-oxidant was an effective method for oxidative esterification, because the oxidation steps are promoted by two pathways associated with the activated photocatalyst and C_2Cl_6 [251]. In the presence of the precursor **A30c** (5 mol%) and eosin Y·Na (5 mol%), the reaction of 3,3-diphenylacrylaldehyde **148** was studied. Although $BrCCl_3$ was less effective for the oxidative esterification of **148**, the use of C_2Cl_6 (three equiv.) led to the formation of ester **149** at a 94% yield.



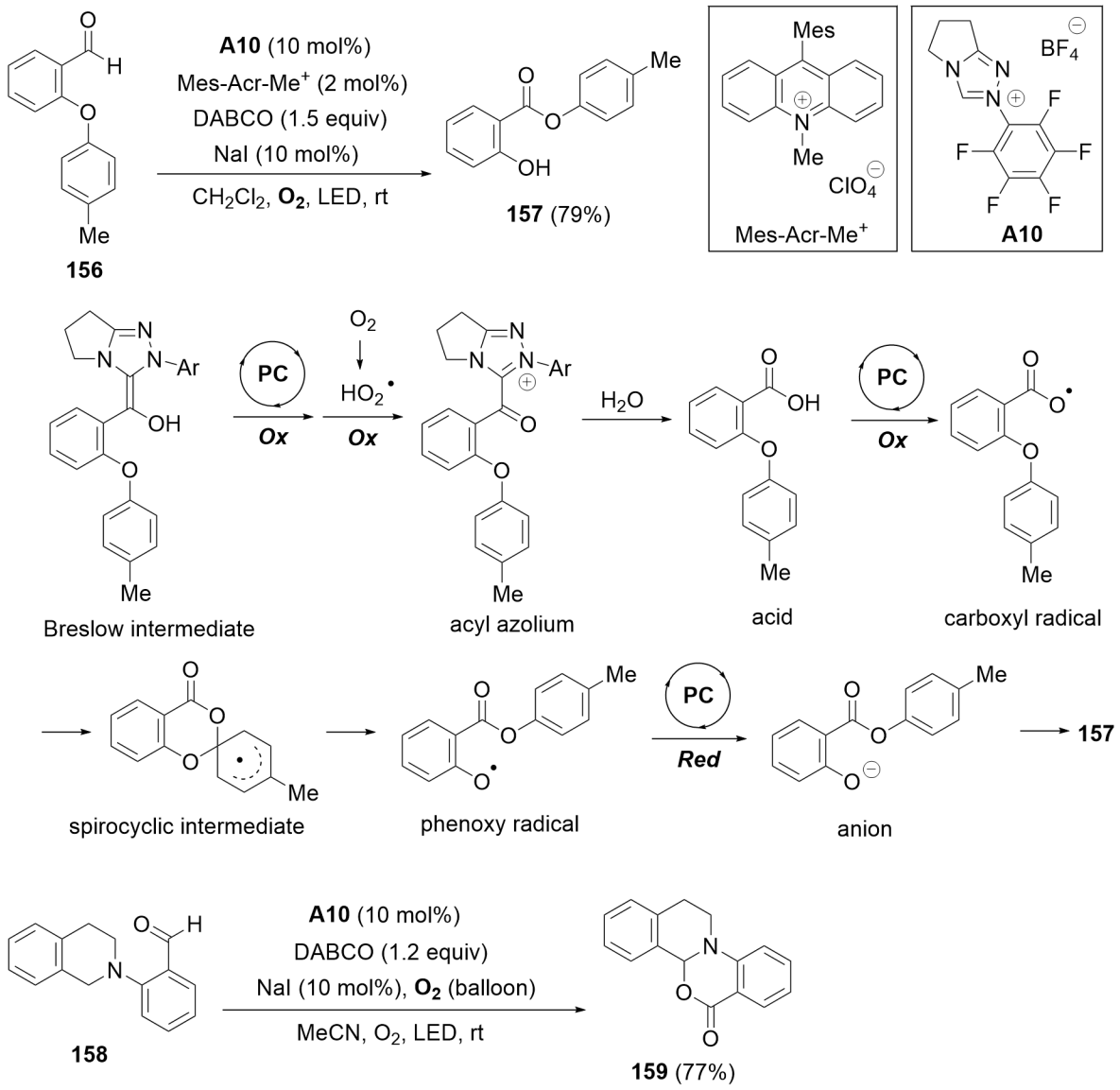
Scheme 49. Cooperation between NHC and organophotocatalyst.

