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Umpolung strategy: advances in catalytic C-C bond formations

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Abstract: This mini-review examines the recent advances in umpolung strategy, devised originally by Corey and Seebach. Although numerous stoichiometric variants have been published to date, this article covers just the catalytic C-C bond forming reactions due to their major benefits such as atom economy, less pollution, and workable simplicity. In the context of umpolung, the studies are evaluated under 3 main titles: enzyme, *N*-heterocyclic carbene, and cyanide ion catalyzed reactions. In particular, enzyme and NHC catalyzed reactions mainly involve asymmetric applications.

Key words: Umpolung, thiamine pyrophosphate (TPP), *N*-heterocyclic carbene, asymmetric synthesis

1. Introduction to umpolung

As an outcome of extensive efforts dedicated to the development of new approaches for the construction of either complex synthetic targets or small synthetic building blocks, numerous synthetic organic methods are now available for a wide range of bond-forming reactions.[1] In particular, carbon-carbon (C-C) bond-forming reactions have been the key point among all the organic reactions in the history of organic synthesis.[2] However, the investigation of catalytic methods for C-C bond formation reactions, while generating functionality, remains a formidable challenge in the ongoing development of effective and reliable chemical processes. Because of the advantages of catalytic methods such as high atom economy,[3] less pollution, and workable simplicity, catalytic C-C bond forming reactions have gathered widespread attention in recent years. Consequently, there is a significant demand to evolve novel practical catalytic methodologies targeting C-C bond construction.

In this regard, umpolung, defined as: "*Any process by which the normal alternating donor and acceptor reactivity pattern of a chain, which is due to the presence of O or N heteroatoms, is interchanged*", has been accepted as a powerful alternative synthetic strategy to traditional C-C bond-forming methods.[4] Umpolung (polarity reversal) of carbonyl groups (acyl anion equivalents) adds new dimensions of flexibility to the design of synthetic targets.

Although acyl anions (d^1 synthons) are not stable, they are traditionally synthesized by functional group manipulation and stoichiometric strong base deprotonation of the corresponding carbonyl compounds. In this respect, the Corey–Seebach reaction, shown in Scheme 1, is the leading example, in which lithiated dithiane **3** stabilized by the 2 sulfur atoms is employed as an acyl anion nucleophile.[5] Nucleophilic entities at the carbonyl center are generally called masked "acyl anion" or "acyl anion equivalents".

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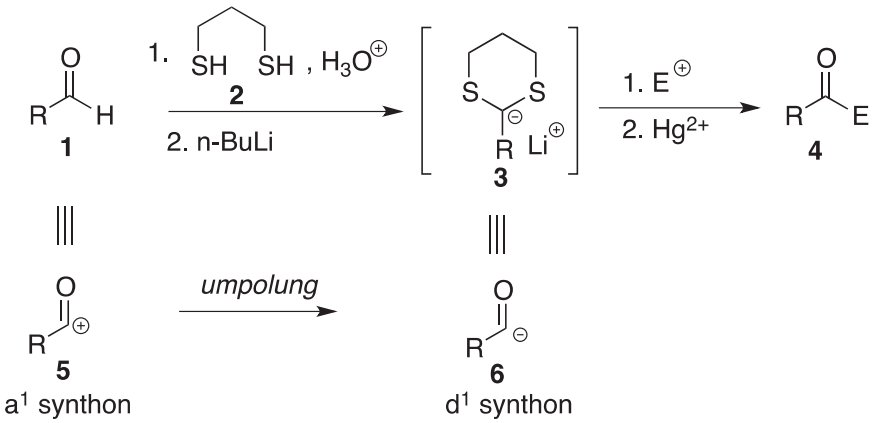
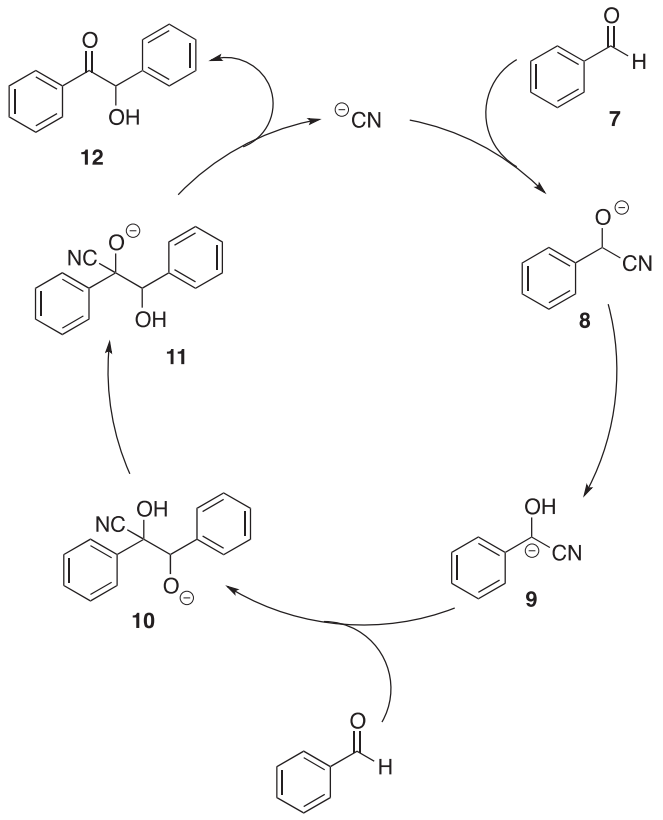
This article is dedicated to the memory of Prof Dr Ayhan S. Demir



Scheme 1. Dithiane umpolung reactivity of carbonyl compounds.

