Review



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*Review*

# NHC-Catalyzed Cross-Coupling of Aldehydes for C(sp²)–O Bond Formation

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**Abstract:** In the past few decades, N-heterocyclic carbenes (NHCs) open the new field of organocatalysis in synthetic organic chemistry. This review highlights the dramatic progress in the NHC-catalyzed C–O bond formation based on the activation of aldehyde C(sp²)–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* is also described.

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

## 1. Introduction

N-Heterocyclic carbenes (NHCs) have gained increasing attention as a powerful and versatile organocatalyst 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(sp²)–H bonds *via* the formation of Breslow intermediates. Particularly, reversing the reactivity of aldehydes "umpolung of aldehydes" opens the new field of organocatalysis [2–7].

In recent years, the use of chiral NHCs has attracted substantial attention for the enantioselective synthesis of various molecules with structural diversity and complexity [8–13]. Furthermore, new methods and strategies for NHC catalysis are emerging continuously, leading to the remarkable progress on the cooperative catalysis with Lewis acid, Brønsted acid, hydrogen-bonding organocatalyst, and transition-metal catalyst [14–17]. More recently, the NHC catalysis has been expanded by the combination with photocatalysis as well as radical catalysis [18–23]. In this review article, we overview the progress on 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 cross-coupling of aldehydes with alcohols [24–33]. The oxidative NHC-catalysis was achieved by using $MnO_2$ or azobenzene as an oxidant (Scheme 1) [24,25]. In the presence of NHC generated from triazolium-based NHC precursor **A1** (10 mol%) and DBU (1.1 equiv), the dehydrogenative cross-coupling of aldehyde **1** with alcohols was performed in $CH_2Cl_2$ at room temperature under the oxidative conditions using $MnO_2$ [24]. The corresponding esters **2** were obtained in good yields. The oxidative esterification of benzaldehyde **3** using precursor **A2** and azobenzene as a stoichiometric oxidant gave the esters **4** [25]. These transformations are initiated by the formation of Breslow intermediate, which is oxidized to acyl azolium by an oxidant. Finally, the reaction of acyl azolium with ROH results in the release of

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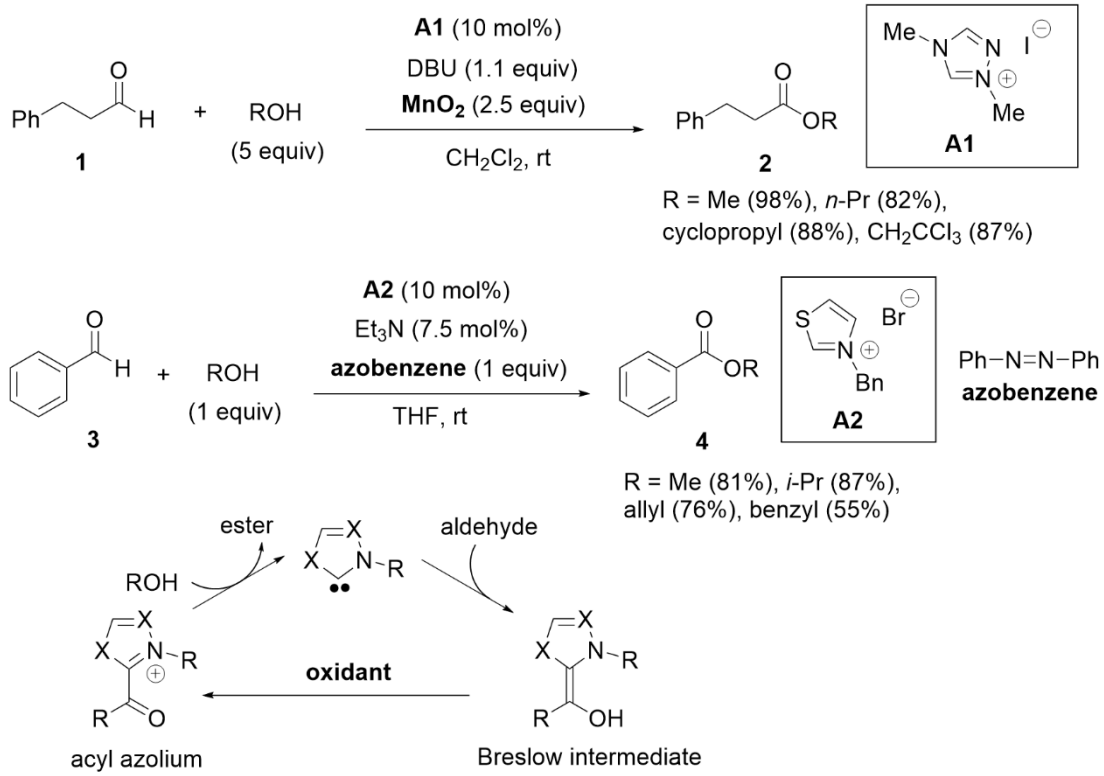
free NHC catalyst and the formation of ester. Furthermore, 3,3,5,5-*t*-butyldiphenoqinone (DQ), phenazine, $CCl_3CN$, phenazine, and *tert*-butyl hydroperoxide (TBHP) are used as an oxidant for the esterification of aldehydes [26–34]. The aerobic or electrochemical oxidations were also used in conjunction with NHC-catalyzed esterification of aldehydes [35–40].




**Scheme 1.** Dehydrogenative cross-coupling of aldehydes with alcohols.

Chiral NHCs have gained increasing attention as an organocatalyst for the enantioselective synthesis. The enantioselective synthesis of β-hydroxyl esters from enals was achieved under the oxidation conditions using chiral NHC catalysts (Scheme 2) [41,42]. Employing 4-nitropyridine *N*-oxide as an oxidant with chiral NHC generated from 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 [41]. 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 [43]. In the presence of 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 [43]. When precursor **(5a*S*,10b*R*)-A5** having 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 [45]. Additionally, chiral NHCs were used for the regioselective functionalization of carbohydrates [46,47]. 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 [46].

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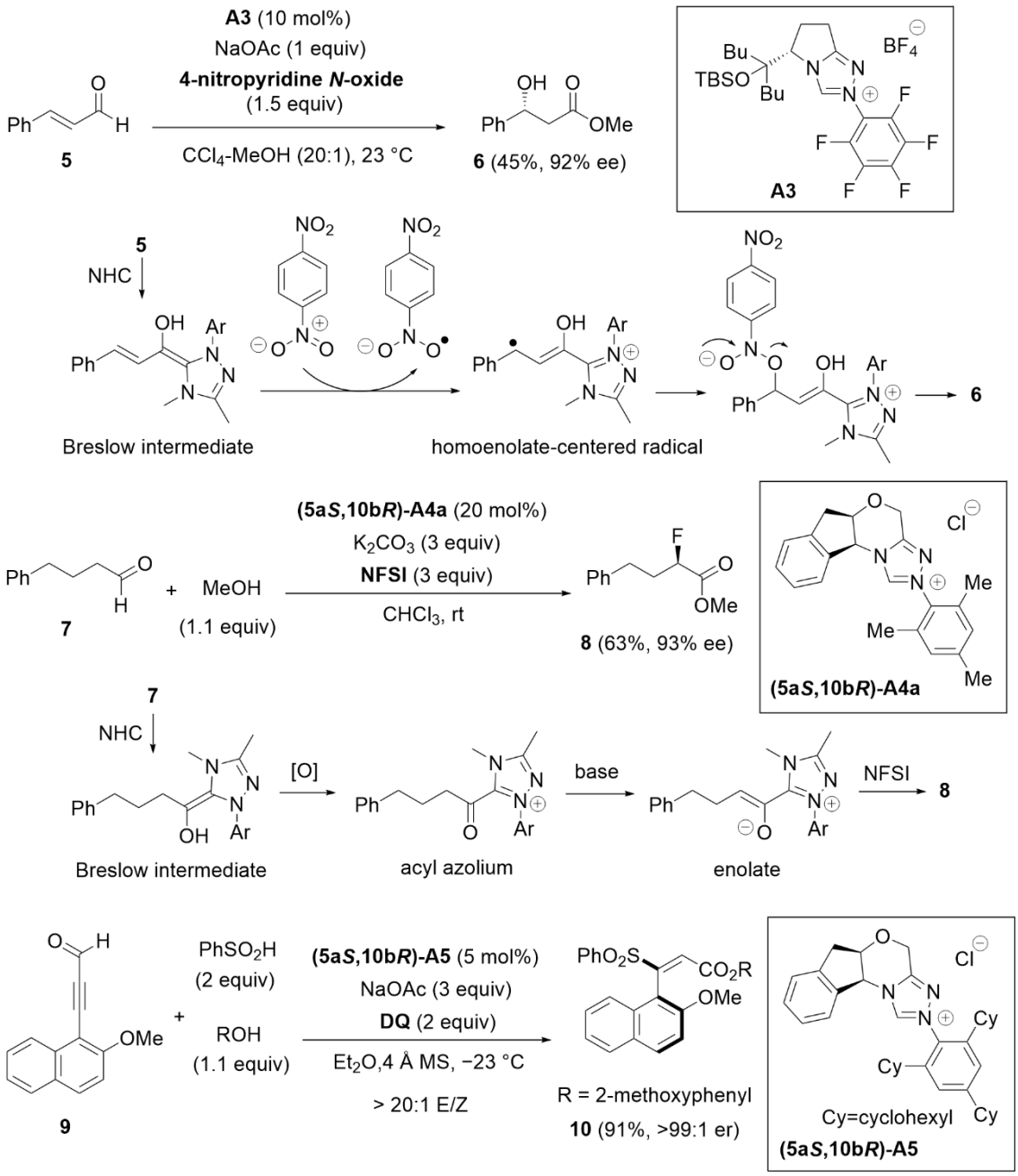


**Scheme 2.** Enantioselective functionalization of aldehydes.

*2.2. Kinetic Resolution*

Chiral NHC-catalyzed oxidative esterification has been used for achieving the kinetic resolution [48–57]. The kinetic resolution of racemic 3-hydroxy oxindole *rac*-**11** was examined by using chiral NHC generated from **(5a*S*,10b*R*)-A6b** (Scheme 3) [48]. 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 by the NHC-catalyzed acylation [52]. 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 temperature under the oxidative conditions using DQ (1.2 equiv) as an oxidant. The corresponding ester **15** was obtained in 96% yield with 98:2 er.

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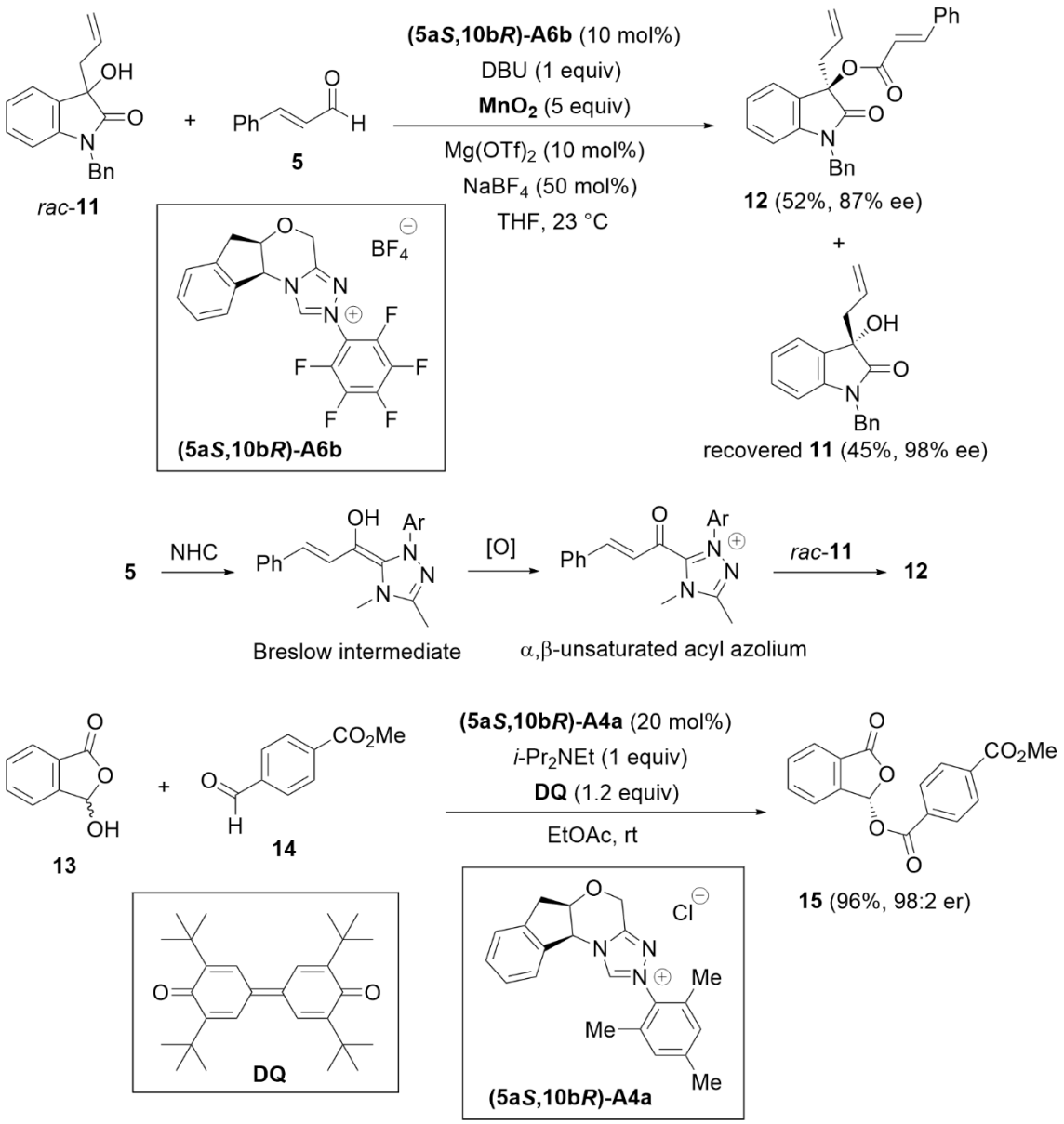


**Scheme 3.** Kinetic resolution by oxidative esterification.

The NHC-catalyzed dynamic kinetic resolution was applied to the synthesis of axially chiral compounds (Scheme 4) [55,56]. Atroposelective dynamic kinetic resolution of racemic biaryl aldehyde **16** was developed by using the oxidative NHC catalysis [55]. In the presence of NHC, generated from 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 [56]. 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** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant led to the chiral binaphthyl compound **21**.

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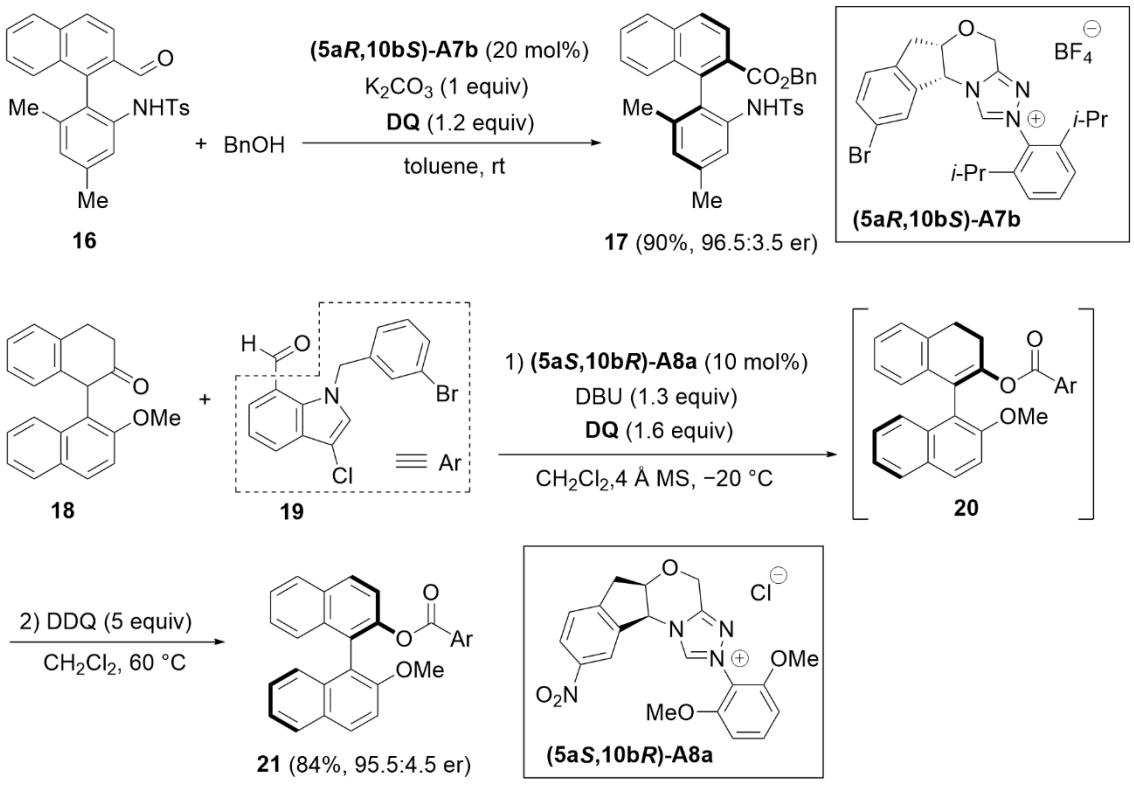
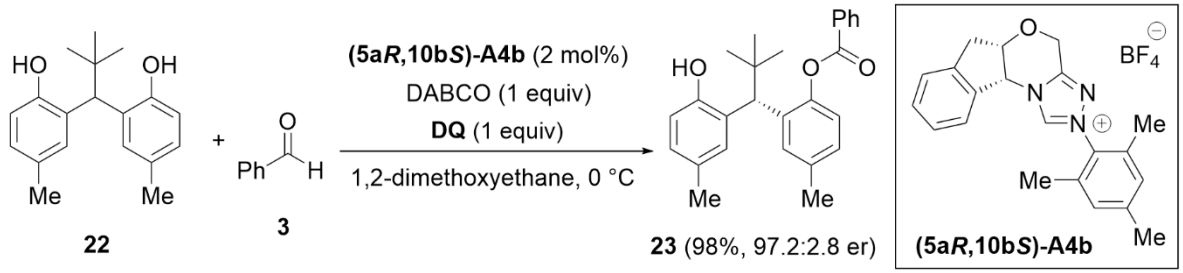



**Scheme 4.** Atroposelective dynamic kinetic resolution.

*2.3. Desymmetrization*

The desymmetrization of diols based on chiral NHC-catalyzed oxidative esterification of aldehydes was studied [58–60]. The desymmetrization reaction of triarylmethane-bisphenol **22** with benzaldehyde **3** was performed under the conditions using precursor **(5a*R*,10b*S*)-A4b**, 1,4-diazobicyclo(2.2.2)octane (DABCO), and DQ as an oxidant in 1,2-dimethoxyethane at 0 °C (Scheme 5) [59]. The desymmetrization product **23** was obtained in 98% yield with 97.2:2.8 er.




**Scheme 5.** Desymmetrization of diols by oxidative esterification.

The chiral NHC-catalyzed oxidative esterification of dialdehydes was studied [61–64]. The NHC-catalyzed atroposelective esterification of biaryl dialdehyde **24** was reported (Scheme 6) [61]. In the presence of precursor **(5a*S*,10b*R*)-A4b**, $Cs_2CO_3$ and DQ, the selective esterification of **24** proceeded to give the axially chiral ester **25** in 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 by the second esterification of undesired enantiomer of ester **25**. The atroposelective esterification of dialdehyde **26** was also studied [63,64]. The NHC-catalyzed desymmetrization of prochiral dialdehyde **26** gave the axially chiral

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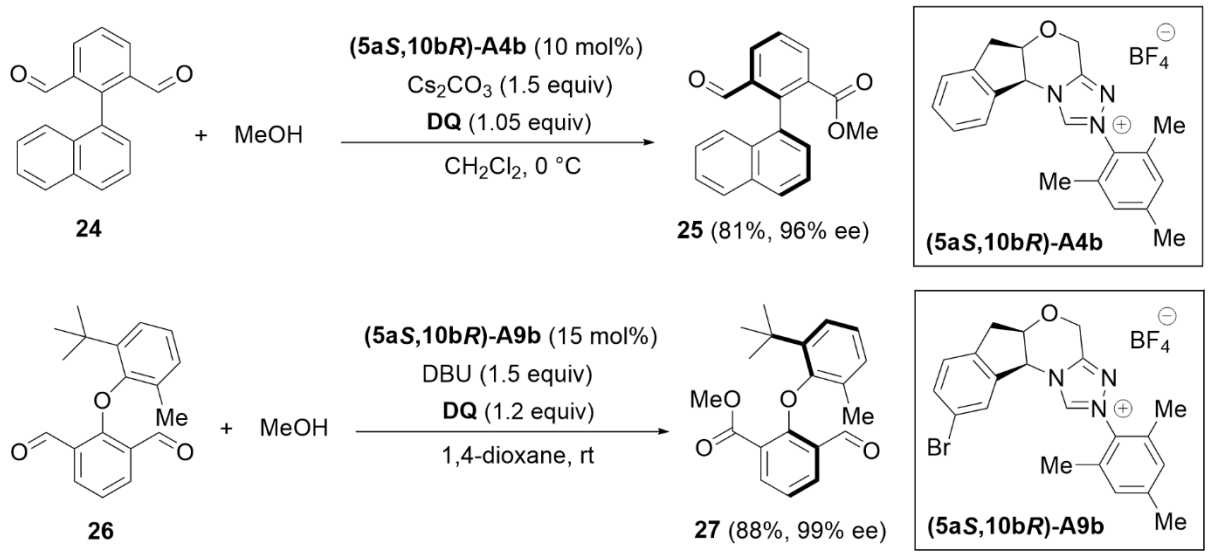
diaryl ether **27** with the excellent enantioselectivity. The enantioselectivity of **27** is also improved by the kinetic resolution leading to diether.