The alkylation and esterification reaction of enal derivatives was achieved via a route involving the radical addition to dienolate derivatives generated from the Breslow intermediates (Scheme 50) [252–255]. When the racemic precursor **racemic A4b** was used in the presence of $Ru(bpy)_3(PF_6)_2$ as a photocatalyst, the reaction of γ-oxidized enal **150** with iodoacetonitrile and MeOH gave the γ-alkylated ester **151** at a 86% yield with exclusive γ-regioselectivity [252]. In these reactions, iodoacetonitrile acted not only as an oxidant for Ru-photocatalysis but also as a radical source giving a cyanomethyl radical. Cyanomethyl radical added to the dienolate intermediate to afford the homoenolate radical. The following photocatalytic oxidation of this radical led to acyl azolium. This reaction was expanded to ε-functionalization by using the enal **152** bearing a vinyl substituent at γ-position. Under similar reaction conditions, the reaction of enal **152** gave the γ-cyanomethylated ester **153** at a 56% yield with exclusive ε-selectivity. The alkylation and esterification reaction also proceeded by using the dienolate generated from cyclopropane enal **154** via NHC-catalyzed ring opening [253,254]. In the presence of several alcohols, the photo/NHC catalysis of **154** and diethyl 2-bromo-2-methylmalonate afforded the corresponding γ-alkylated ester **155**.



Scheme 50. Alkylation and esterification reaction.

The esterification of aldehydes based on oxidative Smiles rearrangement was developed (Scheme 51) [256]. The oxidative Smiles rearrangement of *O*-aryl salicylaldehyde **156** was performed under the cooperative catalysis conditions, using NHC and 9-mesityl-10-methyl-acridin-10-ium as organophotocatalysts. In the presence of NaI (10 mol%) as an additive to facilitate electron transfer, the reaction of **156** proceeded effectively to give the aryl salicylate **157** in 79% yield. The continuous oxidation of the Breslow intermediate by the activated photocatalyst and hydroperoxide radical, in situ generated from molecular oxygen, led to acyl azolium. The acid intermediate was generated via the hydrolysis of acyl azolium. Subsequently, the photocatalytic oxidation of acid intermediate promoted Smiles rearrangement to give a phenoxy radical via the spirocyclic intermediate. Finally, the reduction of this radical via photocatalysis gave the aryl salicylate **157**. In the absence of a photocatalyst, the combined use of NHC catalysis and the photoredox reaction has gained increasing attention as a novel catalysis [257]. Under similar reaction conditions, the intramolecular reaction of tetrahydroisoquinoline-derived benzaldehyde **158** was investigated. The oxidative cyclization of aldehyde **158** proceeded effectively, even in the absence of a photocatalyst under blue LED irradiation, to give the cyclized product **159** at a 77% yield. In this reaction, a photo-excited Breslow intermediate was proposed for explaining the photooxidation process.



Scheme 51. Oxidative Smiles rearrangement.

9. Conclusion and Outlook

N-Heterocyclic carbenes are the highly reactive organocatalysts that induce synthetically valuable chemical transformations. Furthermore, enantioselective NHC catalysis has attracted substantial attention, since highly functionalized compounds with multiple stereo-centers can be synthesized. The oxidative reaction of aldehyde C(sp^2)–H bonds with alcohol O–H bonds has been recognized as a straightforward and atom-economical cross-dehydrogenative coupling reaction [258,259]. Furthermore, the oxidative C–O bond-forming reactions have been used for the synthesis of biomass-derived compounds as a sustainable alternative to petroleum compounds [260–263]. As summarized above, the various synthetic strategies and methodologies have been developed as a cooperative catalysis. The recent dramatic progress in NHC-induced catalysis offers opportunities for further exploration with intriguing possibilities in organocatalysis for synthetic organic chemistry.

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Conflicts of Interest: The authors declare no conflicts of interest.

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