A typical example of umpolung strategy is the benzoin condensation reaction, cyanide ion catalyzed dimerization of 2 aldehydes, which was fortuitously discovered by Liebig and Wöhler in 1832.[6] Benzoin condensation is an important strategy to create new C-C bonds leading the formation of α-functionalized carbonyl compounds. This unique process and its mechanism have been intensively studied. In 1903, Lapworth was the first to establish the mechanism of cyanide ion catalyzed benzoin condensation and to determine the formation of crucial carbanion intermediate **9** (Scheme 2).[7]

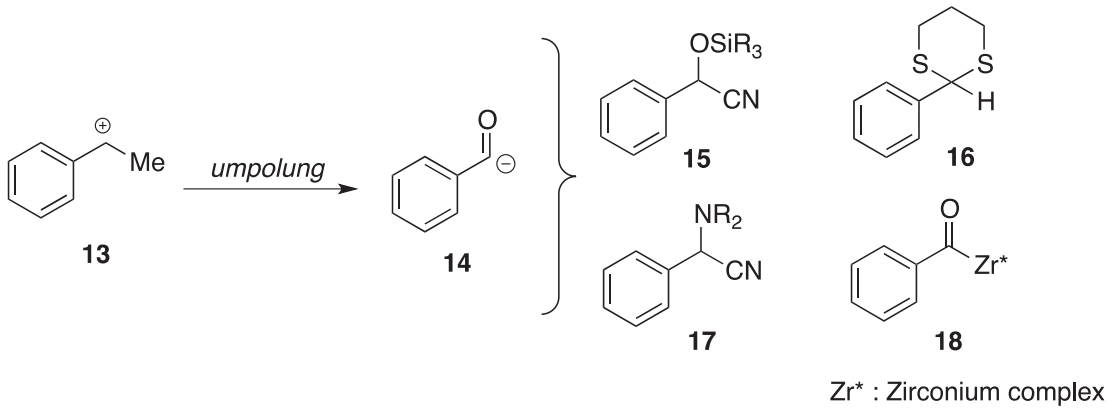


Scheme 2. Cyanide catalyzed benzoin condensation mechanism.

Although one of the easiest and most efficient ways to synthesize α-hydroxy ketones is benzoin condensa-

tion, it often suffers from intrinsic drawbacks. Benzoin condensation has a very limited substrate scope since the aromatic aldehydes with strong electron-donating or electron-withdrawing groups do not furnish the resultant product with consistent yields. Furthermore, cyanide ion does not catalyze the benzoin condensation between aliphatic aldehydes, because they tend to undergo aldol condensation. Another drawback of benzoin condensation is incomplete conversion of reaction caused by reversible steps in the mechanism. Benzoin condensations under classical reaction conditions are also limited to the synthesis of symmetrical homobenzoins.

Well-known examples of acyl anion equivalent, shown in Scheme 3, rely on the carbanion stabilizing capacity of certain functional groups. Although umpolung chemistry (acyl anion chemistry) is a promising field in synthetic organic chemistry, syntheses of acyl anion precursors are not economical in terms of atoms or labor. Therefore, recently impressive progress has been made in catalytic methods for the generation of these valuable umpolung entities.[8]



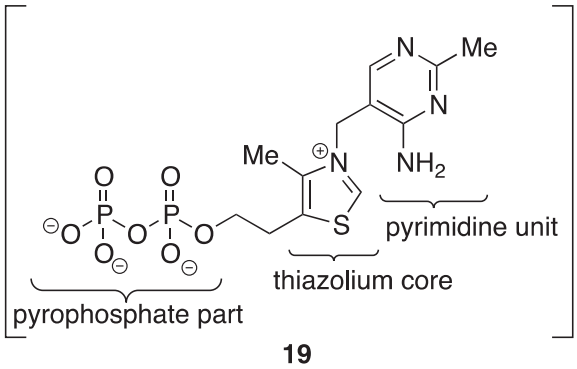
Scheme 3. Known examples of acyl anion equivalents.

Although numerous stoichiometric variants of acyl anion generation have been reported to date,[9] due to the major benefits of catalytic applications, this mini-review concerns the development of catalytic umpolung methods for C-C bond formation. With this in mind, the catalytically generated acyl anion equivalents (d^1 synthons) will be the main topic for the remaining part of this mini-review.

2. Enzyme catalyzed umpolung reactions

The biocatalytic methods that use enzymes have received great attention and been used in various C-C bond-forming reactions. Numerous enzymes such as acetohydroxyacid synthase (AHAS), benzoylformate decarboxylase (BFD), and benzaldehyde lyase (BAL) catalyze both nucleophilic acylation and benzoin condensation reactions under mild reaction conditions via an umpolung on the carbonyl carbon in order to form an acyl anion equivalent synthon. A cofactor thiamine pyrophosphate (TPP) **19** facilitates the catalytic function of these enzymes (Figure 1).

A cofactor TPP facilitates the catalytic function of these enzymes and is mainly involved in a diverse array of C-C bond-forming reactions. Each unit of TPP, as given in Figure 1, has a crucial role in enzymatic catalysis.[10] It was stated by Ukai in 1943 that thiazolium salts have the ability to catalyze benzoin reaction.[11] Mizuhara later revealed that the thiazolium unit of thiamine is responsible for the catalytic activity of TPP.[12] The function of TPP is similar to that of the cyanide ion in benzoin condensation. Based on this, a mechanistic model for thiazolium salt catalyzed benzoin condensation was proposed by Breslow in 1958.[13]



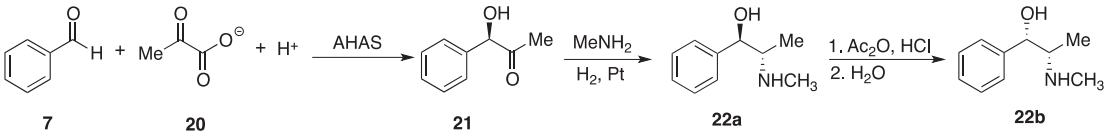
19

Figure 1. Thiamine pyrophosphate structure.

This part of our review covers recent and relevant developments in the field of C-C bond-forming reactions catalyzed by TPP-dependent enzymes.

2.1. Acetohydroxyacid synthase (AHAS)

Acetohydroxyacid synthase (EC 2.2.1.6), a TPP-dependent enzyme, is a noteworthy enzyme in particular from the industrial point of view since it catalyzes the synthesis of (*R*)-phenylacetylcarbinol ((*R*)-PAC) **21**, which is a crucial intermediate in the production of ephedrine **22a** and pseudoephedrine **22b** (Scheme 4).[14] AHAS also has the ability to catalyze the first common step in the pathway for the biosynthesis of branched-chain amino acids.[15]

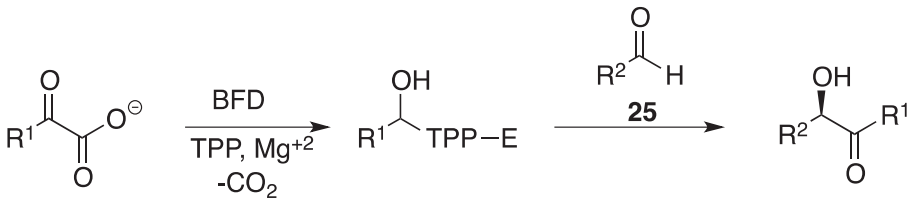


7 **20** **21** **22a** **22b**

Scheme 4. AHAS catalyzed acyloin condensation and synthesis of ephedrine and pseudoephedrine.