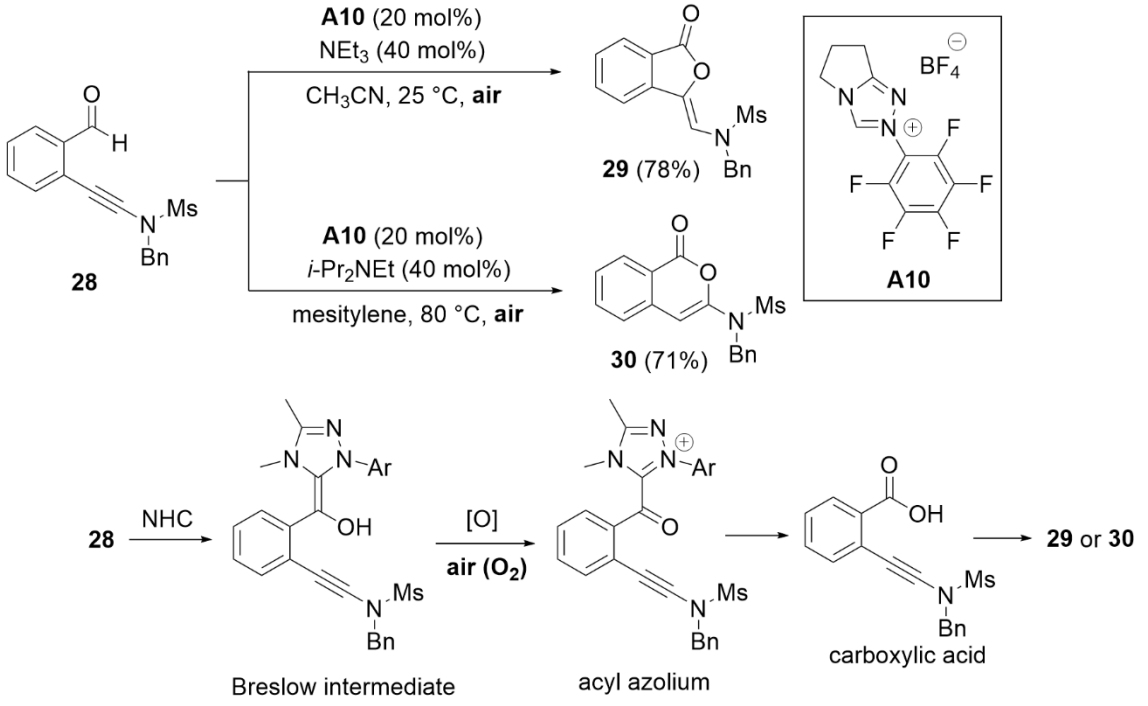



**Scheme 6.** Desymmetrization of dialdehydes.

## 3. Oxidative Cyclization and Annulation

### *3.1. Cyclization*

Several examples of the oxidative cyclization were reported [65–68]. The NHC-catalyzed aerobic oxidation of ynamide-tethered benzaldehyde **28** was studied (Scheme 7) [67]. 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 is generated through the aerobic oxidation of Breslow intermediate. Next, the base-promoted regioselective cyclization of carboxylic acid toward the ynamide moiety affords **29** or **30**. Furthermore, chiral NHC-catalyzed macrocyclization was developed for the atroposelective synthesis of planar-chiral indoles [68].



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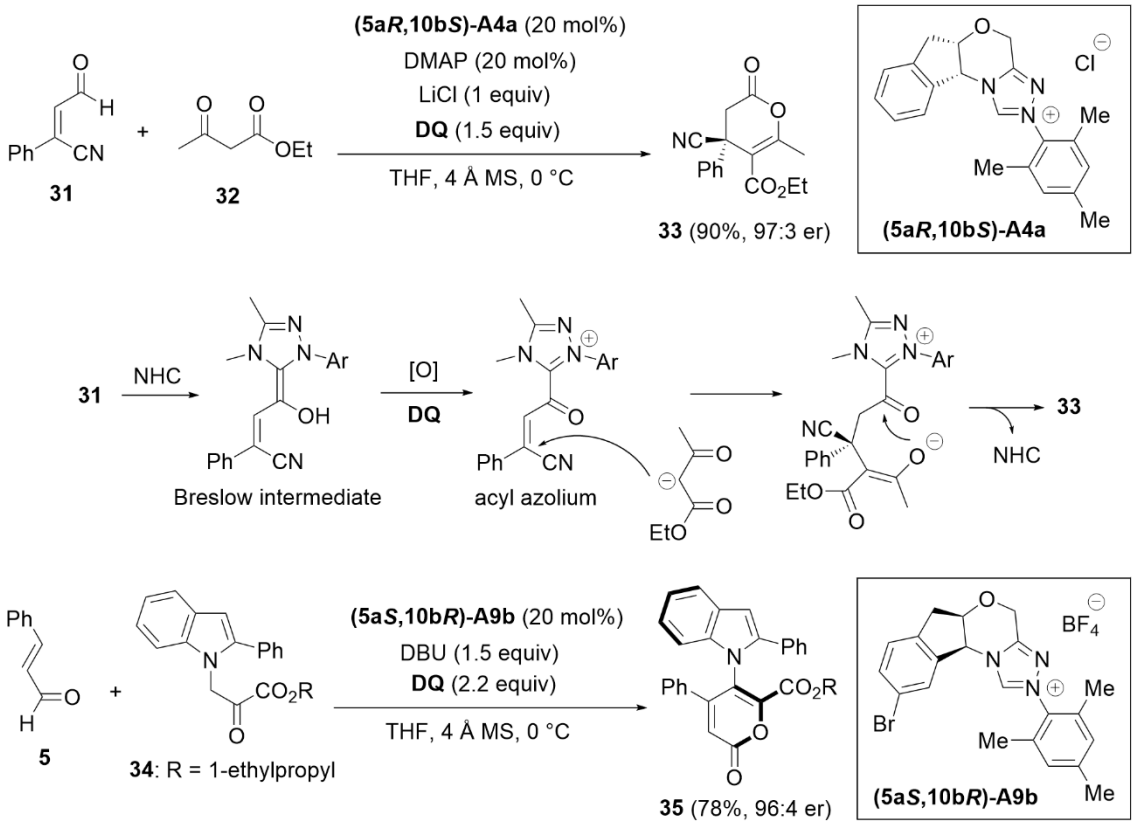
**Scheme 7.** Regioselective oxidative cyclization.

*3.2. [3 + 3] Annulation*

In the NHC catalysis, the α,β-unsaturated acyl azoliums are Michael acceptors acting as a C3 synthon for the [3 + 3] annulation [69–77]. The oxidative reaction of β-cyano-substituted α,β-unsaturated aldehyde **31** and ethyl acetoacetate **32** was studied (Scheme 8) [70]. 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 an oxidant, dihydropyran-4-carbonitrile **33** bearing a quaternary carbon center was obtained in 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 is initiated by the generation of Breslow intermediate, which is 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 NHC catalyst. Asymmetric synthesis of axially chiral molecules was achieved by oxidative [3 + 3] annulation [76] 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 by merging with Claisen rearrangement (Scheme 9) [78]. 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 the oxidative esterification and the subsequent Claisen rearrangement.

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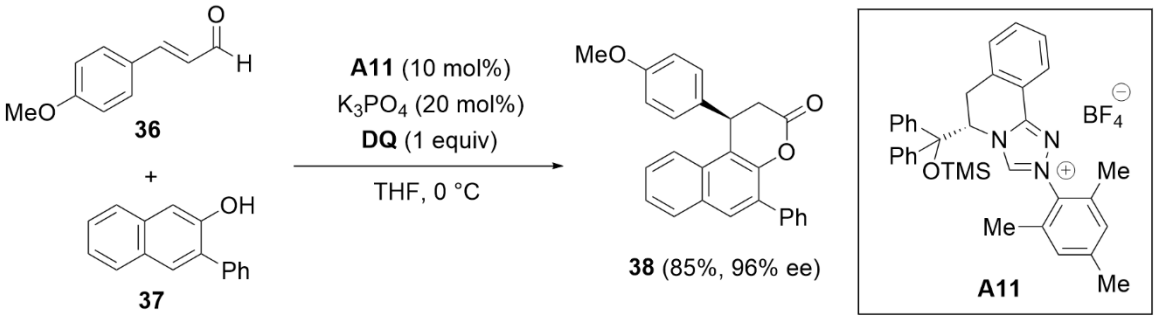


**Scheme 9.** NHC-catalyzed annulation via Claisen rearrangement.

*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) [79–81]. In the presence of precursor **(5a*R*,10b*S*)-A4a** (10 mol%), DBU (20 mol%), LiCl (50 mol%) and DQ (1 equiv) as an oxidant, the reaction of aldehyde **5** with oxindole **39** was carried out in DME, affording spirooxindole-γ-lactone **40** in 78% yield with 90:10 er [79]. In this reaction, the α,β-unsaturated acyl azolium is Michael acceptor acting as a C3 synthon for [3 + 2] annulation; thus, the enolate, generated from **39** under basic conditions, adds to α,β-unsaturated acyl azolium in a 1,4 fashion. When aldehyde **5** and oxindole **39** were treated with 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 [80]. Since both radicals from enolate and homoenolate were observed by 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.

Oxidative [3 + 2] annulation reactions involving the activation of the nitrogen atoms of the aromatic π-rings were investigated [82,83]. In the presence of chiral NHC generated from 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) [82]. In this catalytic cycle, a key step is 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**.

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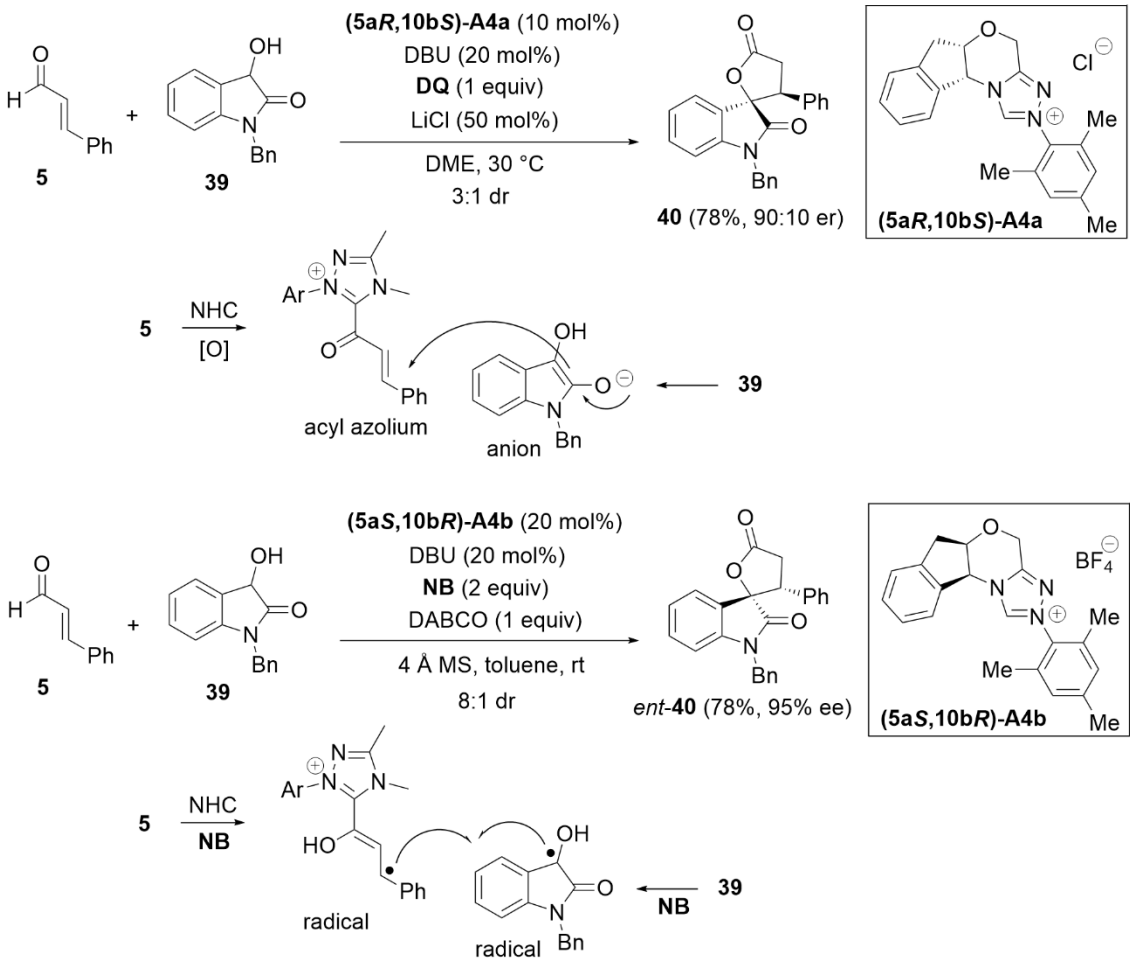
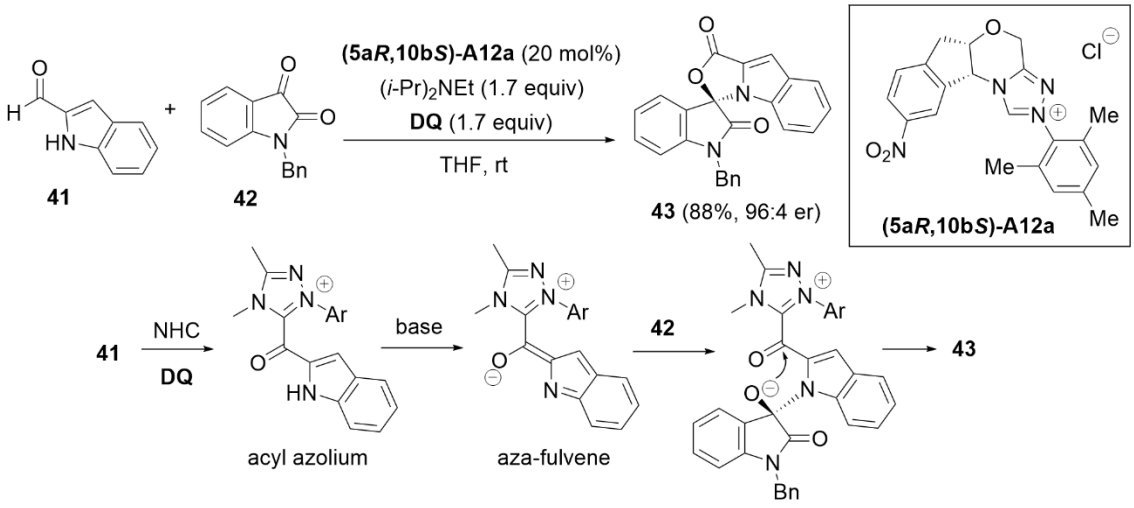



**Scheme 10.** Oxidative [3 + 2] annulation.




**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 the [4 + 2] annulation (Scheme 12) [84–88]. The oxidative γ-functionalization of α,β-unsaturated aldehydes with trifluoroacetophenone **45** was studied under the NHC catalysis [84]. The high enantioselectivities were achieved by the NHC and Sc/Mg-based Lewis acid cooperative catalysis. In the presence of

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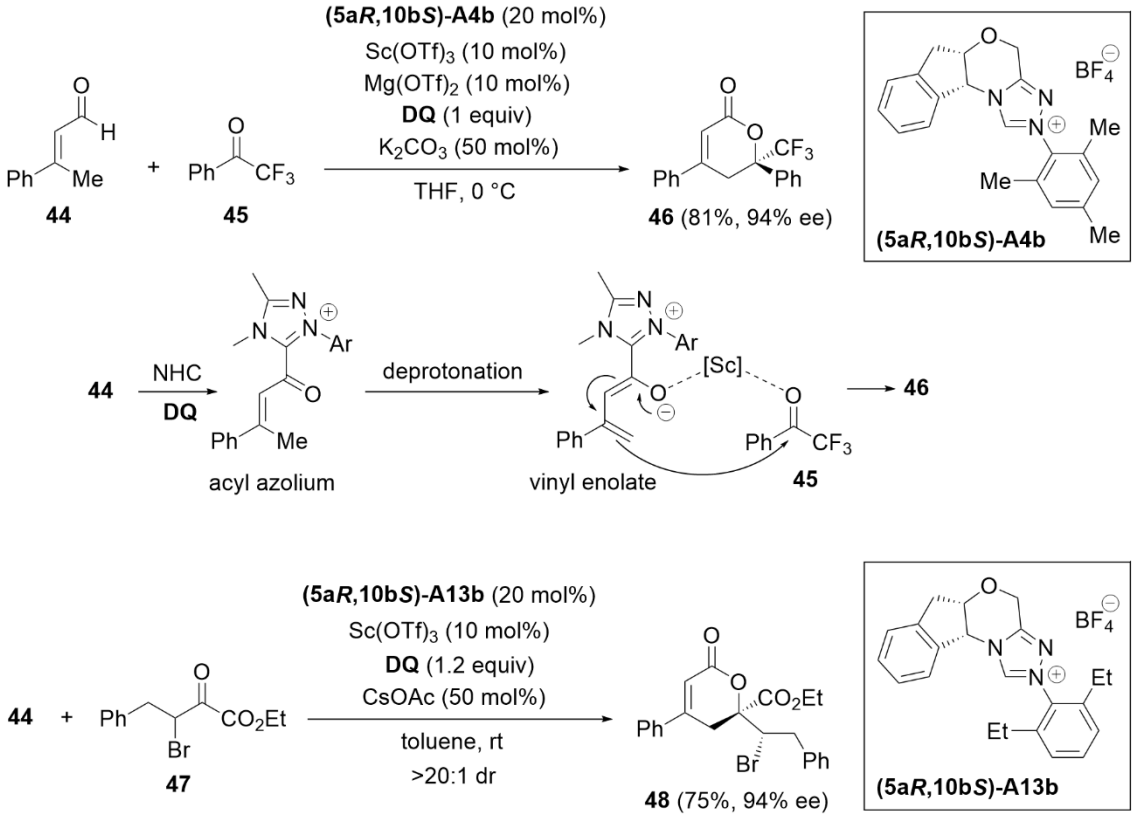
precursor **(5a*R*,10b*S*)-A4b**, $Sc(OTf)_3$, $Mg(OTf)_2$, $K_2CO_3$ and DQ as an oxidant, α,β-unsaturated aldehyde **44** reacted with ketone **45** to give δ-lactone **46** in 81% yield with 94% ee. In this reaction, a key step is the activation of γ-carbon of α,β-unsaturated acyl azolium. The γ-CH deprotonation of α,β-unsaturated acyl azolium leads to the NHC-linked vinyl enolate bearing a nucleophilic γ-carbon, which adds 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 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 [85]. 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 [89,90]. Additionally, the [4 + 2] annulation using azolium enolate as a C2 synthon was also developed [91,92].




**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) [93]. In the presence of 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, Lewis acidic $Bi(OTf)_3$ promotes the addition of indole-2-carboxaldehyde **49** to *p*-quinone methide **50**, generating *in situ* the Friedel–Crafts adduct as a racemic intermediate. Subsequently, chiral NHC and $Bi(OTf)_3$ catalyzed the oxidative lactonization of racemic Friedel–Crafts adduct with good enantioselectivity *via* the dynamic kinetic resolution process.

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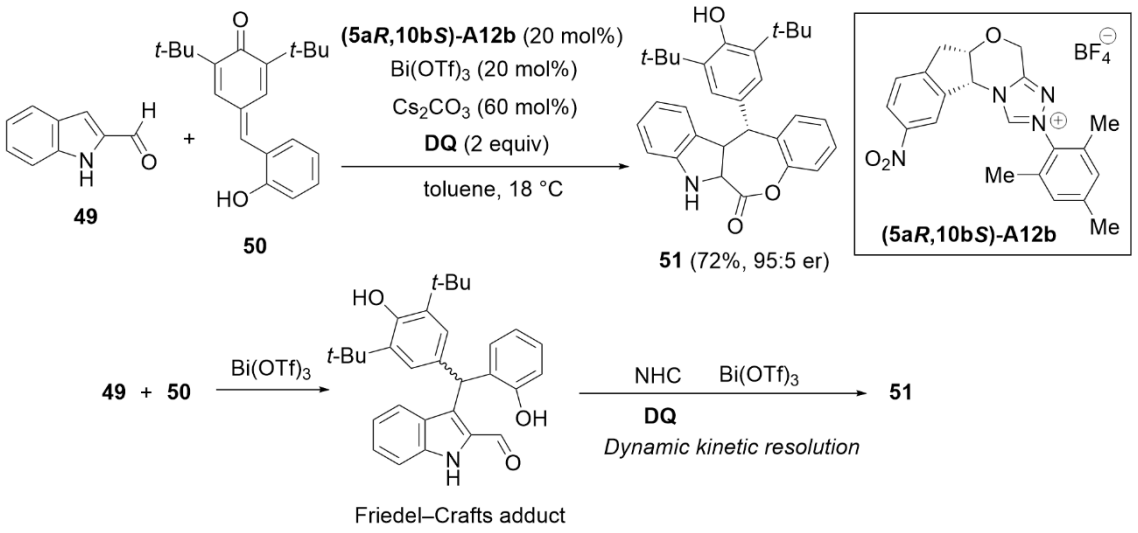
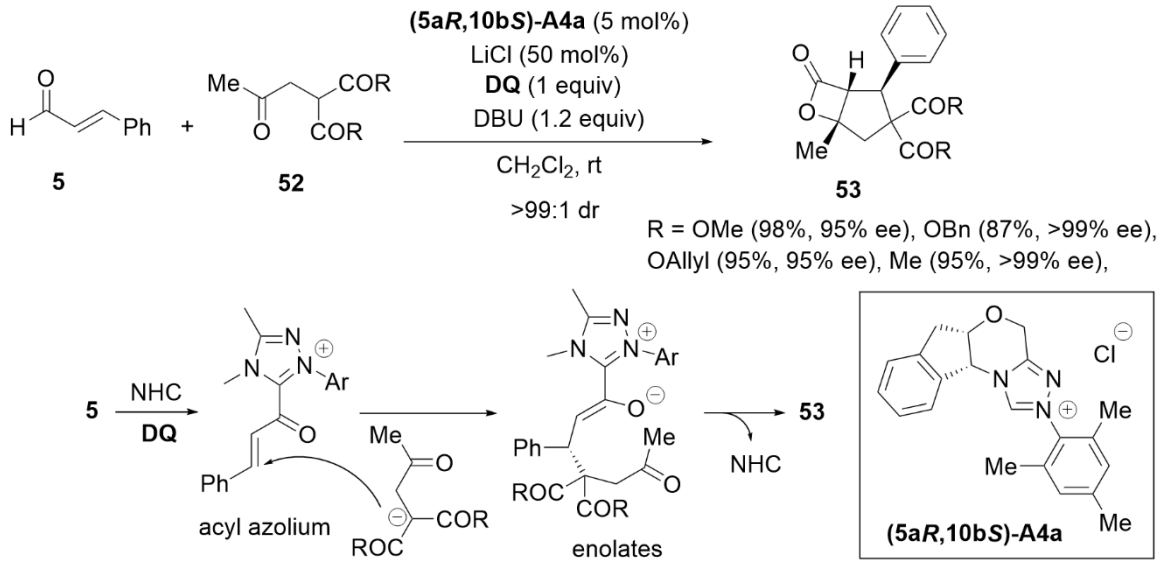



**Scheme 13.** NHC-Lewis acid cooperative catalyzed [4 + 3] annulation.

*3.6. Cascade Annulation*

Cascade annulation *reactions* using chiral NHC catalyst have been studied [94–99]. Enantioselective *cascade reaction of* cinnamaldehyde **5** *with* malonates or β-diketone **52** *was developed* (Scheme 14) [94]. 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 the NHC catalysis, Michael addition of anions, generated from **52**, to α,β-unsaturated acyl azolium leads 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 in 86% yield with 99% ee (Scheme 15) [97]. This *cascade* annulation is also initiated by the oxidation of Breslow intermediate to α,β-unsaturated acyl azolium. The bicyclic product **55** is formed by Michael addition of malonate **54**

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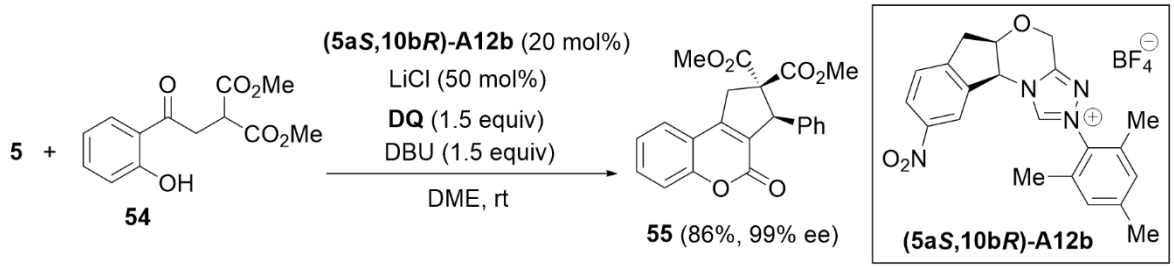
to α,β-unsaturated acyl azolium, the subsequent intermolecular aldol reaction and the final lactonization.



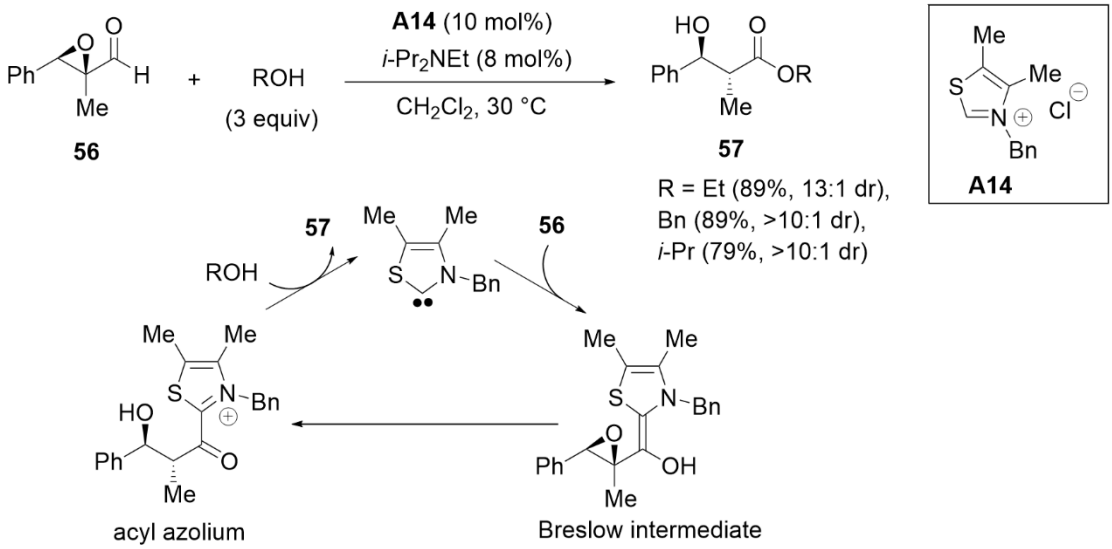

**Scheme 15.** Oxidative cascade annulation.

## *4.* Redox Esterification of Aldehydes

### *4.1. Esterification of Aldehydes under Redox Conditions*

The redox esterification can be achieved by the incorporation of a reducible functionality into aldehyde substrates. In the absence of oxidants, the redox esterification of α,β-epoxy aldehydes, or α-haloaldehydes takes place due to the **simultaneous** reduction of epoxy moiety or halogen *substituent* on substrate [100–106].

The NHC-catalyzed redox esterification of α,β-epoxy aldehyde **56** led to the formation of β-hydroxy esters **57** in good yields (Scheme 16) [100]. This transformation proceeds *via* the formation of Breslow intermediate followed by the epoxide-opening step leading to acyl azolium. The subsequent reaction with alcohols provides esters **57**, accompanied by the regeneration of NHC catalyst.




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

The enantioselective redox esterification of α,α-dichloroaldehydes was studied using chiral NHC catalyst (Scheme 17) [102]. Employing chiral NHC precursor **(5a*S*,10b*R*)-A6b**, the redox reaction of α,α-dichloroaldehyde **58** with phenol gave α-chloroester **59** in 79% yield with 93% ee. Initially, aldehyde **58** reacts with NHC catalyst to give Breslow intermediate. The subsequent dehalogenation and the stereoselective α-protonation of chiral α-chloroenolate led to chiral α-chloroester **59**. The redox esterification of α-bromoenals proceeds, because α-bromoenals react with NHC catalyst to afford α,β-unsaturated acyl azoliums in the absence of oxidant *via* debromination [105,106]. The NHC-catalyzed three-component tandem β-sulfonylation/esterification of α-

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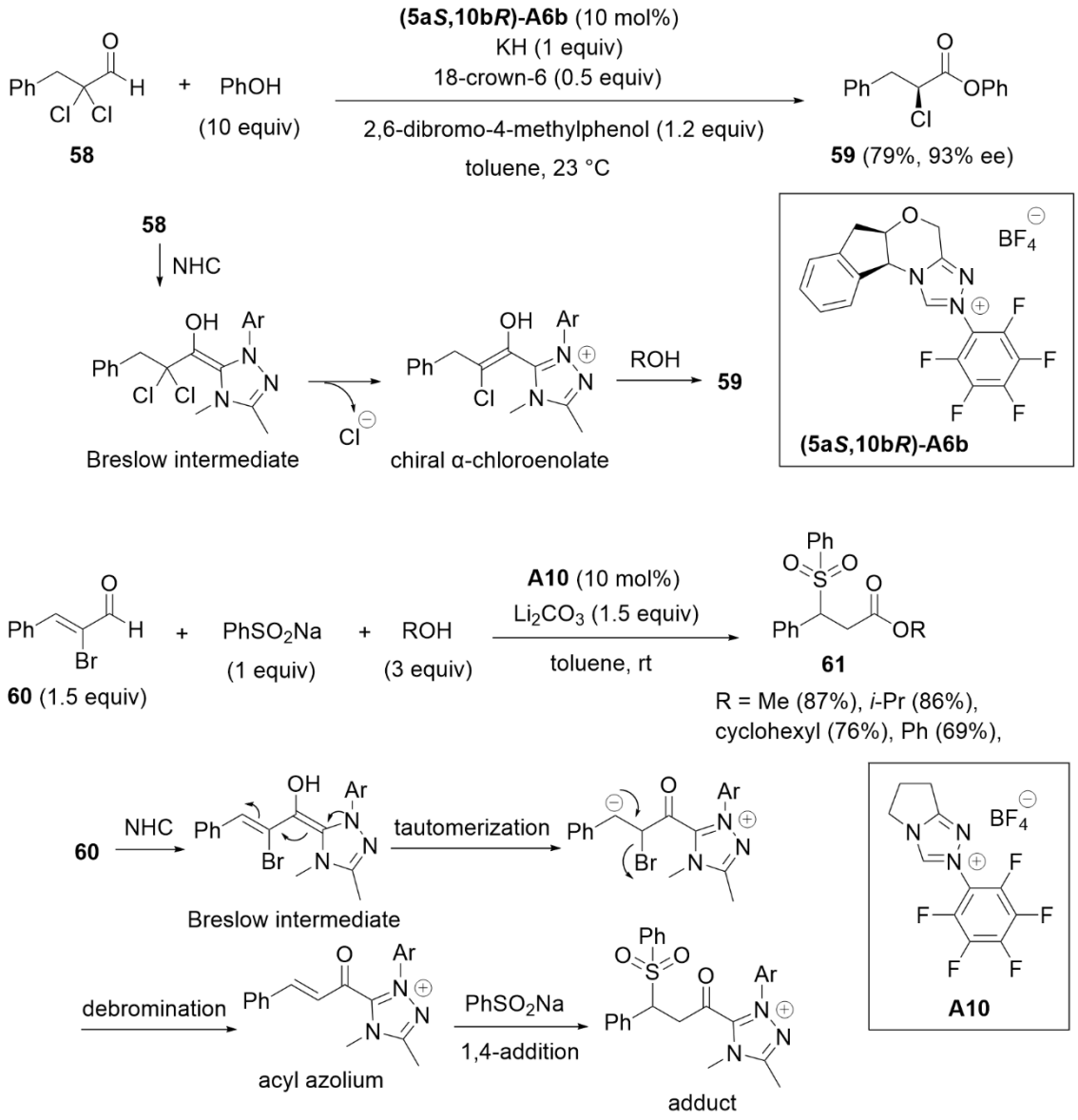
bromoenals was developed [105]. Under the optimized conditions using precursor **A10**, three-component reaction of α-bromoenal **60** with sodium sulfinate and alcohols gave sulfone esters **61**. The addition of NHC to α-bromoenal **60** leads to the formation of Breslow intermediate, which is transformed 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, the redox esterification was also achieved by using the aldehydes having cyclopropyl moiety or *leaving group* as a reducible functionality [107–109]**.**




**Scheme 17.** Redox esterification of α-haloaldehydes.

The α,β-unsaturated aldehydes are widely used as reducible substrates for the redox esterification [110–115]. In the absence of oxidant, the NHC-catalysis of α,β-unsaturated aldehydes leads to the redox esterification accompanying with the reduction of C=C bond to C–C bond or C≡C bond to C=C bond.

Interestingly, the combined use of 2-phenyl-indol-3-one **62** as a reducible substrate with simple aldehydes led to the redox esterification (Scheme 18) [116]. In the presence of precursor **A15** and $Cs_2CO_3$, the hydroacylation of **62** with benzaldehyde **3** proceeded effectively to give 1*H*-indol-3-yl

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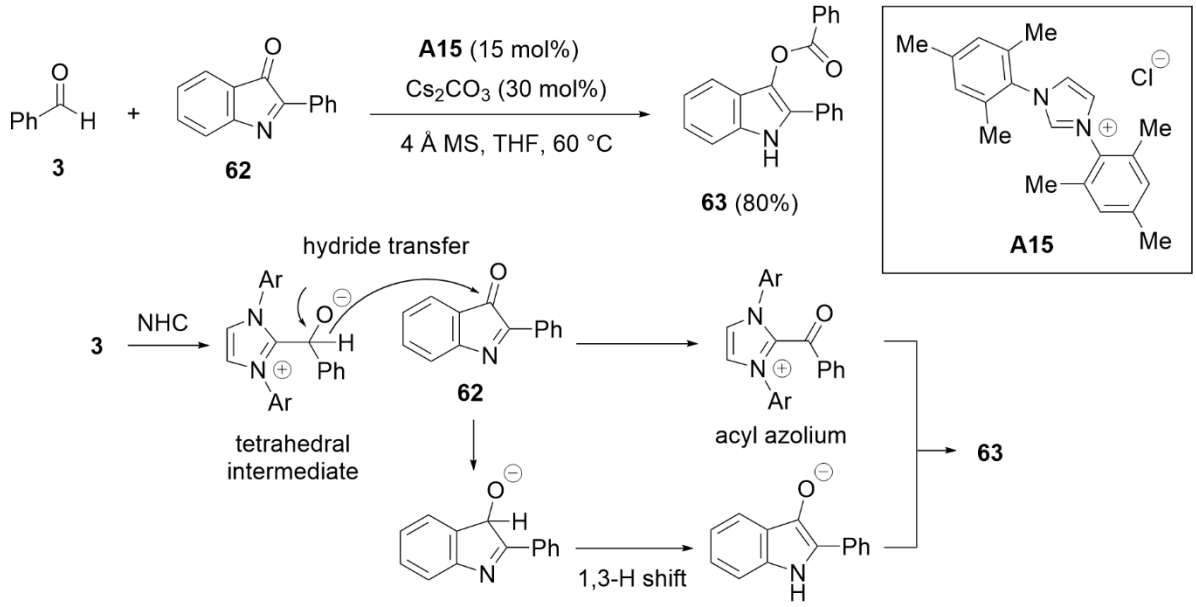
ester **63** in 80%. The proposed reaction mechanism involves a reductive hydride transfer from NHC-linked tetrahedral intermediate to the carbonyl of **62**.




**Scheme 18.** Redox esterification involving hydride transfer process.

*4.2. Cascade Redox Esterification of Aldehydes*

The cascade redox esterification of enals was achieved *via* the pathway involving the reaction of NHC-linked homoenolate intermediates with electrophiles [117–124]. In the presence of chiral NHC generated from 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) [118]. This transformation is initiated by the formation of the NHC-linked homoenolate from cinnamaldehyde **5**. Next, the 1,4-addition of homoenolate to nitroalkene **64** generates the acyl azolium. Finally, δ-nitroester **65** is obtained by 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 [119]. Chiral NHC-catalyzed reaction of cinnamaldehyde **5** with isatin ketimine **66** gave the highly functionalized oxindole-γ-amino ester **67** in 86% yield with 95% ee. Recently, the NHC-catalyzed reactions involving radical intermediates were developed [125,126]. The asymmetric β-pyridylation of cinnamaldehyde **5** with pyridinium salt **68** was reported [126]. In the presence of 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 is the key to achieve the excellent enantioselectivity. The proposed mechanism involves the formation of homoenolate radical from NHC-linked homoenolate by the single-electron-transfer (SET). The final product **69** will be obtained *via* the addition of homoenolate radical to the C4 position of pyridinium salt **68**.

Furthermore, cascade redox esterification reactions were developed using NHC-linked dienolates (vinylogous NHC-linked enolates) [127], NHC-linked enolate [128], and NHC-linked *p*-quinodimethane [129].