2.2. Benzoylformate decarboxylase (BFD)

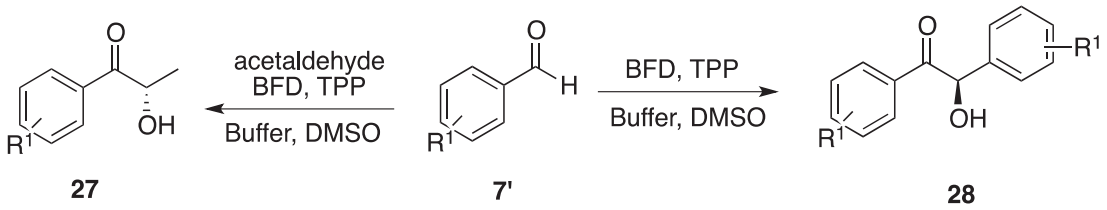
Benzoylformate decarboxylase from *Pseudomonas putida* (EC 4.1.1.7) is a well-studied TPP dependent enzyme.[16] The carboligase activity of BFD was first introduced by Wilcoks et al. in 1992 and was described as an effective catalyst for the conversions of benzoylformates **23** to acyloin compounds **26** (Scheme 5).[17] Since then, BFD has been used as an efficient catalyst for the enantioselective production of α-hydroxy ketones.



23 **24** **26**

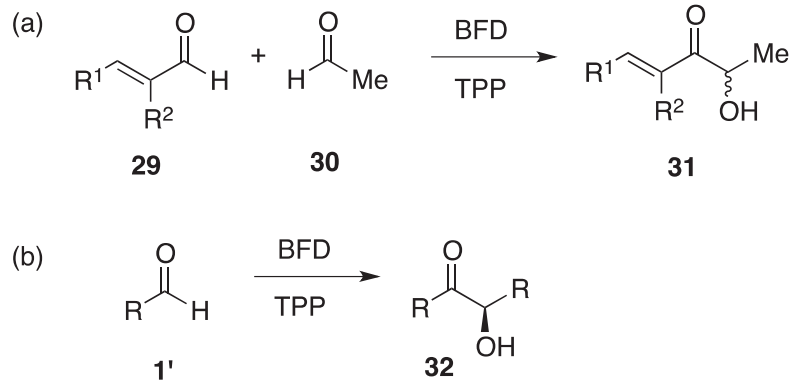
Scheme 5. BFD catalyzed synthesis of α-hydroxy ketones from benzoyl formates.

Demir et al. introduced the first example of the enzyme catalyzed synthesis of enantiomerically pure (*R*)-benzoin and substituted benzoin derivatives from aromatic aldehydes via BFD catalyzed C-C bond formation (Scheme 6).[18]



Scheme 6. BFD catalyzed synthesis of symmetrical and unsymmetrical acyloins.

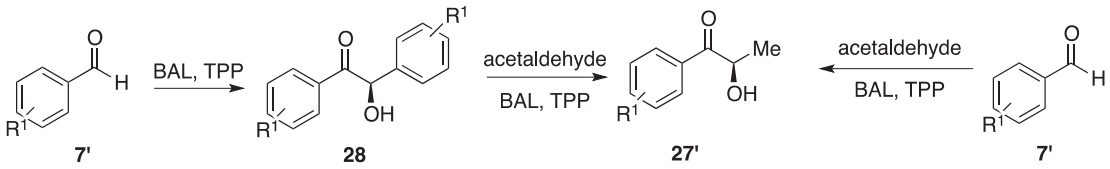
Müller later showed that BFD is also an efficient catalyst for the asymmetric ligation of aliphatic and α, β- unsaturated aldehydes (Scheme 7).[19]



Scheme 7. Asymmetric ligation of aliphatic and α,β- unsaturated aldehydes.

2.3. Benzaldehyde lyase (BAL)

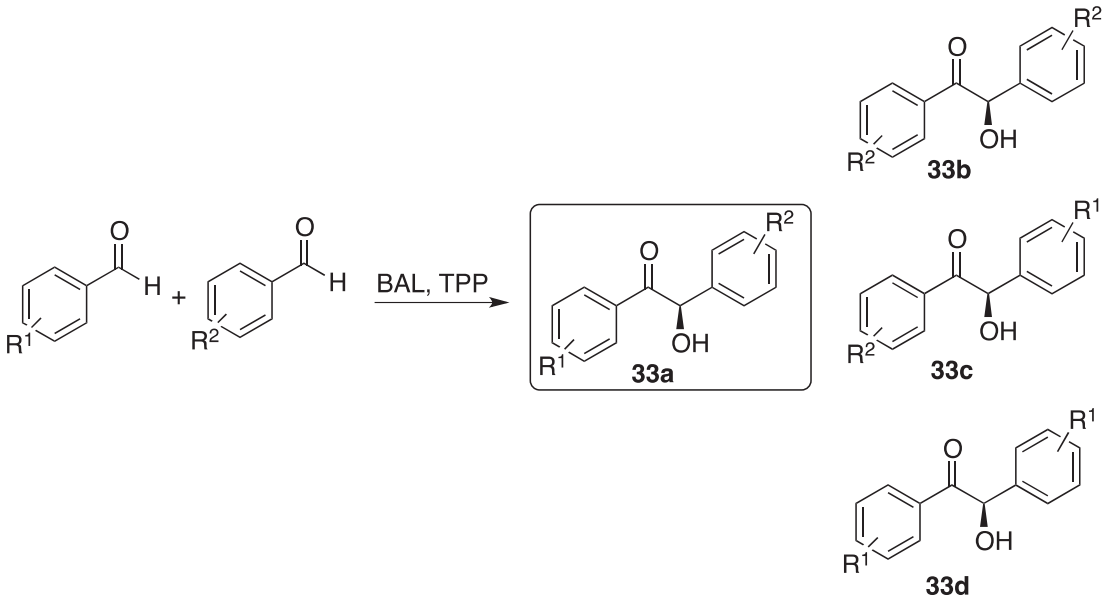
Benzaldehyde lyase (EC 4.1.2.38) from *Pseudomonas florescens* Biovar I is a rather important class of enzymes that catalyzes various important reactions, including C-C bond formations.[20] BAL catalyzed enantioselective formation of (R)- and (S)-benzoin and (R)-2-hydroxypropiophenone derivatives **27′** via C-C bond formation and C-C bond cleavage was first reported by Demir et al. in 2001 (Scheme 8).[21]



Scheme 8. BAL catalyzed acyloin condensations.