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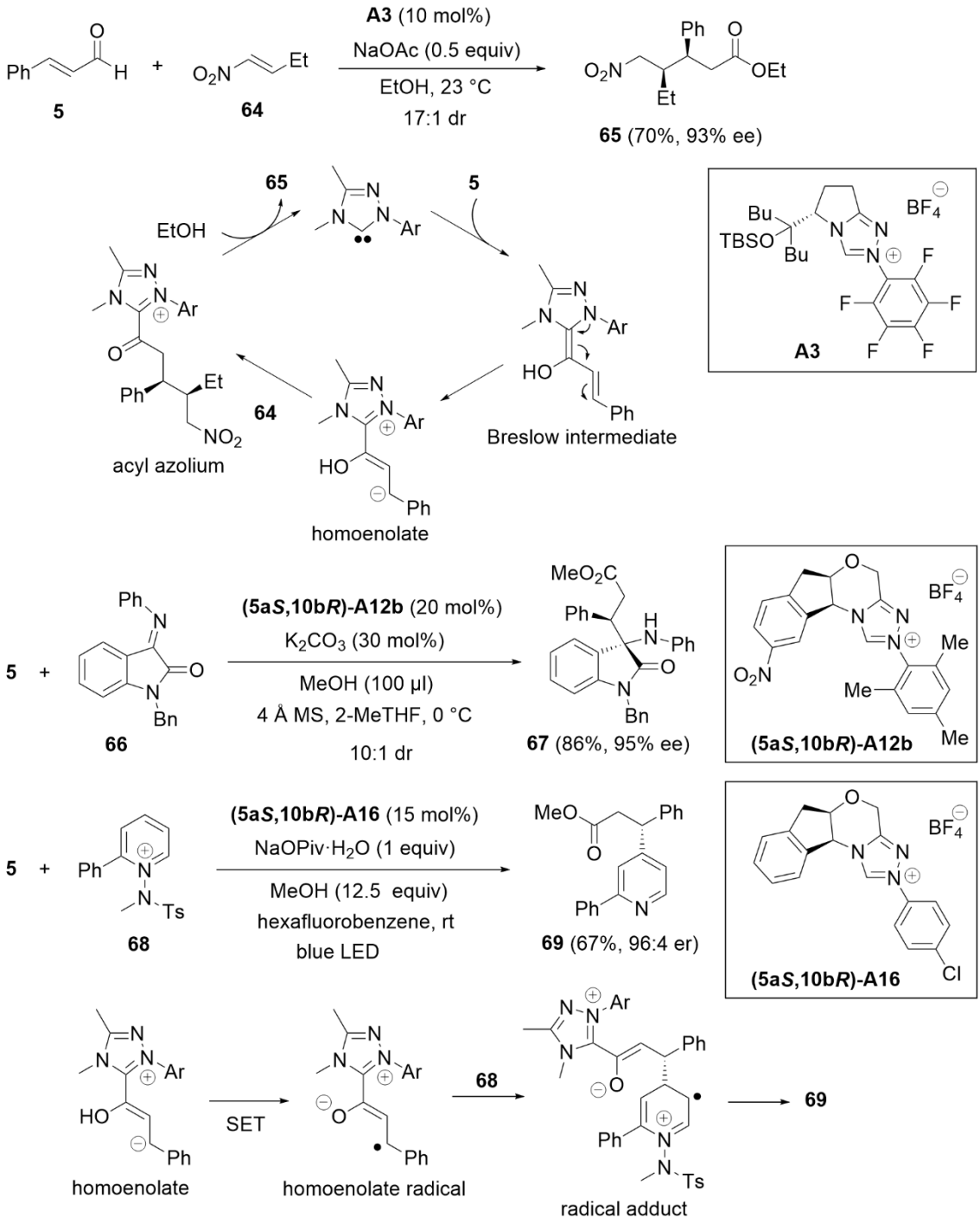


**Scheme 19.** Cascade redox esterification *via* NHC-linked homoenolate intermediates.

*4.3. Kinetic Resolution*

The kinetic resolution has been studied by chiral NHC-catalyzed redox esterification [130–135]. The kinetic resolution of racemic anilide *rac*-**70** was achieved by the redox esterification using alkynal **71** as a reducible substrate (Scheme 20) [130]. 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 [131]. The acylation of **73** with cinnamaldehyde **5** was performed in toluene at 0 °C under the optimized conditions using **(5a*S*,10b*R*)-A18b** (10 mol%) and $PhCO_2Na$ (40 mol%). The corresponding ester **74** was obtained in 90% yield with 95:5 er.

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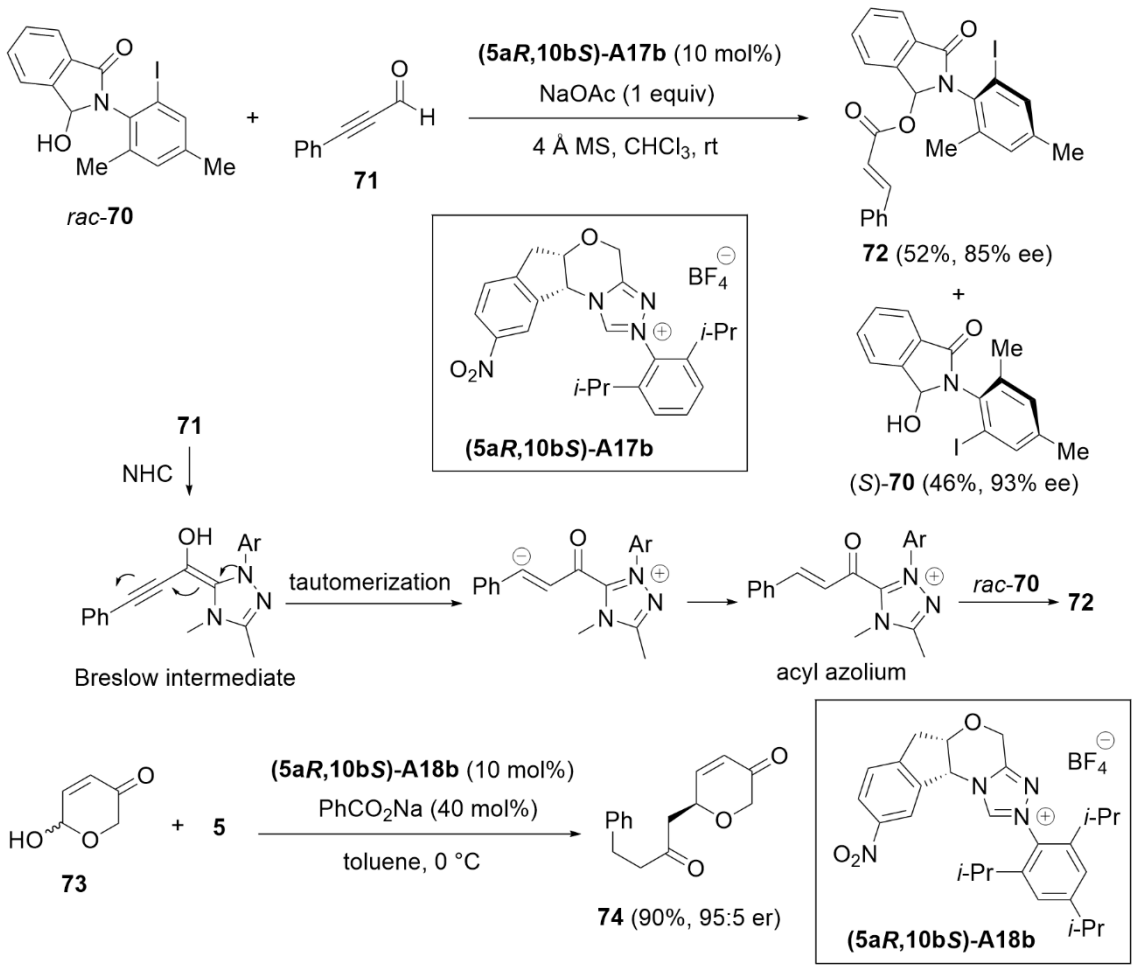


**Scheme 20.** Kinetic resolution by redox esterification.

*4.4. Desymmetrization*

Chiral NHC-catalyzed desymmetrization of the cyclohexadienone-tethered enals was studied (Scheme 21) [136,137]. The redox cyclization of enal-tethered cyclohexadienone **75** was achieved *via* the esterification of formyl group [136]. Treatment of **75** with 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** in 83% yield with 96% ee. This transformation involves the desymmetric Michael addition of NHC-linked homoenolate intermediate to the prochiral cyclohexadienone moiety. Similarly, asymmetric desymmetrization of the cyclohexadienone-tethered enal **77** was also achieved [137].

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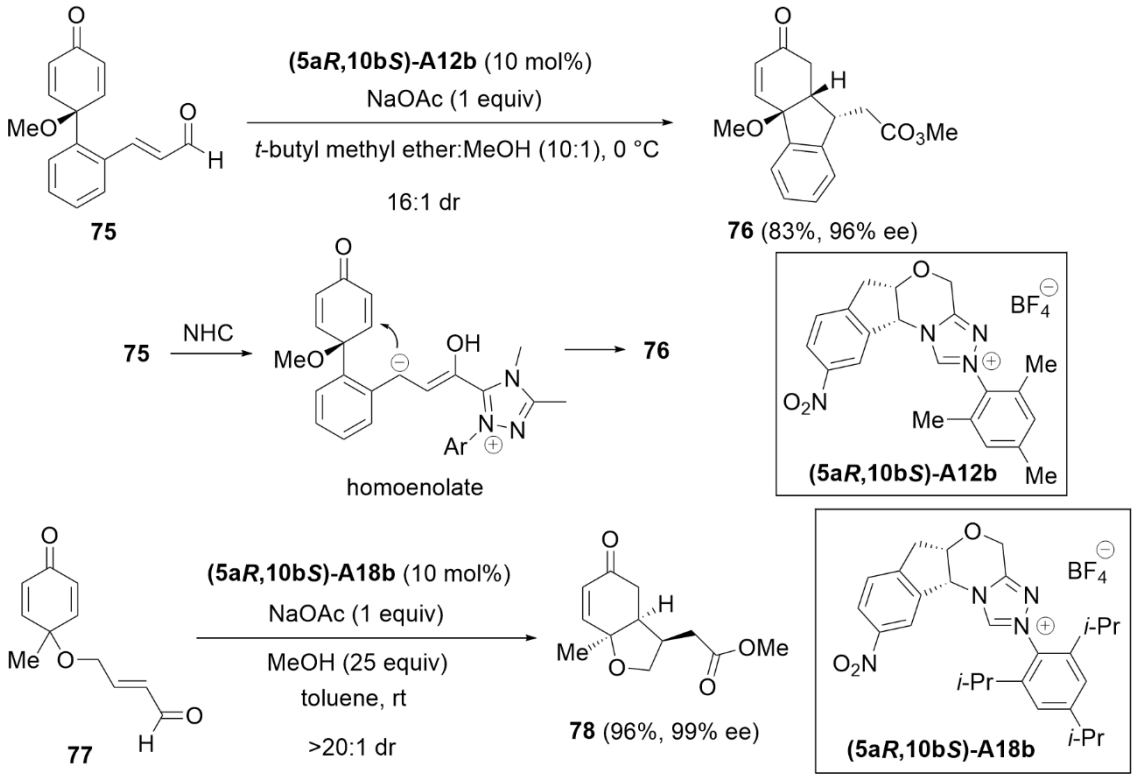
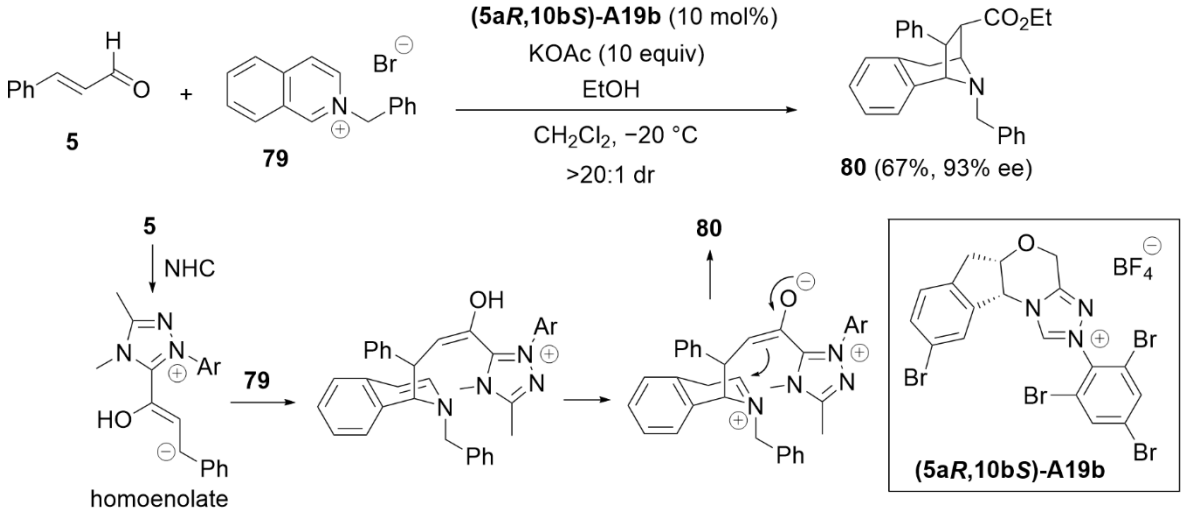



**Scheme 21.** Desymmetrization using redox esterification.

*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) [138]. Employment of 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** having four contiguous stereocenters in 67% yield with 93% ee. The reaction is initiated by the catalytical generation of NHC-linked homoenolate from Breslow intermediate. Subsequent double Mannich addition of homoenolate to **79** leads to the formation of tropane derivative **80**.




**Scheme 22.** NHC-catalyzed dearomatizing annulation reaction.

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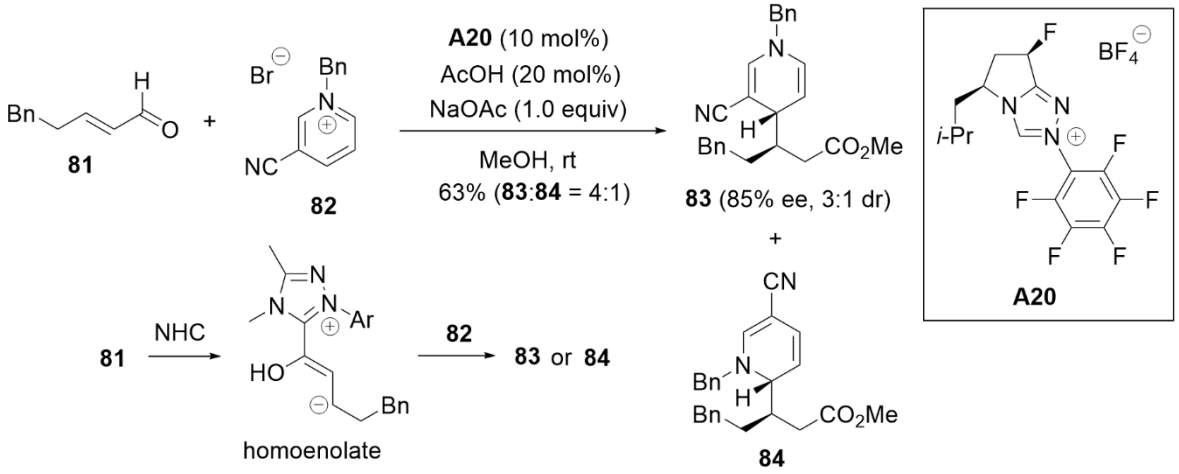
Asymmetric induction into the prochiral alkyl pyridinium **82** was achieved by chiral NHC-catalyzed dearomatization based on the addition of NHC-linked homoenolate (Scheme 23) [139]. Under the optimized conditions using precursor **A20**, the dearomatization of pyridinium **82** with enal **81** gave 1,4-dihydropyridine **83** with 85% ee as a major product, accompanied with 1,4-dihydropyridine **84** as a regioisomer.

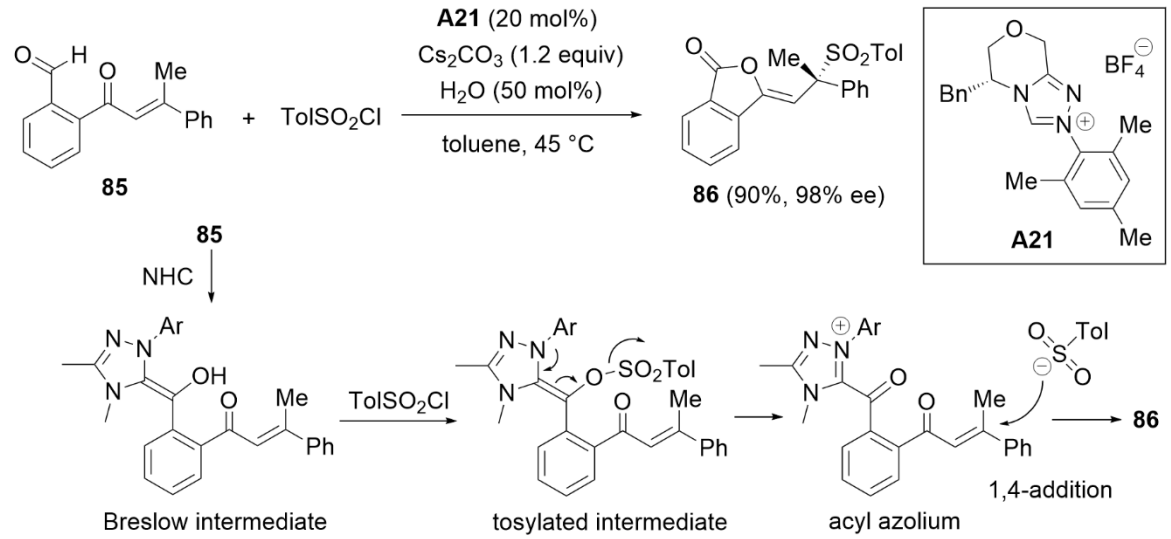



**Scheme 23.** Dearomatizing reaction of prochiral aromatic nitrogen-heterocycle.

## 5. Redox Cyclization and Annulation

### *5.1. Cyclization*

Several redox cyclization reactions were reported [136–138,140]. In the presence of precursor **A21**, $Cs_2CO_3$ and $H_2O$, treatment of **85** with tosyl chloride in toluene at 45 °C gave the cyclized product **86** in 90% yield with 98% ee (Scheme 24) [140]. As a proposed reaction mechanism, this transformation involves the oxidation of Breslow intermediate by tosyl chloride leading to the formation of tosylated intermediate. Next, the tosylated intermediate is 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 nucleophile but also oxidant; thus, this reaction may also be considered one of the oxidative cyclization.




**Scheme 24.** Redox cyclization of enal-tethered cyclohexadienone.

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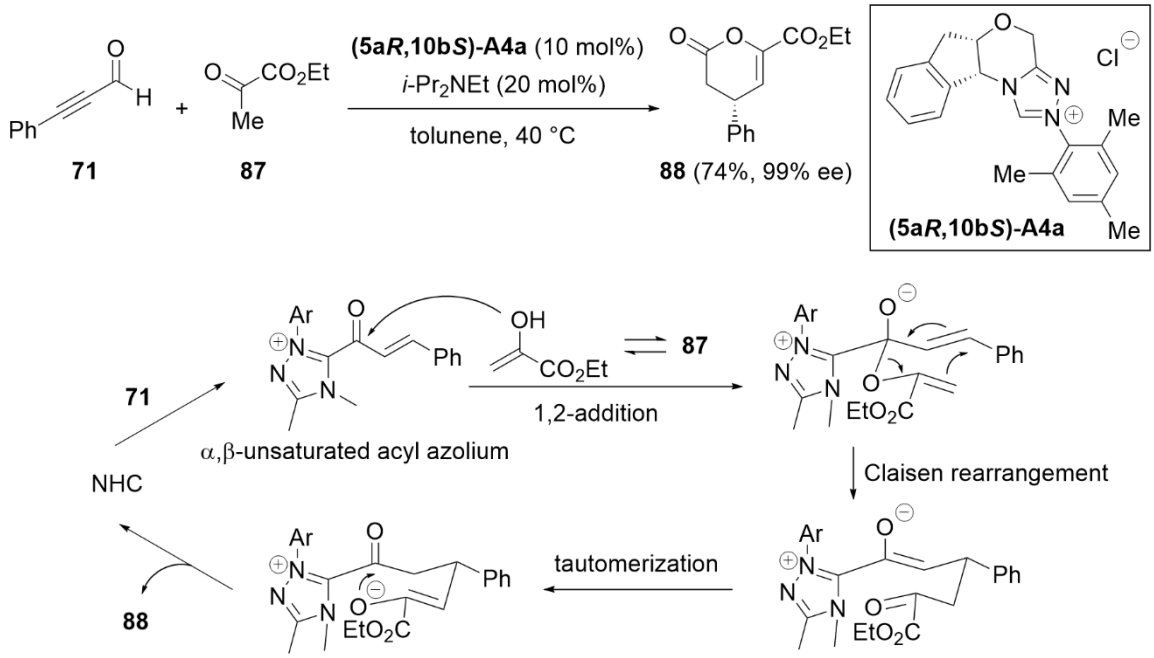
*5.2. [3 + 3] Annulation*

In the NHC-catalyzed redox [3 + 3] annulation, the α,β-unsaturated acyl azoliums are Michael acceptors acting as a C3 synthon [141–144]. In the absence of oxidant, the [3 + 3] annulation of ynals proceeds *via* the formation of α,β-unsaturated acyl azolium intermediates (Scheme 25) [141]. The ynal **71** is used as a reducible substrate for the redox transformation. Under the optimized conditions using precursor **(5a*R*,10b*S*)-A4a**, the redox reaction of ynal **71** with ethyl pyruvate **87** gave the annulation product **88**. As a possible mechanism, the pathway involving Claisen rearrangement was proposed. This catalysis is initiated by 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 Claisen rearrangement, tautomerization, and lactamization.

Furthermore, the redox [3 + 3] annulation using α-bromoenals was developed, because α-bromoenals react with NHC catalyst to afford α,β-unsaturated acyl azoliums in the absence of oxidant *via* debromination [142–144].




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

*5.3. [3 + 2] Annulation*

For the redox [3 + 2] annulation, the reducible aldehydes are employed [145–155]. The NHC-linked homoenolate derivatives act as a C3 synthon for [3 + 2] annulation [145–153]. The NHC-linked homoenolate, generated from α,β-unsaturated aldehyde **44** and NHC catalyst, reacts as a C3 synthon (Scheme 26) [145]. Employing the precursor **A22** (10 mol%), $K_3PO_4$ (50 mol%) and *o*-fluorobenzoic acid (1 equiv) as Brønsted acid, the [3 + 2] annulation of aldehyde **44** with *N*-methyl isatin **89** led to the formation of spirooxindole **90** in 83% yield with 92:8 er. The reactivity and diastereo- and enantioselectivity were dependent on the acid cocatalyst; thus, 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 [154]. In the presence of 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** by treatment of the reaction mixture with $K_3PO_4$ (2 equiv) as additional base at 60 °C. This transformation is initiated by the formation of azolium cumulenolate intermediate form alkynal **91**. The subsequent

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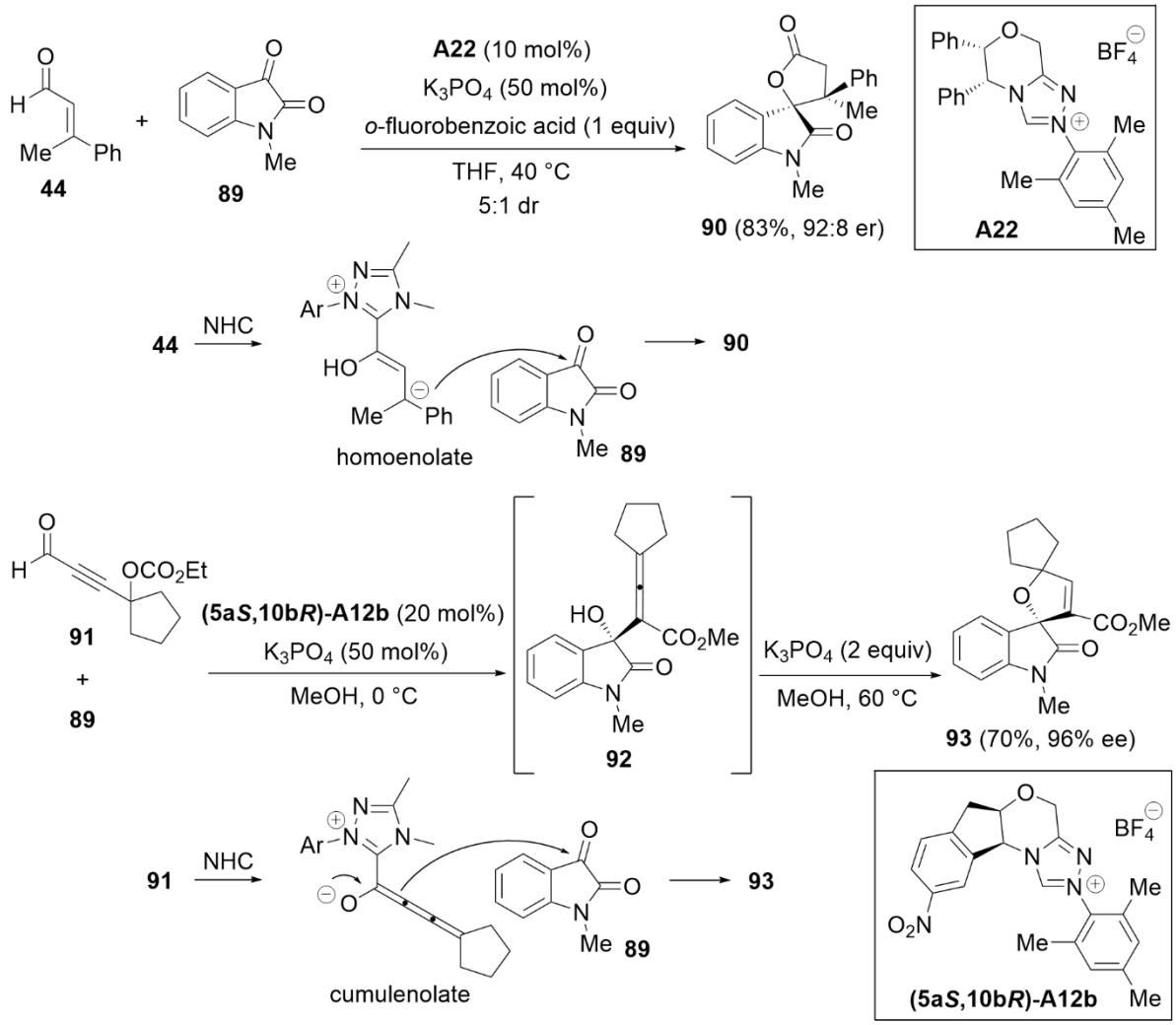
addition of the $\alpha$-carbon on cumulenolate to isatin **89** affords the allene product **92**. Additionally, the NHC-linked enolate was used as a C2 synthon for [3 + 2] annulation [155].




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

*5.4. [4 + 2] Annulation*

The NHC-linked enolates act as a C2 synthon for the [4 + 2] annulation [156–168]. In the presence of precursor **(5a*R*,10b*S*)-A4a** (10 mol%) and $Et_3N$ (1.6 equiv), the [4 + 2] annulation reaction of $\alpha$-chloroaldehyde **94** with *N*-phenyl-*N´* -benzoyl-diazene **95** proceeded effectively to give 1,3,4-oxadiazin-6-one **96** in 75% yield with 98% ee *via* the generation of the NHC-linked enolate from $\alpha$-chloroaldehyde **94** (Scheme 27) [156]. The [4 + 2] annulation of with cinnamaldehyde **5** with nitroalkene **97** was studied [157]. Under the optimized reaction conditions using precursor **(5a*R*,10b*S*)-A13b**, the desired dihydrocoumarin **98** was obtained in 90% yield with 99% ee. The reaction is initiated by the formation of homoenolate, which is converted to azolium enolate by proton transfer. This NHC-linked enolate reacts as a C2 synthon with nitroalkene **97** to give the annulation product **98**.

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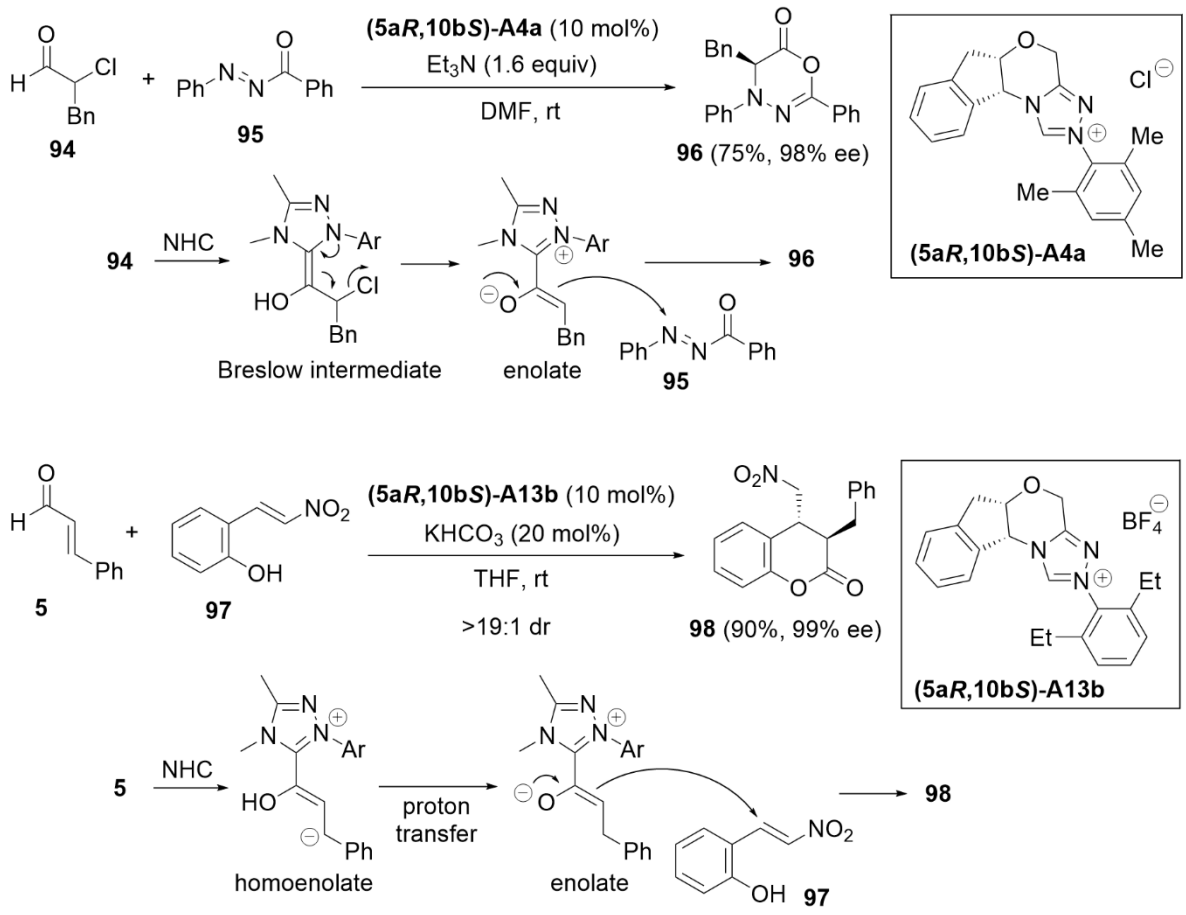


**Scheme 27.** Redox [4 + 2] annulation reactions using NHC-linked enolate.

The redox [4 + 2] annulation using the NHC-linked dienolate (vinyl enolate) as a C4 synthon was developed (Scheme 28) [169]. In the presence of chiral NHC catalyst generated from 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, Breslow intermediate is formed by the addition of NHC to enal **99**. Breslow intermediate is transformed to $\alpha,\beta$-unsaturated acyl azolium *via* debromination. The subsequent deprotonation at $\gamma$-H on $\alpha,\beta$-unsaturated acyl azolium leads to the NHC-linked dienolate (vinyl enolate), which undergoes nucleophilic addition to *N*-methylisatin **89**. Similarly, the [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 by the dearomative 1,4-elimination of HCl [170].

The annulation using the NHC-linked aza-dienolate as a C4 synthon was reported (Scheme 29) [171,172]. In the presence of precursor **A23** and $Cs_2CO_3$, treatment of 2*H*-azirine-2-carbaldehyde **103** with ketone **45** in THF gave the cyclized product **104** in 81% yield [171]. This transformation involves the formation of NHC-linked aza-dienolate form Breslow intermediate of aldehyde **103**.

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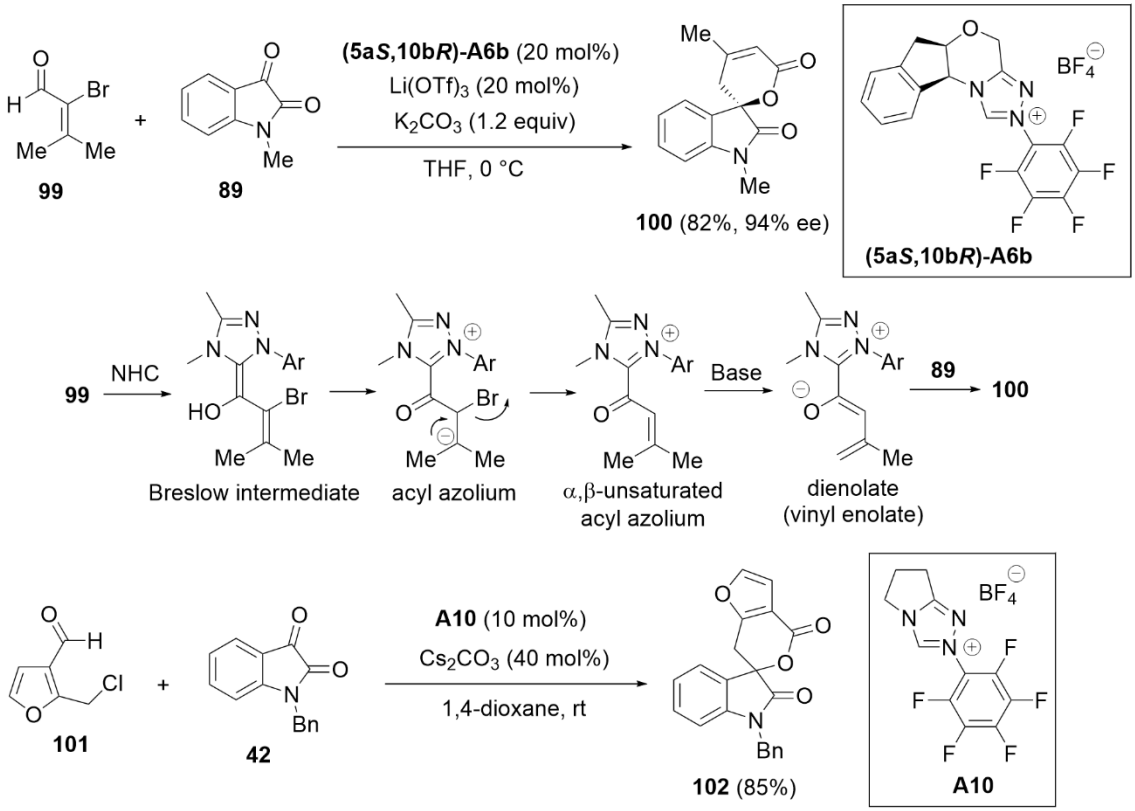
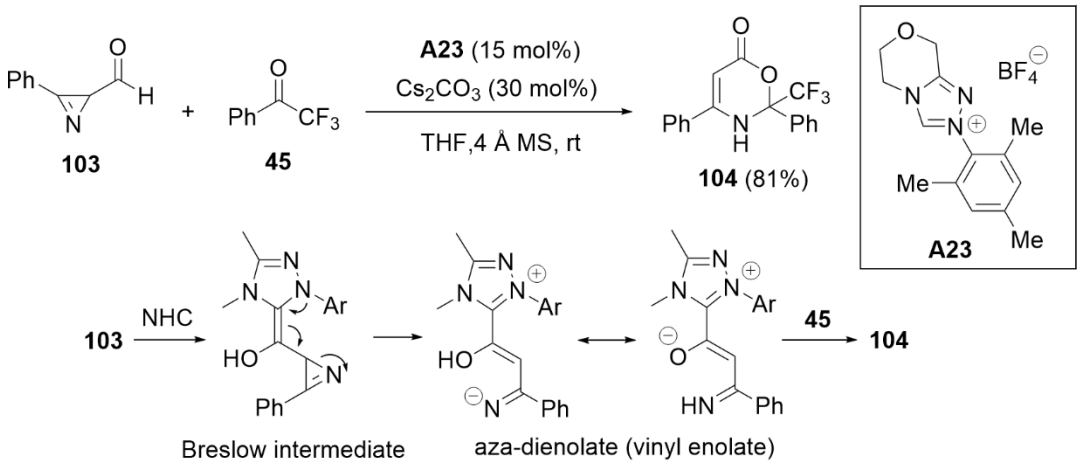



**Scheme 28.** Redox [4 + 2] annulation using NHC-linked dienolate.




**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 [4 + 3] annulation [173–179]. The enantioselective reaction of isatin-derived enal **105** with *o*-hydroxyphenyl-substituted *p*-quinone methide **50** was reported (Scheme 30) [177]. In the presence of precursor **A23** (20 mol%) and $Et_3N$ (1.5 equiv), treatment of enal **105** with *p*-quinone methide **50** in $CHCl_3$ at 0 °C gave the oxindole-ε-lactone **106** in 84% yield with 94:6 er. This annulation proceeds *via* the 1,6-addition of NHC-linked homoenolate, generated form enal **105**, to the hydroxy donor−1,6-Michael acceptor **50** followed by the lactonization leading to ε-lactone **106**.

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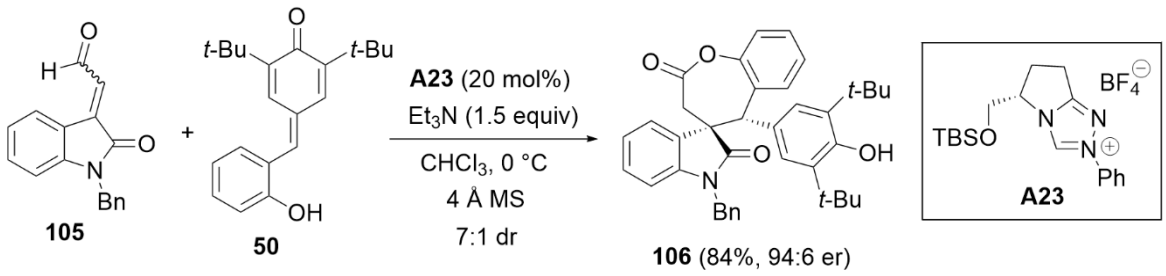
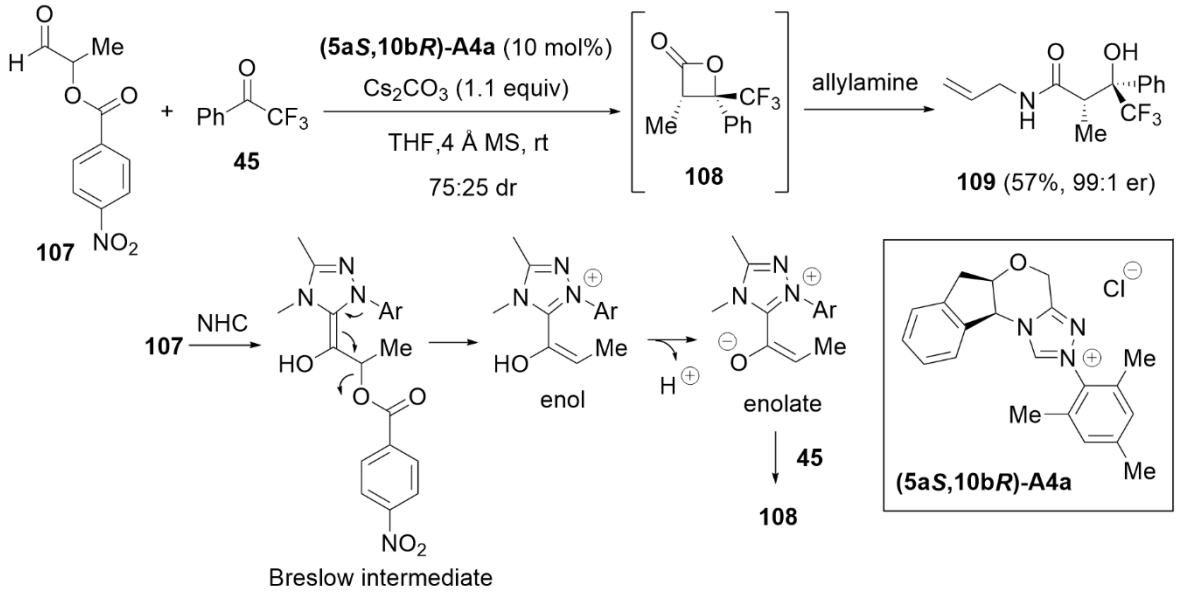



**Scheme 30.** Redox [4 + 3] annulation using NHC-linked homoenolate.

*5.6. [2 + 2] Annulation*

The NHC-linked enolate is used as a C2 synthon for [2 + 2] annulation (Scheme 31) [180]. 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 *para*-nitrobenzoate form Breslow intermediate leads to azolium enol. Subsequent deprotonation gives enolate, which undergoes the formal [2 + 2] cycloaddition with ketone **45**. Additionally, the similar oxidative [2 + 2] annulation was also reported [181].