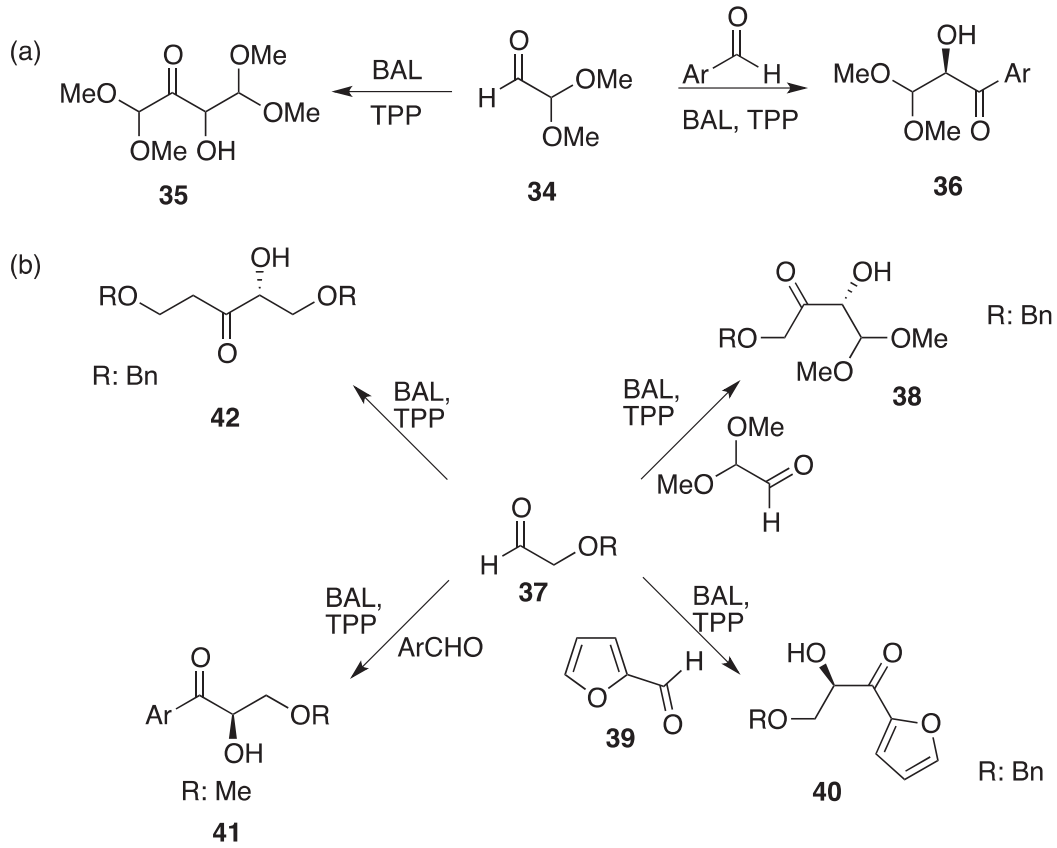
Demir et al. studied the synthetic potential of BAL regarding its ability to catalyze C-C bond formation on a preparative scale for the synthesis of enantiomerically pure 2-hydroxy ketones.[21] As shown in Scheme 8, various symmetric benzoin derivatives **28** were synthesized via BAL catalyzed self-condensation reactions.

BAL catalyzed benzoin condensation has been reported to provide cross benzoin products **33a** from a carefully selected pair of benzaldehyde (Scheme 9).[22] This variant requires a halogen in the *ortho* position of the acceptor aldehyde, but a range of substitution patterns is possible for the donor aldehyde. Although this is the first example for the enantioselective cross benzoin condensation reaction in the literature, it actually seems not to be a proper donor aldehyde–acceptor aldehyde concept; rather it is the preference of the enzyme to accept *ortho* substituted aldehydes as acceptors.



Scheme 9. Selective crossed benzoin condensation.

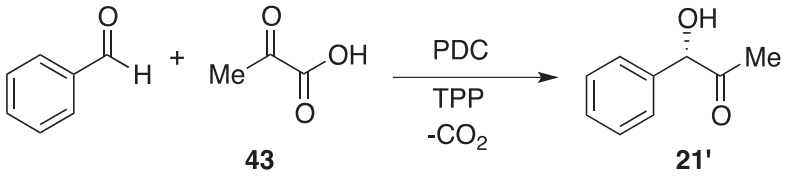
Scheme 10 shows BAL catalyzed self- and cross-acyloin condensation reactions with functionalized aliphatic aldehydes, which have been studied extensively by Demir et al.[23]



Scheme 10. Selected examples for acyloin condesations of α-functionalized acetaldehydes.

2.4. Pyruvate decarboxylase (PDC)

Pyruvate decarboxylase (EC 4.1.1.1) is a key enzyme in the glycolytic pathway and ethanol fermentation. It catalyzes the nonoxidative decarboxylation of pyruvic acid to acetaldehyde. The catalytic activity of PDC for C-C bond formations was perfectly reasonable to make at the time of Neuberg's work in 1921.[24] Since then, PDC has been evaluated for use in various carboligation reactions such as the synthesis of PAC, as shown in Scheme 11.[25] Two main reactions are catalyzed by TPP dependent PDC, namely decarboxylation and carboligation.



Scheme 11. Synthesis of (*S*)-phenylacetylcarbinol.

3. N-Heterocyclic carbene (NHC) catalyzed umpolung reactions

The nature of coenzyme thiamine catalyzed biochemical processes as nucleophilic acylations inspires organic chemists to construct practical and easily accessible acyl anion precursors engaging in catalytic C-C bond forming reactions. Ukai and co-workers reported in 1943 that thiazolium salts **44** could catalyze benzoin condensation.[11] In 1958, Breslow suggested a mechanism for thiazolium salt catalyzed benzoin condensation (Scheme 12).[13]

According to the proposed mechanism, deprotonating of thiazolium salt **44** gives the resulting ylide **45** (in equilibrium with the singlet carbene **46**), which attacks the carbonyl group of the benzaldehyde. Rearrangement of the intermediate **47** to **48** creates an umpolung of the carbonyl group. This umpolung enables the formation of the new C-C bond. The carbanion (d^1-synthon) **48** attacks a new aldehyde to form **49** in stereoselective fashion. A proton shift triggers a detachment of the acyloin **12**.

Explanation of the mechanism of thiazolium salt catalyzed acyloin condensation has opened an avenue for a series of investigations for new nucleophilic carbene based catalysts (Figure 2).[26]

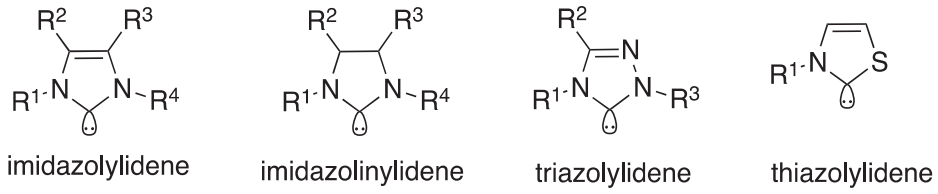
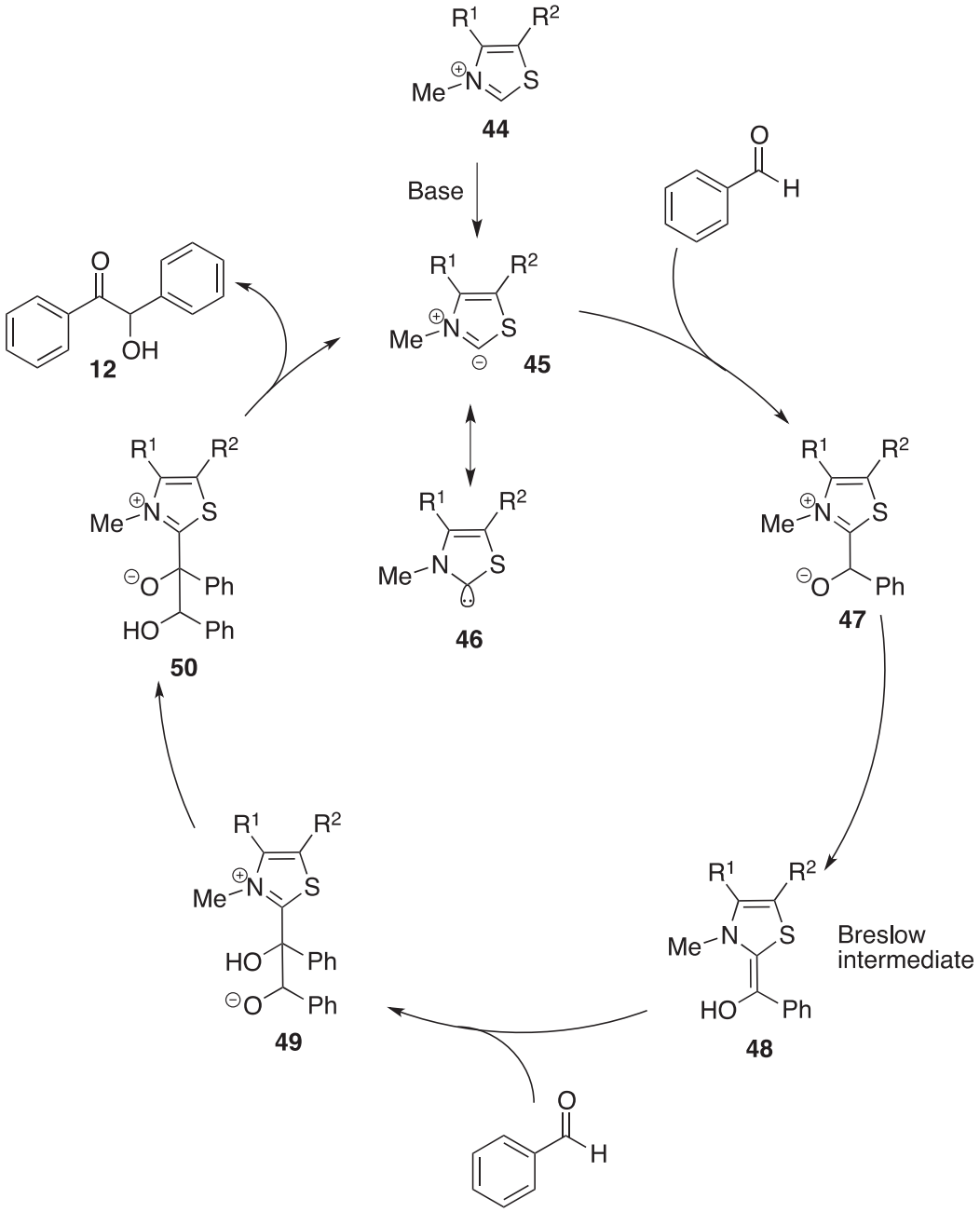


Figure 2. General structures of NHC organocatalysts.

In this section, we give a general overview of the NHC catalyzed umpolung reactions with various electrophiles.

3.1. C=O electrophiles

The use of heteroazolium salts in their deprotonated carbenes form as catalyst for umpolung reactions has always attracted researchers interested in the construction of bifunctional targets. Benzoin condensation was always at the center of these umpolung strategies. Since the inspiration of these studies originated from nature's C-C bond forming reactions utilizing thiazolium salts as cofactor, the prevalent chirality of the products possessed by the natural transformations was always an important aspect.



Scheme 12. Catalytic cycle of thiazolium salt catalyzed benzoin condensation.