**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 [182–192]. The α,β-unsaturated acyl azoliums are Michael acceptors acting as a C2 synthon for the cascade annulation reactions [182–187]. Under the optimized conditions using 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** in 98% yield with 97.2% ee (Scheme 32) [183]. In this reactions, α,β-unsaturated acyl azolium is initially formed from Breslow intermediate *via* bromide elimination. The subsequent aza-Michael addition of **110** to α,β-unsaturated acyl azolium provides enolate, which undergoes the intramolecular Michael addition. Finally, the cyclized product **111** is obtained by the lactonization. The cascade reaction between α-bromocinnamaldehyde **60** and imine **112** having the benzylic carbon of 4-nitrobenyl group was achieved [184]. The tetrahydrochromeno[4,3-b]pyrrole derivative **113** was obtained in 82% yield with 98:2 er under the

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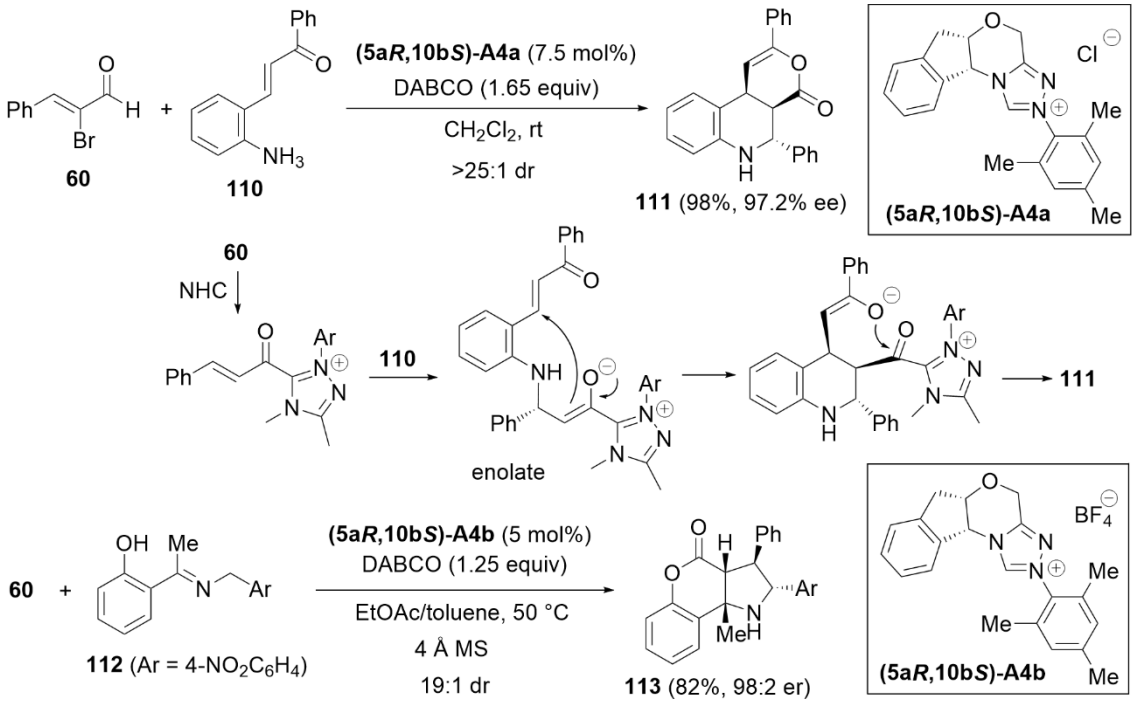
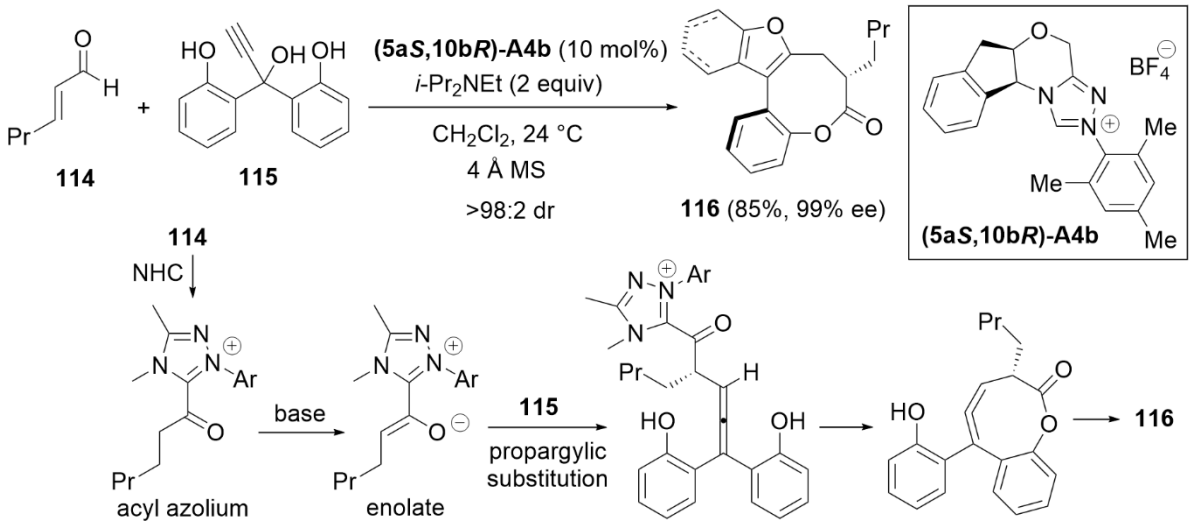
redox catalysis using precursor **(5a*R*,10b*S*)-A4b** and DABCO. The cyclized product **113** is obtained through Michael addition of anion of imine **112** to α,β-unsaturated acyl azolium.




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

The atropo-enantioselective synthesis of bridged biaryls was achieved by the NHC-catalyzed cascade reaction (Scheme 33) [188]. Employing the precursor **(5aS,10bR)-A4b** and *i*-Pr2NEt, the cascade reaction of α,β-unsaturated aldehyde **114** with triol **115** led to the formation of bridged biaryl **116** having an eight-membered lactone in 85% yield with 99% ee. This NHC-catalyzed transformation proceeds through the propargylic substitution of propargylic alcohol **115** with NHC-linked enolate. Furthermore, the redox cascade reactions using NHC-linked homoenolates was also developed [189–191].




**Scheme 33.** Cascade reaction using NHC-linked enolate.

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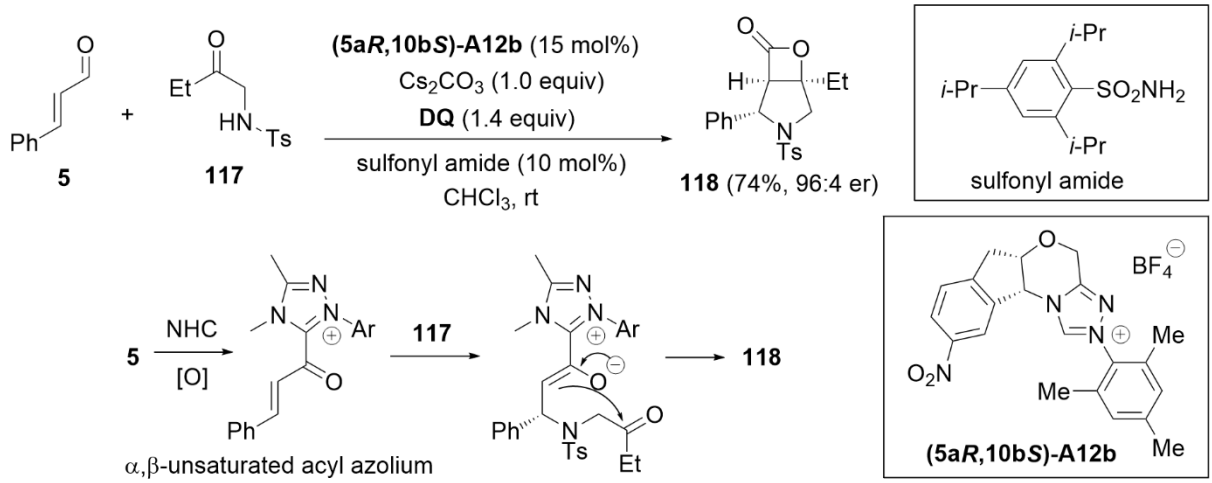
## 6. Cooperative catalysis with Brønsted acid and hydrogen-bonding catalyst

### *6.1. Cooperative Catalysis using Brønsted Acid*

Since the Rovis's group reported the cooperative NHC catalysis using Brønsted acid [193], the use of Brønsted acid has widely been demonstrated in the NHC-catalyzed activation of aldehyde C($sp^2$)−H bonds for C−O bond formation [194–200].

In the presence of 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 N-Ts amino ketone **117** gave the cyclized product **118** having β-lactone moiety in 74% yield with 96:4 er (Scheme 34) [197]. 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 chiral Brønsted acid in NHC catalysis has gained increasing attention as a novel method to improve the enantioselectivity. The NHC-catalyzed enantioselective synthesis of medium-ring lactones was developed [198]. The desymmetrization of prochiral 1,3-diol **119** was studied under the oxidative conditions using DQ (1.2 equiv) as an oxidant (Scheme 35). In the presence of 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** in 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 proceeds *via* the oxidation of Breslow intermediate to acyl azolium.

Glorius's group developed [4 + 2] annulation of ketone **45** with 2-(bromomethyl)-benzaldehyde **121** as a substrate having a leaving group at the *ortho*-benzylic position (Scheme 36) [199]. However, the use of chiral NHC led to only moderate enantioselectivity for product **122**. Later, the Rovis's group achieved the highly enantioselective [4 + 2] annulation of identical starting materials by using chiral phosphoric acid and chiral NHC [197]. In the presence of 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** in 68% yield with 95% ee. In this reaction, the extrusion of the bromide within Breslow intermediate leads to dienolate, which undergoes [4 + 2] annulation with ketone **45**.

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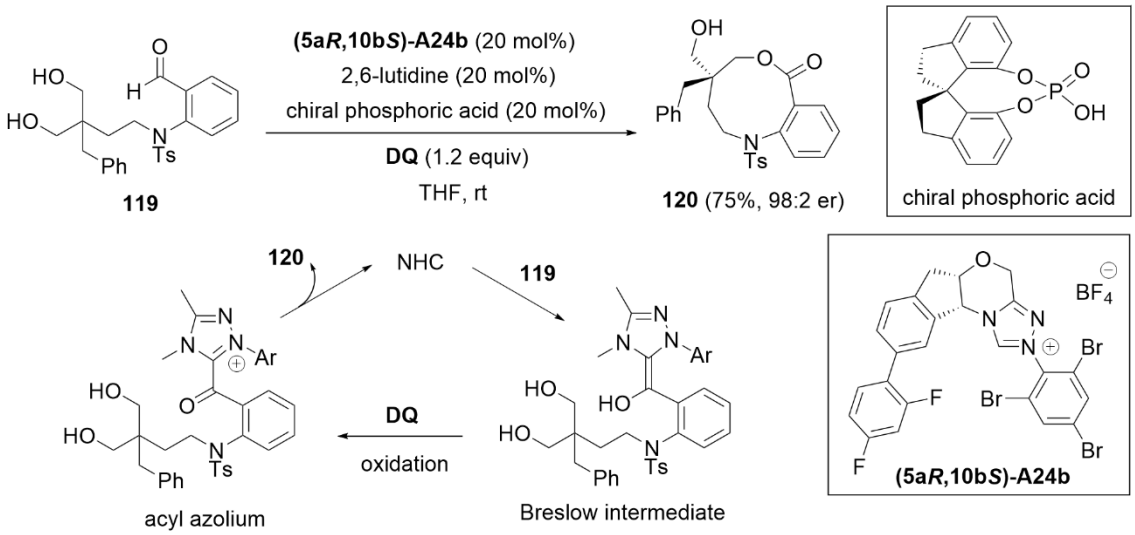
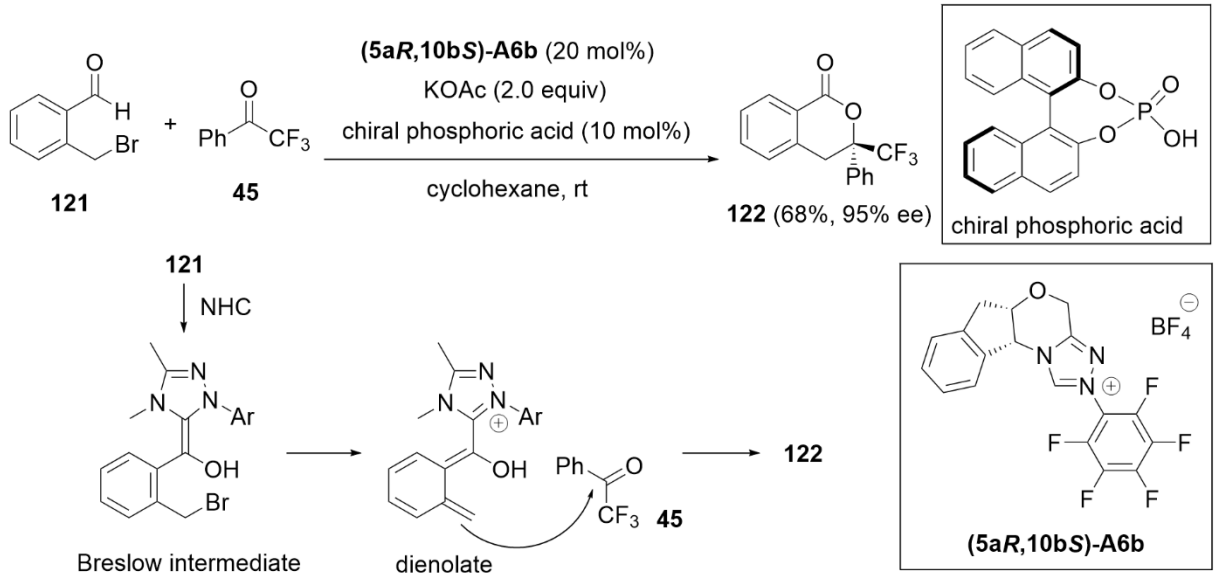



**Scheme 35.** Medium-ring lactone synthesis by desymmetrization of 1,3-diol.




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

*6.2. Cooperative Catalysis using Hydrogen-Bonding Catalyst*

The dual catalysis using NHC and hydrogen-bonding catalyst has been developed [201]. The cooperative catalysis using cinchonine as chiral bifunctional organocatalyst with achiral NHC catalyst was reported [202]. In the presence of 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 is initiated by 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 nucleophile and electrophile, respectively.

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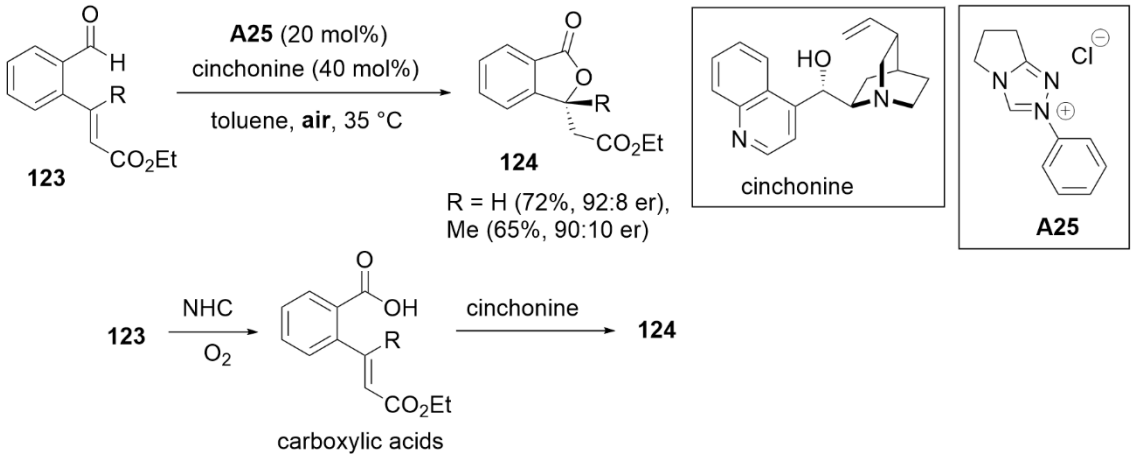
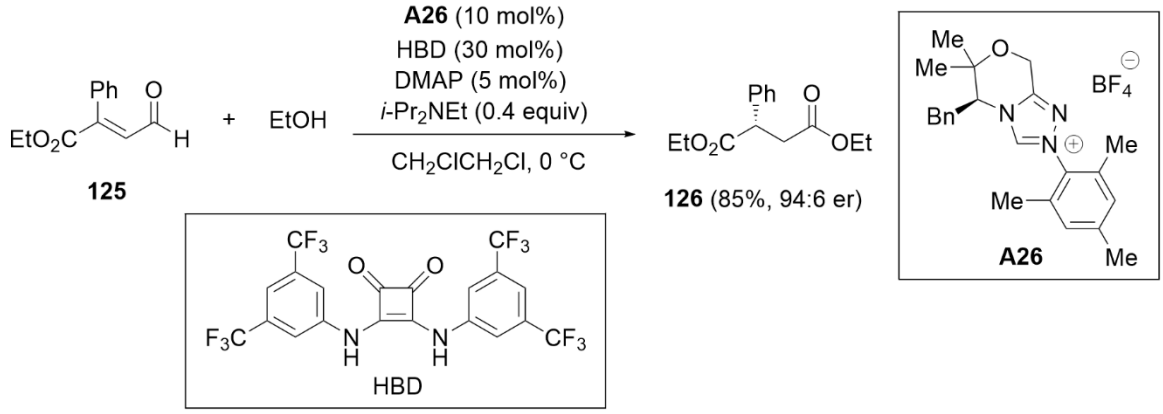



**Scheme 37.** Use of cinchonine as chiral hydrogen-bonding catalyst.

The cooperative catalysis using chiral NHC catalyst and H-bond doner catalyst (HBD) was reported to achieving the enantioselective β-protonation in the redox esterification of α,β-unsaturated aldehydes (Scheme 38) [203]. In the presence of precursor **A26** (10 mol%), H-bond doner catalyst (HBD, 30 mol%), DMAP (5 mol%) and *i*-Pr2NEt (0.4 equiv), the reaction of β-ethyl ester **125** with ethanol was performed at 0 °C. The saturated bis-ester **126** was obtained in 85% yield with 94:6 er. The coordination of HBD to β-ethyl ester group would enhance the enantioselectivity by 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 the NHC catalysis for the C–O bond formation of aldehydes [204–207]. The NHC-catalyzed annulation of enals and α-ketoesters was studied (Scheme 39) [204]. In this reaction, the combined use of $Ca(OMe)_2$ as Lewis acid and thiourea **B1** as a H-bond doner catalyst enhanced the enantioselectivity and yield of products. Under the optimized conditions using 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 by the addition of homoenolate, generated from **5** and NHC, to α-ketoester **127**.