In 1966, Sheehan and Hunneman reported the first asymmetric benzoin condensation employing the chiral thiazolium salt **51** as the catalyst precursor.[27] Yet the enantiomeric excess of the benzoin product was as low as 22%. Nearly 7 years later, the same research group was able to obtain enantiomeric excesses of up to 52% with thiazolium salts such as **52** (Figure 3).[28]

A breakthrough in this field came in 2002, when Enders et al. discovered triazolium-derived NHCs catalyzed highly enantioselective intermolecular benzoin condensation reactions (Scheme 13).[30]

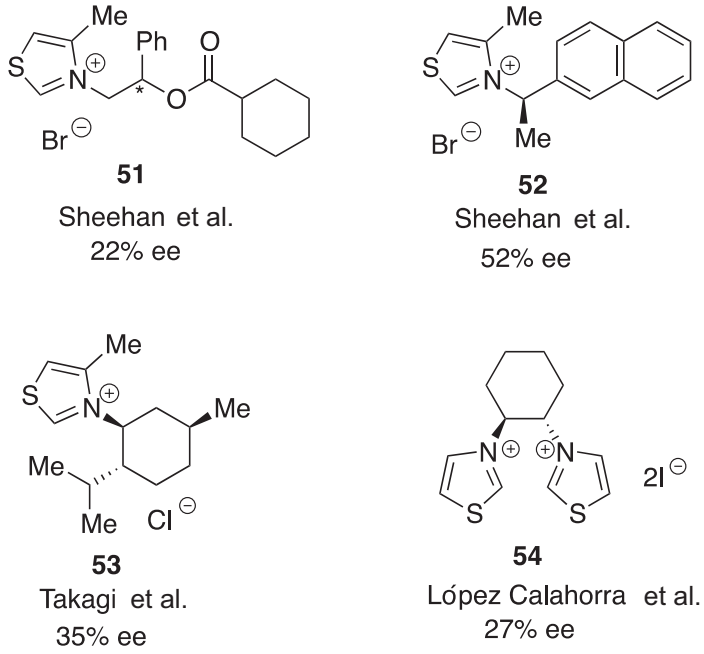
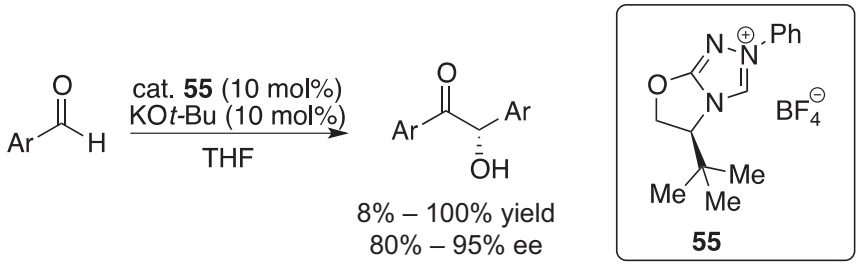


Figure 3. A literature selection of thiazolium salts used in benzoin condensation of benzaldehyde.[28,29]

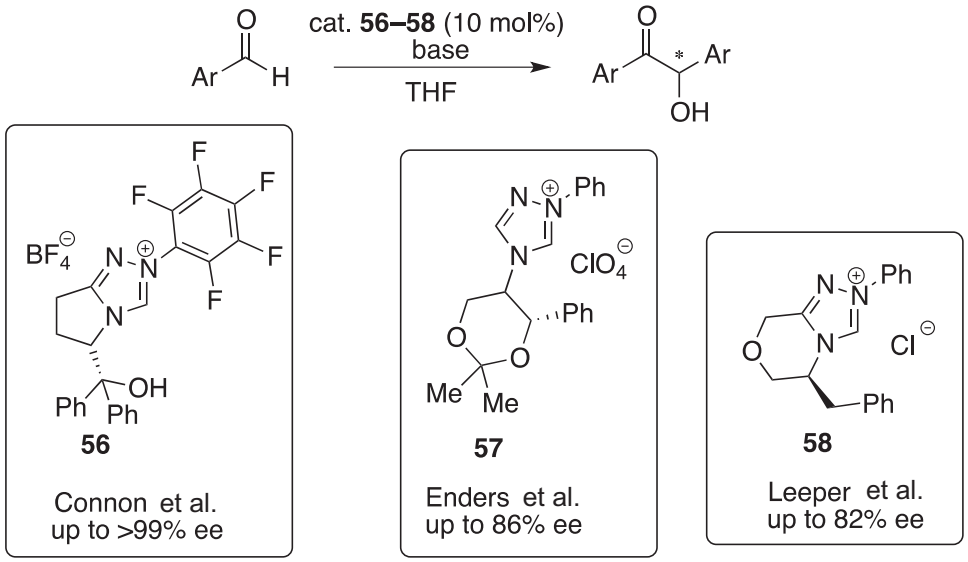


Scheme 13. Enantioselective benzoin condensation catalyzed by triazolium salt **55**.

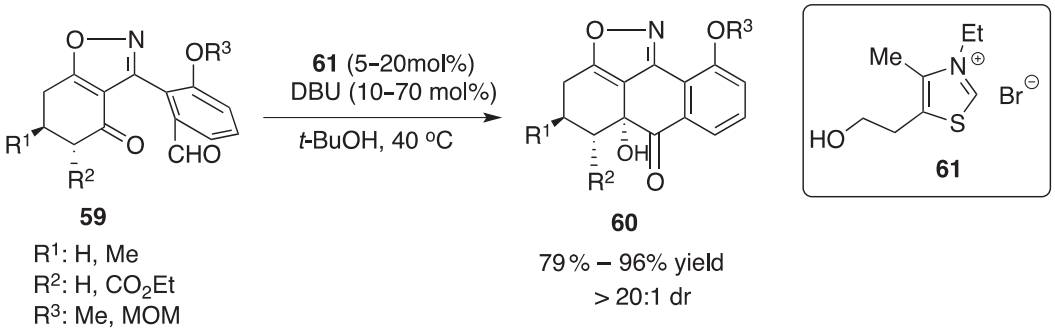
Inspired by these initial studies, great efforts have been devoted to the design and synthesis of novel chiral NHCs that catalyze benzoin condensation reactions more selectively. The most remarkable chiral NHCs, **56**–**58**, are shown in Scheme 14.[31]

Considering the difficulties with the cross benzoin condensation demanding the regioselective coupling of 2 different aldehydes, it is not unexpected that there is no catalytic method for the intermolecular crossed aldehyde-ketone benzoin reactions. However, in 2003, Suzuki and co-workers conducted the first intramolecular crossed aldehyde-ketone benzoin reactions catalyzed by thiazolium bromide **61** in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in the course of a well-designed natural product synthesis (Scheme 15).[32] This is the first catalytic chemical aldehyde–ketone coupling process reported.