Sequential three-component reaction of nitroalkenes **129**, 3-phenylpropanal **1** and cinnamaldehyde **5** was achieved by one-pot procedure (Scheme 40) [205]. The use of two different NHC catalysts, generated from achiral precursor **A10** and 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 nitroalkenes **129** and aldehyde **1** leads to the *in situ* generation of enone intermediates *via* the nitro-Stetter/elimination sequence [206]. Next, 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

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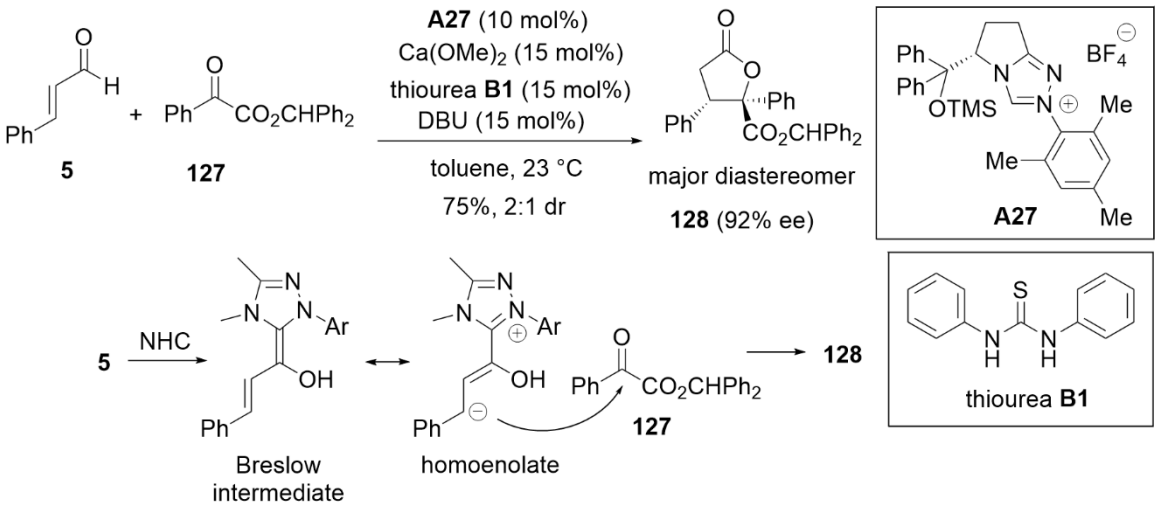
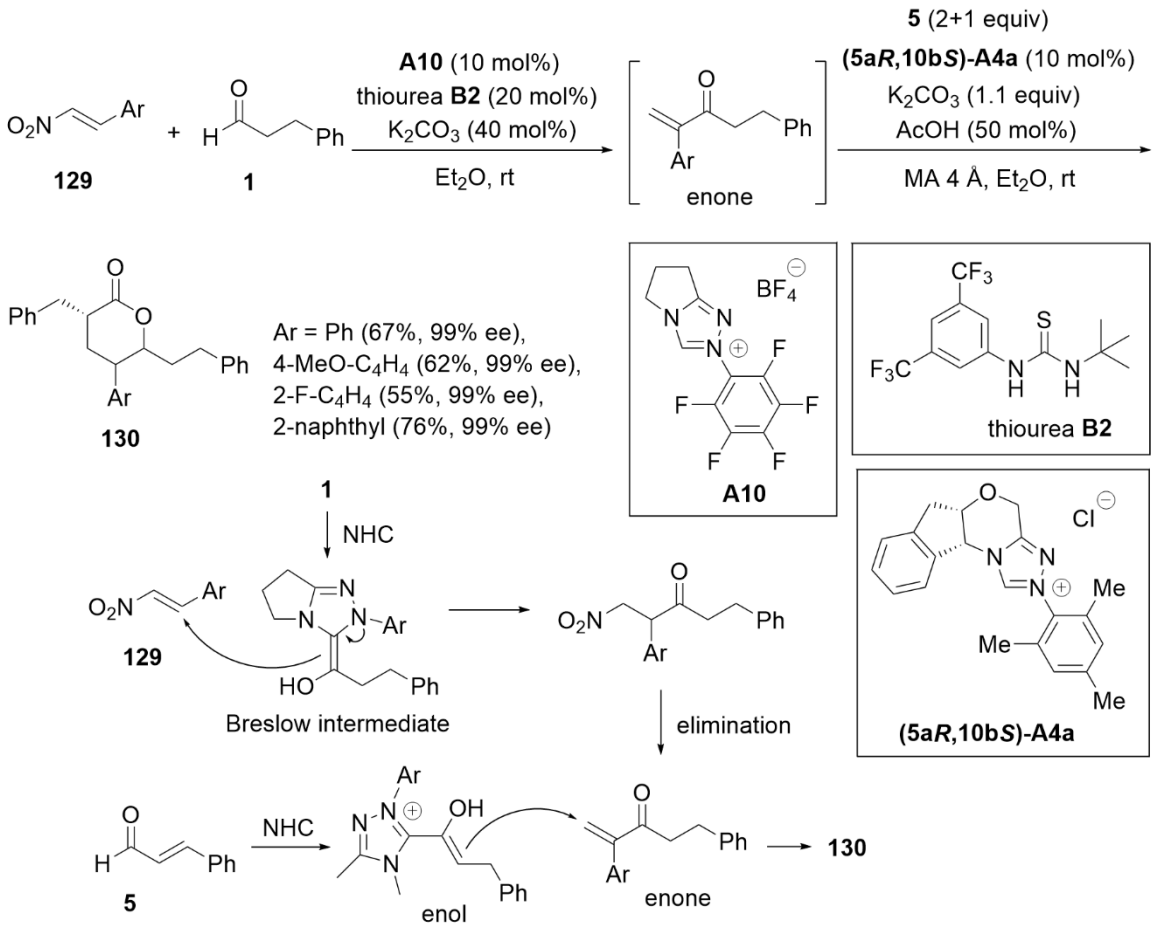
for annulation. The dihydropyranone **130** are obtained *via* Michael addition of chiral NHC-linked enol to β-unsubstituted enones followed by lactonization.




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




**Scheme 40.** Sequential NHC-catalyzed reaction.

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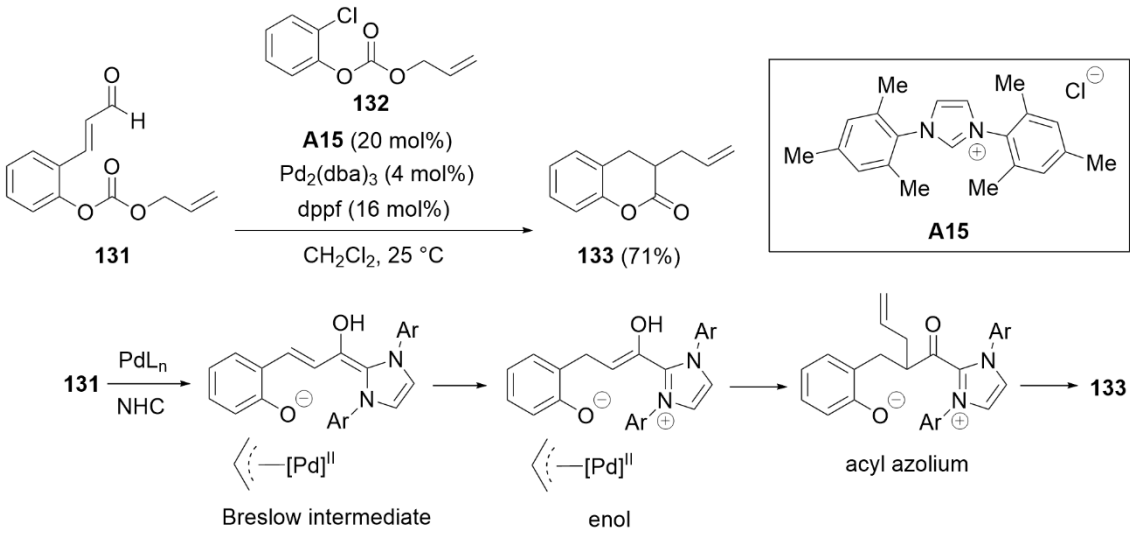
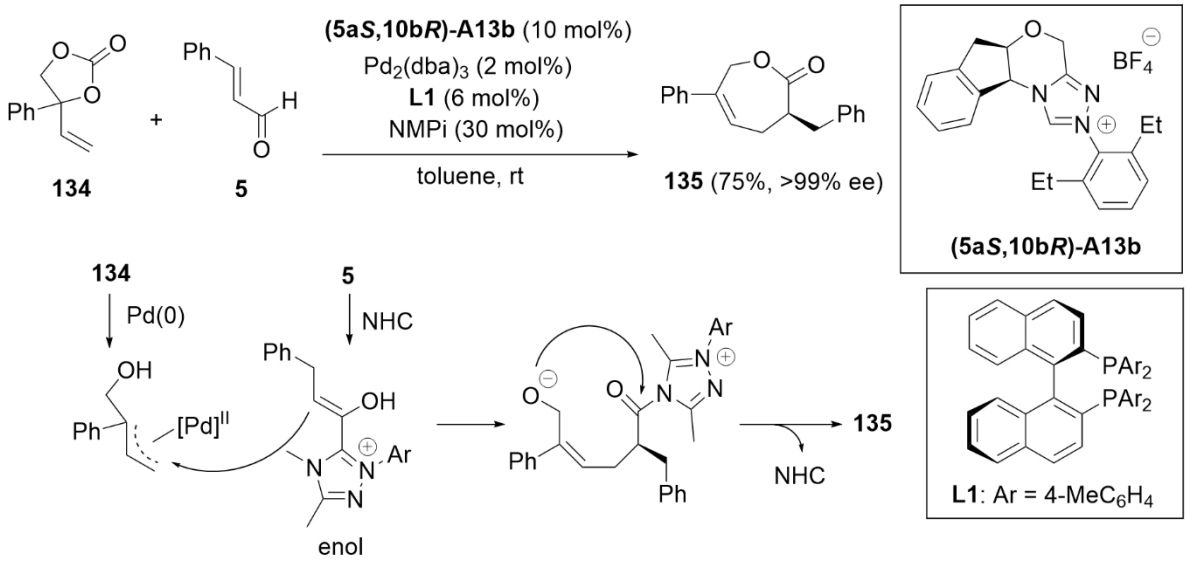
## 7. Cooperative Catalysis with Transition-Metal Catalyst

### *7.1. Cooperative Catalysis using Palladium Catalyst*

Scheidt's group reported the cooperative catalysis involving the simultaneous activation of substrates using NHC catalyst and palladium catalyst (Scheme 41) [208]. In the presence of 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 π-allyl palladium intermediate. The substrate **131** reacts with NHC catalyst and palladium catalyst to give Breslow intermediate and π-allyl palladium. This cooperative transformation is based on the addition of enol, generated from Breslow intermediate, into π-allyl palladium intermediate.




**Scheme 41.** Cooperation between NHC and palladium catalyst.




**Scheme 42.** Enantioselective cooperative catalysis.

The palladium-catalyzed allylic substitution is applied to the enantioselective cooperative catalysis by using chiral NHC catalyst [209–215]. Glorius's group reported the enantioselective catalysis using the combination of chiral NHC, generated from precursor **(5a*S*,10b*R*)-A13b**, and chiral

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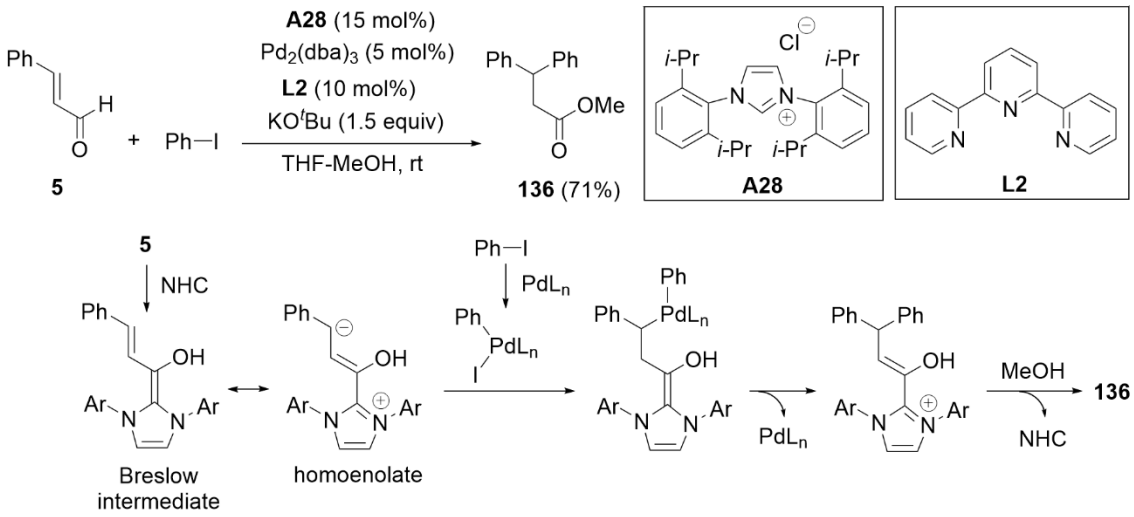
palladium catalyst, generated from $Pd_2(dba)_3$ and ligand **L1** (Scheme 42) [211]. Under the optimized conditions, the [5 + 2] annulation reaction between phenyl vinylethylene carbonate **134** and cinnamaldehyde **5** gave the annulation product **135** with an excellent enantioselectivity. NHCs 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 the 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 NHC catalyst.

Recently, [3 + 2] annulation reaction for the synthesis of enantioenriched α,β-disubstituted γ-butyrolactones was reported by using chiral NHC and chiral iridium catalysts [212,213]. Furthermore, the umpolung allylic and propargylic substitution reactions of enals were also achieved by using chiral NHC and nickel catalysts [214,215].

The umpolung 1,4-addition of aryl iodides or vinyl bromides to enals was developed under the cooperative NHC/palladium reaction conditions [216,217]. The 1,4-addition of iodobenzene to cinnamaldehyde **5** was promoted by the combination of NHC, generated from precursor **A28**, and palladium catalyst, generated from $Pd_2(dba)_3$ and ligand **L2** to give methyl β,β-diphenyl propanoate **136** in 71% yield (Scheme 43) [216]. Initially, the homoenolate equivalent is generated from cinnamaldehyde **5** and NHC. Next, the nucleophilic homoenolate reacts with the activated $PhPdI(L_n)$, which is generated by the oxidative addition of palladium catalyst to iodobenzene. The subsequent reductive elimination provides the NHC-bonding intermediate, which reacts with MeOH to afford methyl β,β-diphenyl propanoate **136**. Additionally, 1,4-addition of vinyl bromides to enals was also studied under the similar reaction conditions [217].




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

*7.2. Cooperative Catalysis using Copper Catalyst*

The copper catalysts are used for the cooperative NHC catalysis [218,219]. In the presence of precursor **A29** (10 mol%), $Cu(CH_3CN)_4PF_6$ (5 mol%) and $Et_3N$ (1.0 equiv), [3 + 3] annulation between the isatin-derived enal **105** and ethynylethylene carbonate **137** led to the formation of spirooxindole δ-lactones **138** with >95:5 dr and 99% ee (Scheme 44) [219]. Initially, copper acetylide is generated from **137** under the basic conditions. The decarboxylation of copper acetylide leads to copper allenylidene. Subsequently, enals **105** react with NHC to form homoenolates, which undergo the formal [3 + 3] cycloaddtion with copper allenylidene to afford δ-lactones **138**. Since NHC serves as a ligand of copper, chiral Cu(I)-NHC complex would participate in the control of stereochemistry, together with chiral NHC catalyst.

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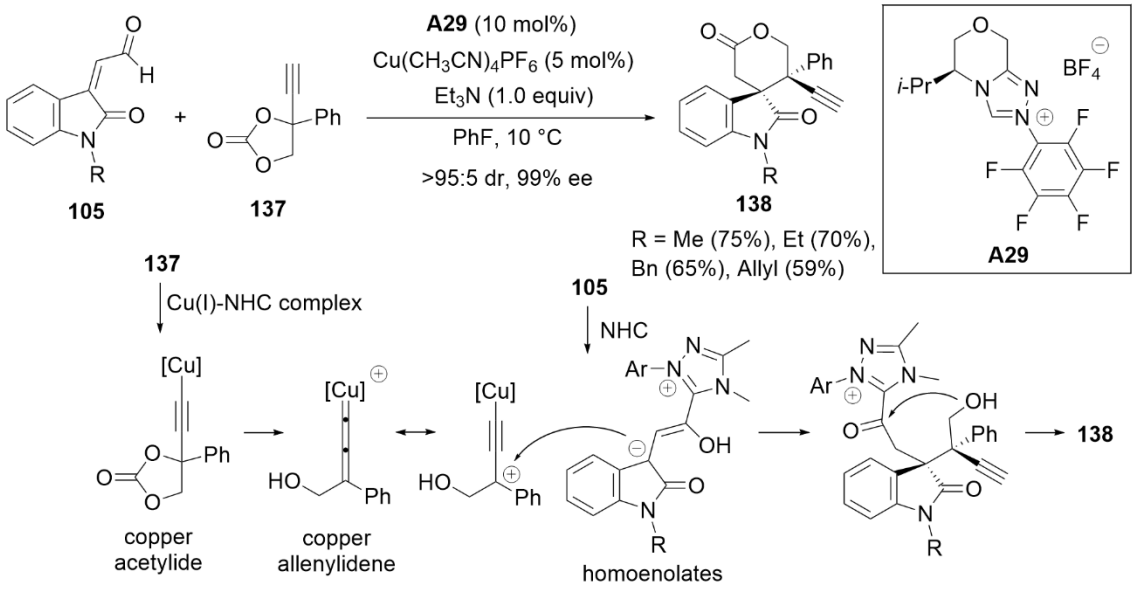
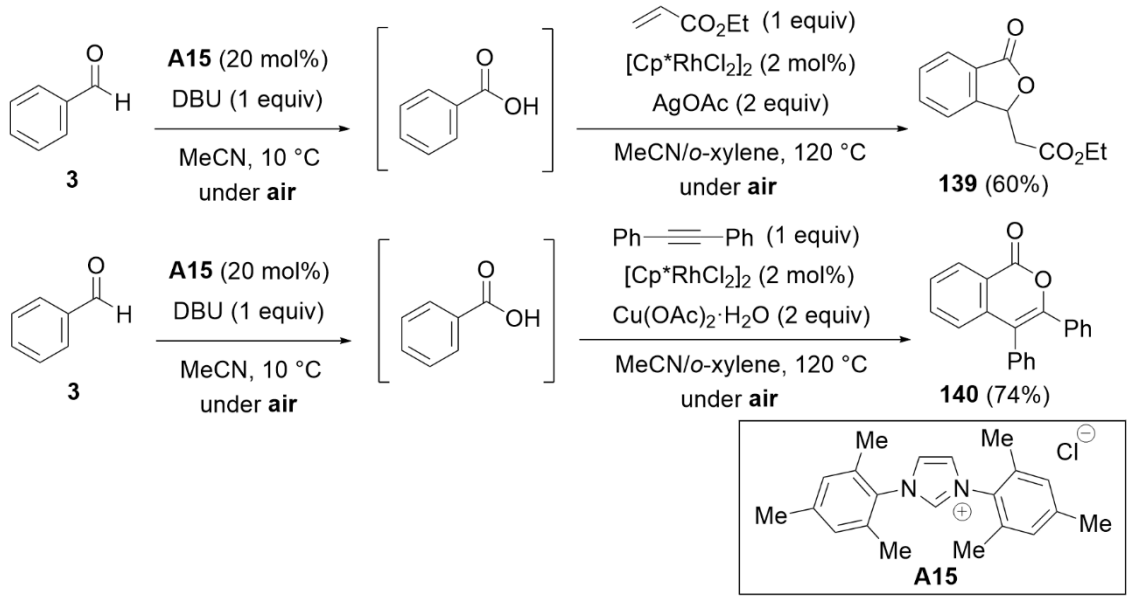



**Scheme 44.** Cooperative catalysis with copper catalyst.

*7.3. Cooperative Catalysis using Rhodium Catalyst*

The one-pot reactions involving NHC catalysis and rhodium(III) catalysis were reported, although these sequential reactions cannot be strictly classified to the cooperative catalysis (Scheme 45) [220]. Initially, the aerobic oxidation of benzaldehyde **3** proceeded smoothly under the conditions using NHC generated from precursor **A15** and DBU to give benzoic acid intermediate. 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 in 60% yield. When 1,2-diphenylethyne was used for the second step, the isocoumarin **140** was obtained in 74% yield. In this case, $Cu(OAc)_2{\cdot}H_2O$ performed better than AgOAc as an oxidant in rhodium(III) catalysis. More recently, the NHC/Rh cooperative catalysis for desymmetric [3 + 3] annulation of oxabicyclic alkenes with enals was developed [221].




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

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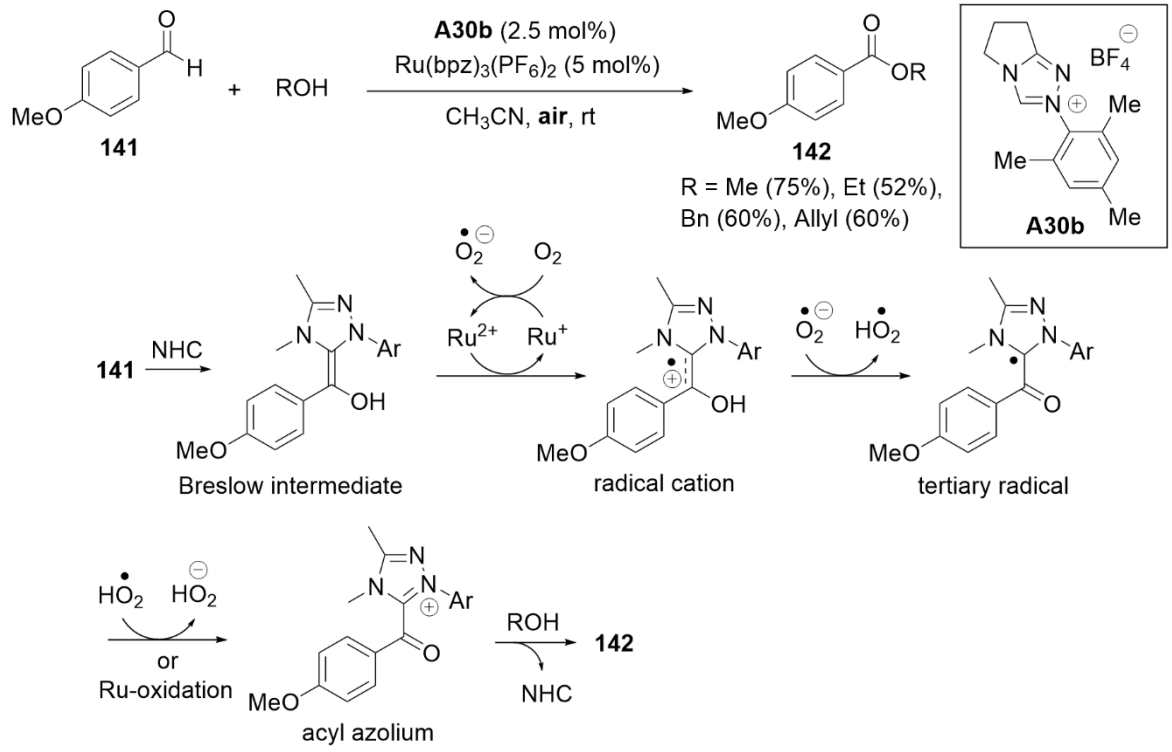
*7.4. Cooperative Catalysis using Ruthenium Catalyst*

The combination of NHC catalysis and ruthenium redox catalysis was investigated [222–224]. The oxidative esterification of aldehydes was achieved by using 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) [222]. The catalytic ruthenium cycle involves the oxidation of Ru(I) complex to Ru(II) complex by molecular oxygen to give the superoxide radical anion. Initially, the Ru(I)-catalyzed oxidation of Breslow intermediate generated from aldehyde **141** leads to the radical cation, which will be further oxidized to the acyl azolium *via* tertiary radical.




**Scheme 46.** Cooperative catalysis with ruthenium catalyst.

The cooperative NHC/ruthenium redox catalysis was used for oxidative [3 + 3] annulation (Scheme 47) [223] The oxidation of Breslow intermediate leads to the formation of α,β-unsaturated acyl azolium acting as a C3 synthon. In the presence of chiral NHC generated from 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** in 98% yield with 93% ee. The proposed reaction mechanism involves the oxidation of Breslow intermediate, generated from NHC and enal **5**, by SET from $RuCl_3$. A second oxidation of radical cation intermediate by $RuCl_3$ gives α,β-unsaturated acyl azolium, which undergoes [3 + 3] annulation with 2,4-pentanedione **143**. In this catalysis, Ru(III) is regenerated through the oxidation of Ru(II) by molecular oxygen.

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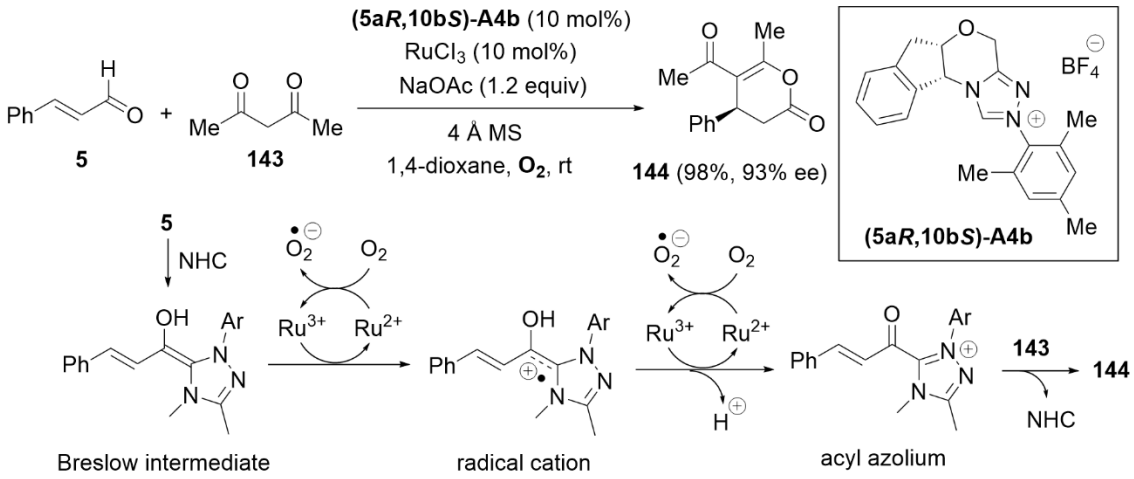
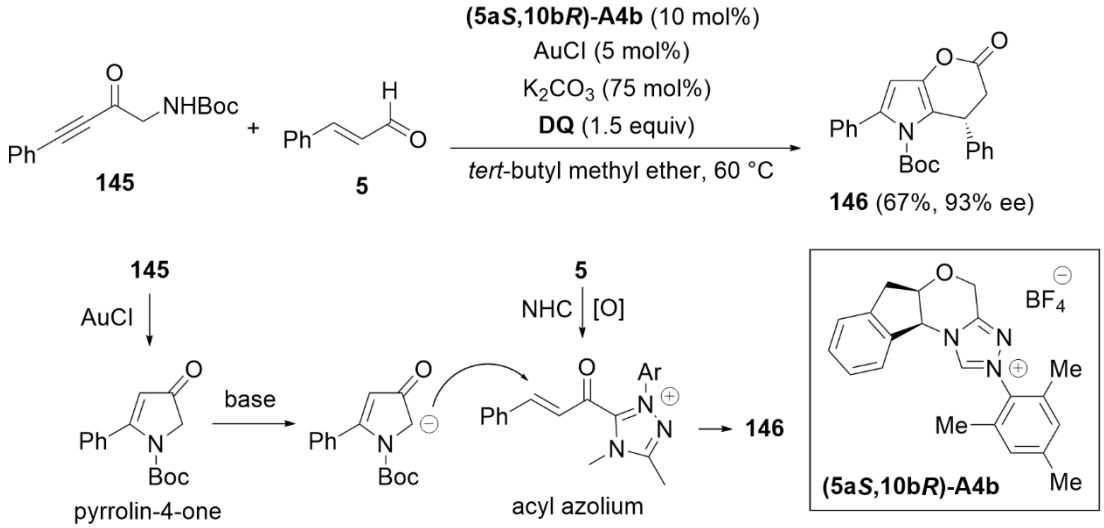



**Scheme 47.** Oxidative [3 + 3] annulation using ruthenium catalyst.

*7.5. Cooperative Catalysis using Gold Catalyst*

The enantioselective gold and NHC relay catalysis was reported (Scheme 48) [225]. The cascade annulation between $\alpha$-amino-ynone **145** and cinnamaldehyde **5** was performed under the oxidative conditions using DQ as an oxidant. Initially, pyrrolin-4-one intermediate was obtained by gold catalysis. The anion of pyrrolin-4-one adds to $\alpha,\beta$-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 [226]. In recent years, the cooperative NHC catalysis with photocatalyst has gained increasing attention as a novel redox catalysis [18–21].

The combined use of NHC and photocatalyst was applied to the oxidative transformation of aldehydes to the corresponding esters [227–234]. The oxidative esterification of aldehydes through the oxidation of Breslow intermediates was achieved by the dual organocatalysis based on the cooperation between NHC and an organophotocatalyst such as rhodamine 6G or eosin Y·Na (Scheme 49) [227,228]. In the presence of triazolium precursor **A30c** (5 mol%) and rhodamine 6G (5 mol%), the use of $BrCCl_3$ (3 equiv) as a co-oxidant promoted the reaction of cinnamaldehyde **5** to give ester **147**

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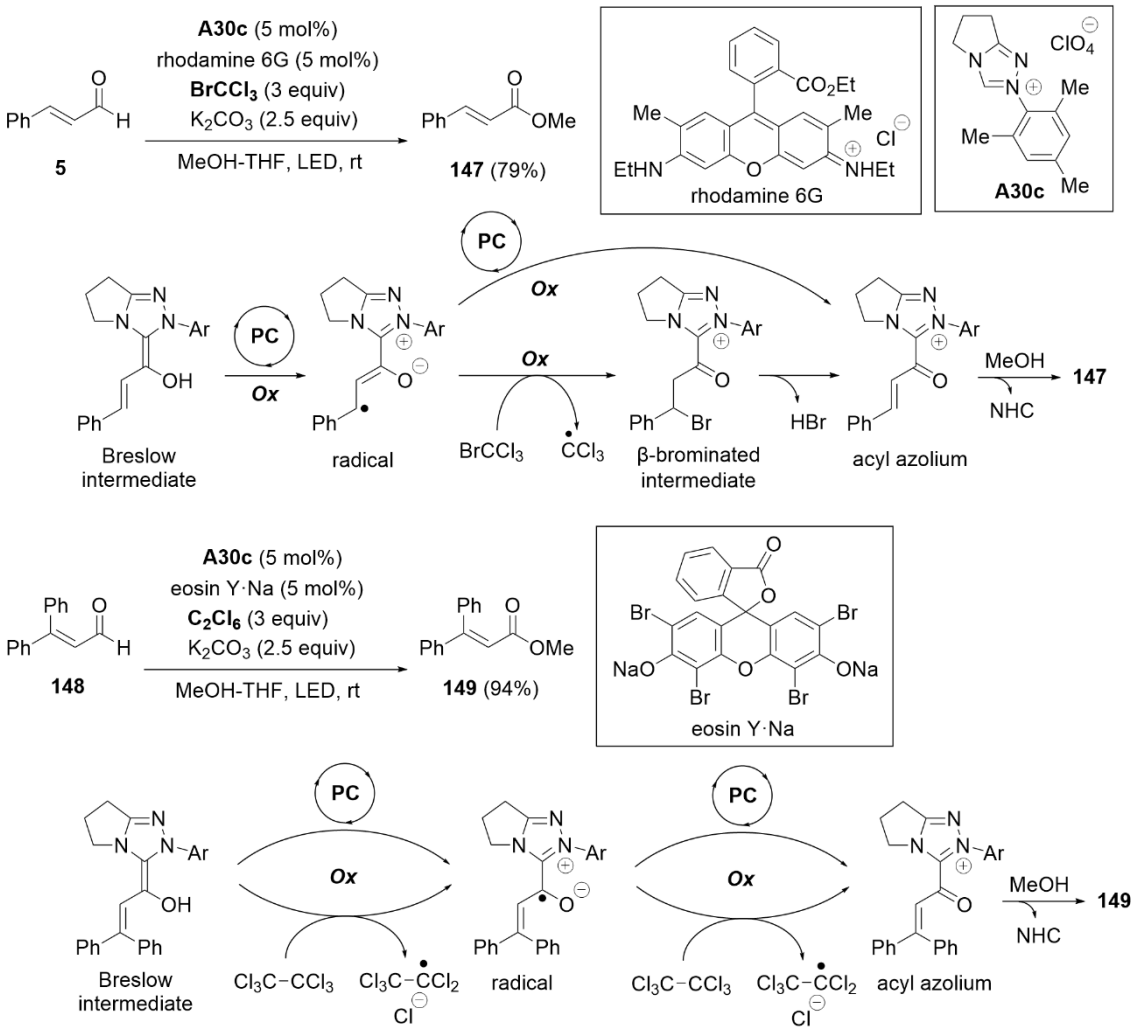
in 79% yield [227]. Initially, it was assumed that electron-rich Breslow intermediate is photocatalytically oxidized to acyl azolium *via* the radical intermediate, whereas co-oxidant $BrCCl_3$ would act as a quencher toward the activated photocatalyst species having the reduction property to turn the catalytic photoredox cycle. After the detailed research [228], it was shown that $BrCCl_3$ promotes the second oxidation as a brominating reagent toward radical intermediate to give the β-brominated intermediate. The acyl azolium is formed *via* the elimination of HBr from β-brominated intermediate. The use of $C_2Cl_6$ as a co-oxidant was the effective method for the oxidative esterification, because the oxidation steps are promoted by two pathways associated with the activated photocatalyst and $C_2Cl_6$ [228]. In the presence of 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 $C_2Cl_6$ (3 equiv) led to the formation of ester **149** in 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 Breslow intermediates (Scheme 50) [229–232]. When 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 γ-alkylated ester **151** in 86% yield with exclusive γ-regioselectivity [229]. In these reactions, iodoacetonitrile acts as not only oxidant for Ru-photocatalysis but also radical source giving cyanomethyl radical. Cyanomethyl radical adds to the dienolate intermediate to afford the homoenolate radical. The following photocatalytic oxidation of this radical leads to acyl azolium. This reaction was expand to

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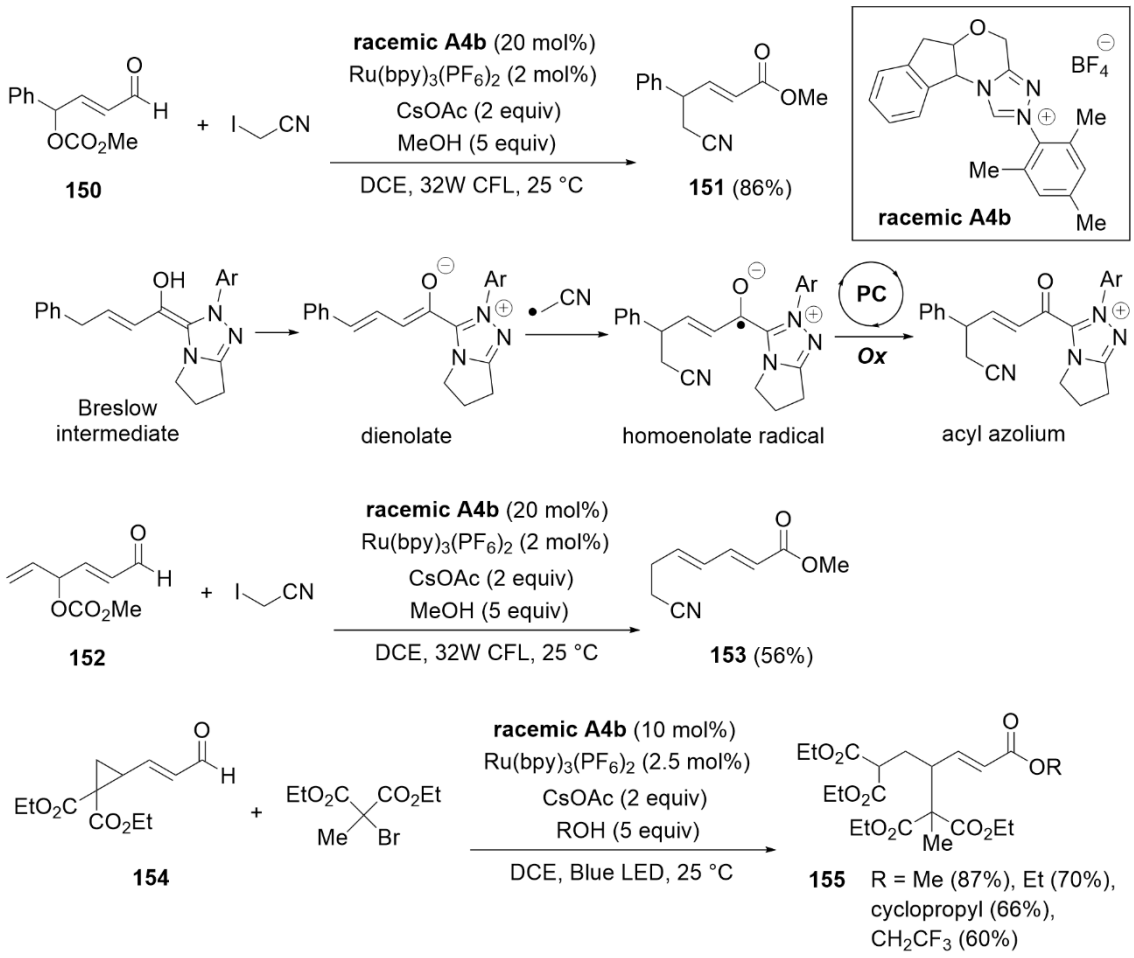
ε-functionalization by using the enal **152** bearing a vinyl substituent at γ-position. Under the similar reaction conditions, the reaction of enal **152** gave the γ-cyanomethylated ester **153** in 56% yield with the exclusive ε-selectivity. The alkylation and esterification reaction also proceeds by using the dienolate generated from cyclopropane enal **154** *via* NHC-catalyzed ring opening [230]. In the presence of several alcohols, photo/NHC catalysis of **154** and diethyl 2-bromo-2-methylmalonate afford the corresponding γ-alkylated esters **155**.




**Scheme 50.** Alkylation and esterification reaction.

The esterification of aldehydes based on oxidative Smiles rearrangement was developed (Scheme 51) [233]. 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 an organophotocatalyst. In the presence of NaI (10 mol%) as an additive to facilitate the electron transfer, the reaction of **156** proceeded effectively to give the aryl salicylate **157** in 79% yield. The continuous oxidation of Breslow intermediate by activated photocatalyst and hydroperoxide radical, *in situ* generated from molecular oxygen, leads to acyl azolium. The acid intermediate is generated by hydrolysis of acyl azolium. Subsequently, the photocatalytic oxidation of acid intermediate promotes Smiles rearrangement to give phenoxy radical *via* the spirocyclic intermediate. Finally, the reduction of this radical by photocatalysis gives the aryl salicylate **157**. In the absence of a photocatalyst, the combined use of NHC catalysis and photoredox reaction has gained increasing attention as a novel catalysis [234]. Under the 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

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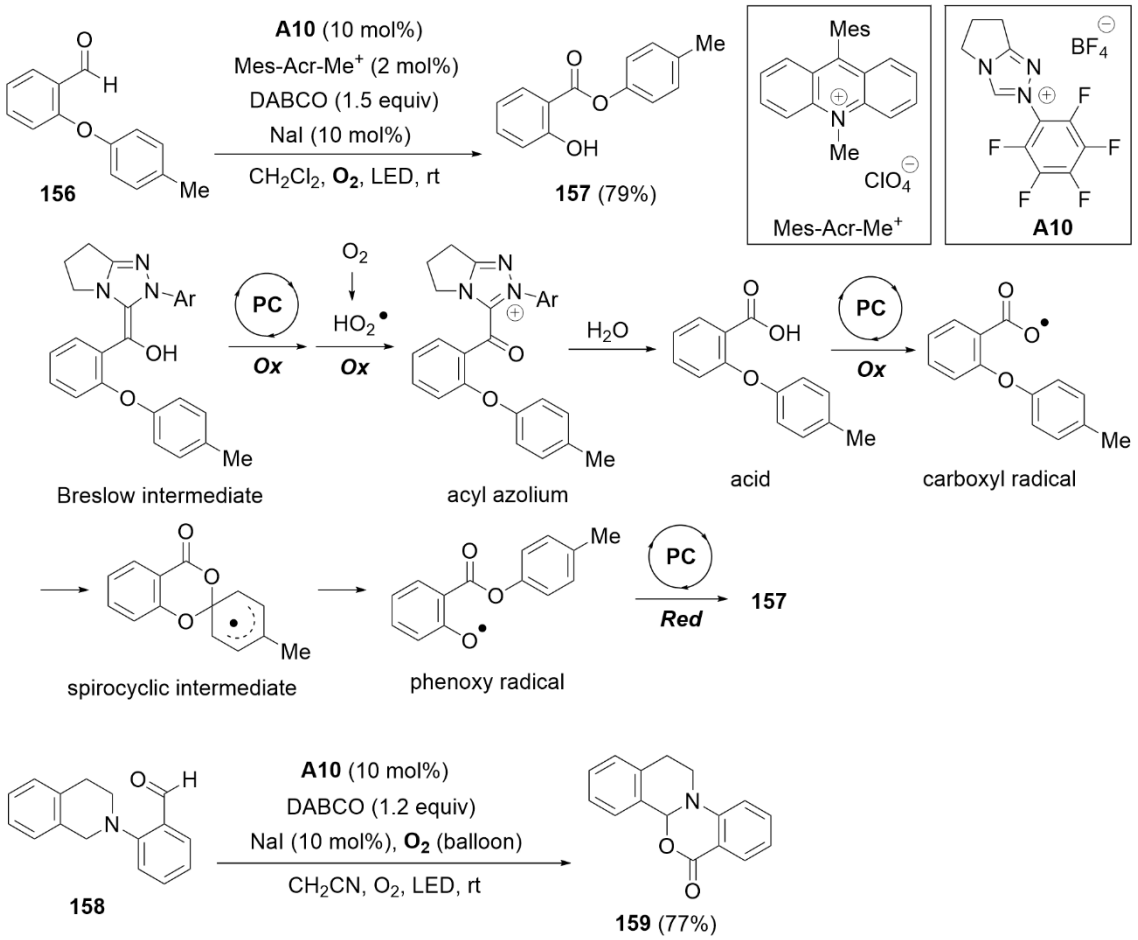
to give the cyclized product **159** in 77% yield. In this reaction, a photo-excited Breslow intermediate is proposed for explaining the photooxidation process.




**Scheme 51.** Oxidative Smiles rearrangement.

## 9. Conclusion and Outlook

N-Heterocyclic carbenes are the highly reactive organocatalysts that induce the synthetically valuable chemical transformations. Furthermore, the enantioselective NHC catalysis has attracted substantial attention, since the highly functionalized compounds with multiple stereo-centers can be synthesized. Additionally, the oxidative reaction of aldehyde C($sp^2$)–H bonds with alcohol O–H bonds is has been recognized as a straightforward and atom-economical cross dehydrogenative coupling reaction [235,236]. As summarized above, the various synthetic strategies and methodologies have been developed as a cooperative catalysis. The recent dramatic progress in NHC-induced catalysis offer opportunities for the further exploration with intriguing possibilities in organocatalysis for the synthetic organic chemistry.

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