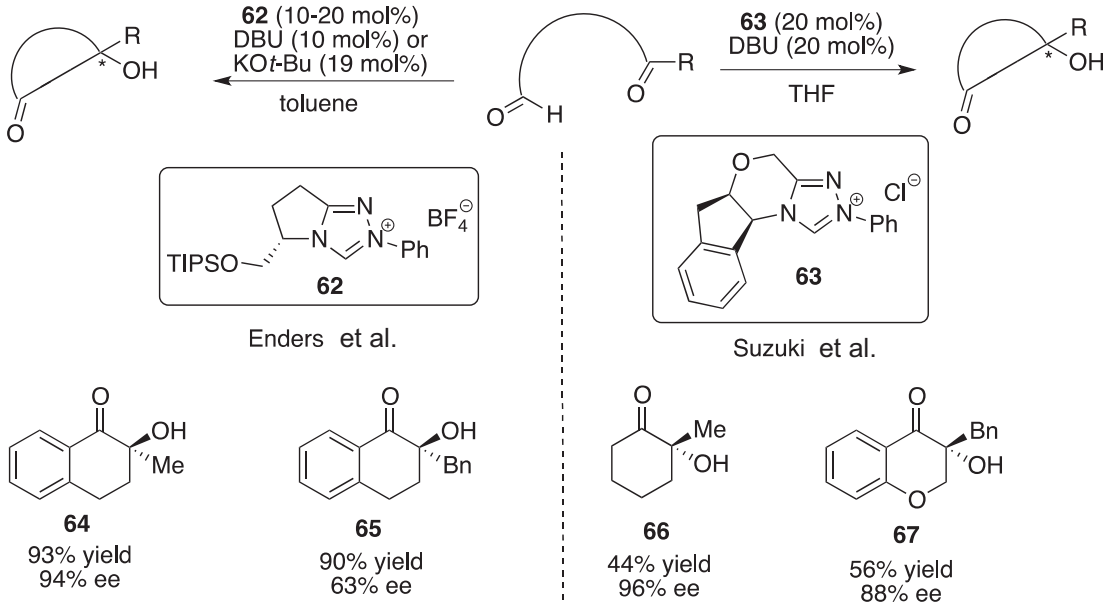
The breakthrough that ketones can serve as electrophiles for intramolecular benzoin-type processes opens a door to new ways for the expansion of catalytic, stereoselective acyloin reactions. Independently, the Enders[33a] and Suzuki[33b] groups reported that a wide variety of 5- and 6-membered chiral cyclic acyloins can be obtained by employing commercially available thiazolium salts **62** and **63** as precatalysts (Scheme 16).



Scheme 14. Selected examples of chiral triazolium salts for enantioselective benzoin reaction.

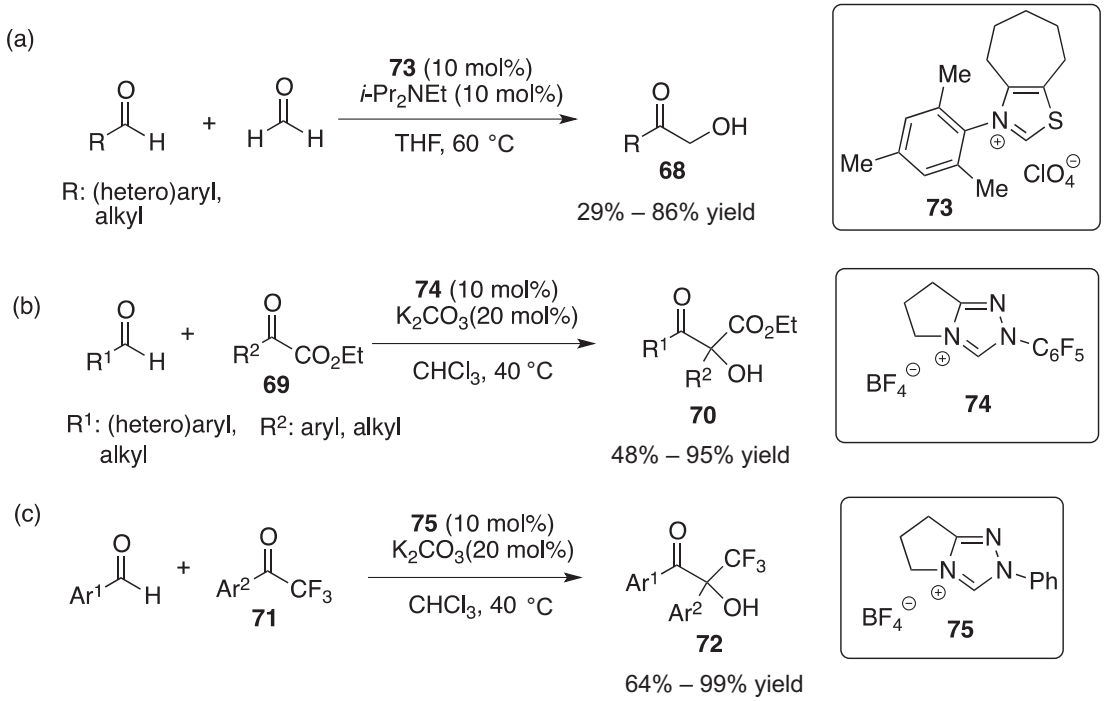


Scheme 15. Intramolecular aldehyde-ketone benzoin coupling.



Scheme 16. Asymmetric intramolecular aldehyde–ketone benzoin coupling.

Intramolecular ketone–aldehyde benzoin condensation has inspired chemists to use new electrophiles bearing C=O bond acceptor components; see Scheme 17.[34]

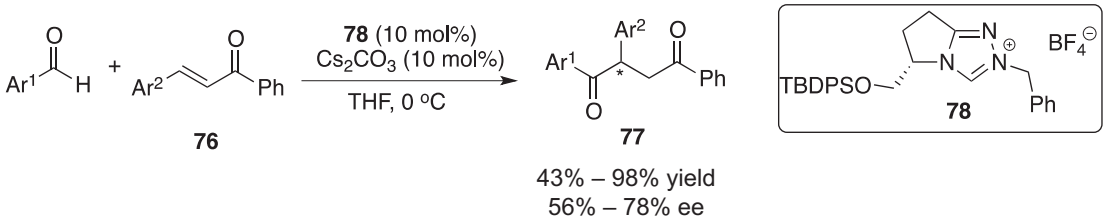


Scheme 17. Popular examples of selective cross-benzoin condensations.

3.2. C=C electrophiles (C-C multiple bonds)

Regarding the nucleophilic nature of *N*-heterocyclic carbenes, they have been enriching the synthetic organic toolbox with various powerful methods, exclusively for the synthesis of C-C bonds. As already mentioned, there are numerous literature precedents for general coupling reactions of acyl anion equivalents generated from *N*-heterocyclic carbenes with sp^2 electrophiles. One of the prominent examples of umpolung methods is the conjugate addition of acyl anion equivalents generated from *N*-heterocyclic carbenes to electrophilic alkenes, known as the Stetter reaction.

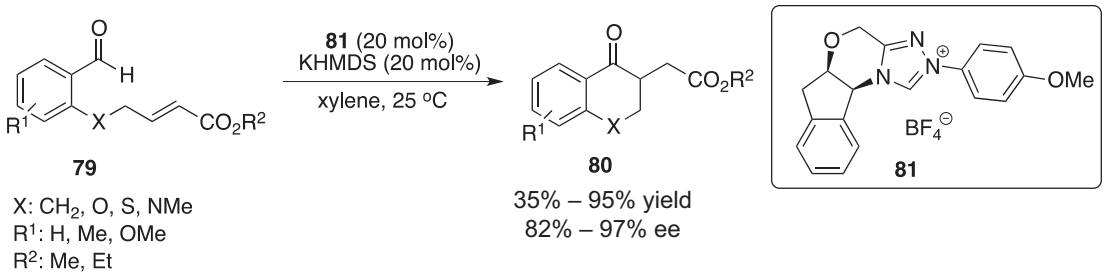
The Enders group has achieved the first asymmetric intermolecular Stetter reaction (Scheme 18).[35] It was catalyzed by a novel triazolium salt **78** derived NHC, leading to 1,4-diketones **77** in moderate to excellent yield (49%–98%) and with moderate to good enantioselectivities (56%–78%).



Scheme 18. Asymmetric intermolecular Stetter reaction.

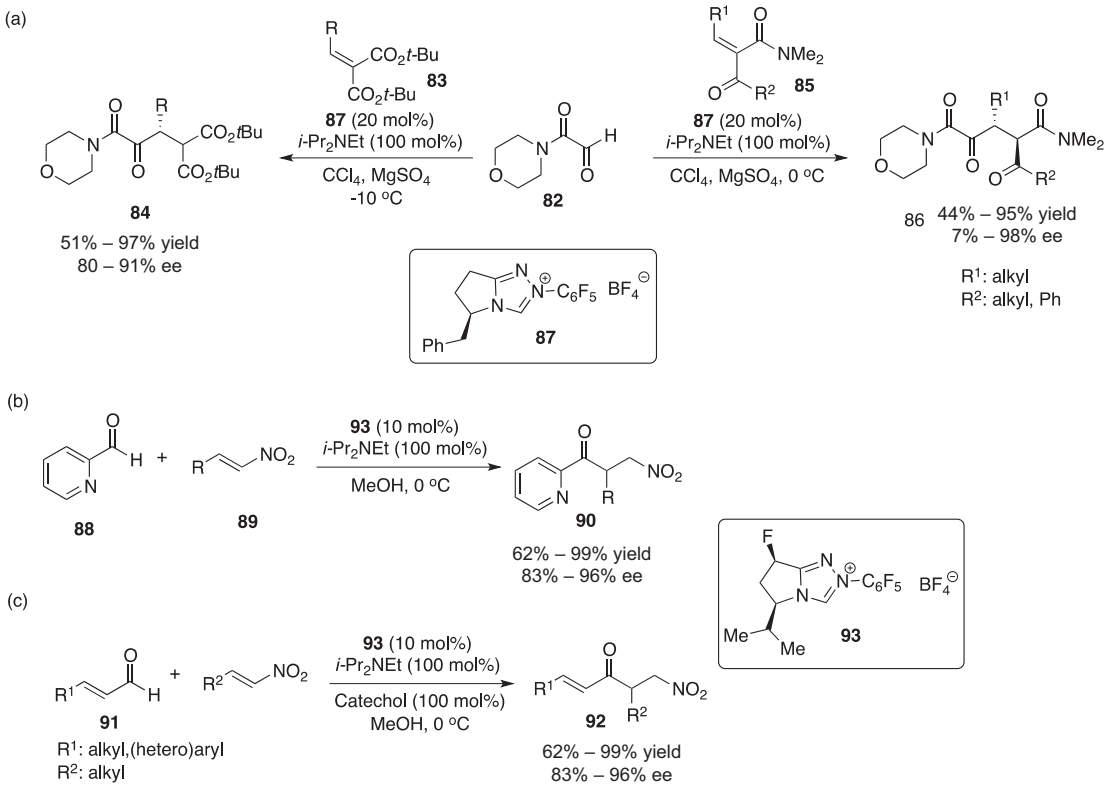
Inspired by this early key study, Rovis and co-workers established the benchmark for enantiocontrol in intramolecular Stetter reactions.[36] As shown in Scheme 19, triazolium carbene catalyst **81** derived from

aminoindanol afforded the annulated products **80** with high enantioselectivity (82%–97% ee) and chemical yield (35%–95%).



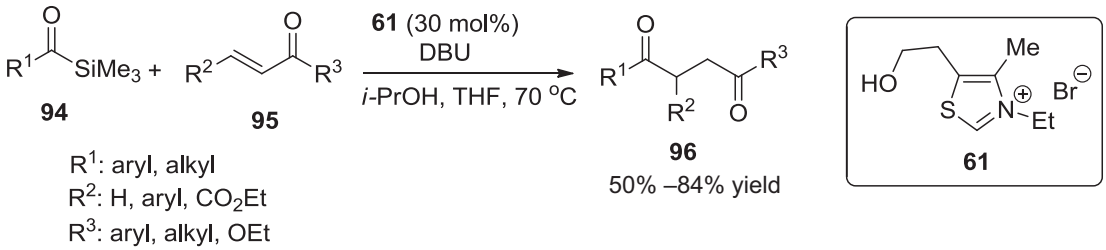
Scheme 19. Asymmetric intramolecular Stetter reaction.

Under the light of these initial findings, the Rovis group has recently reported several examples of triazolylidene carbene catalyzed asymmetric intermolecular Stetter reactions (Scheme 20).[37]



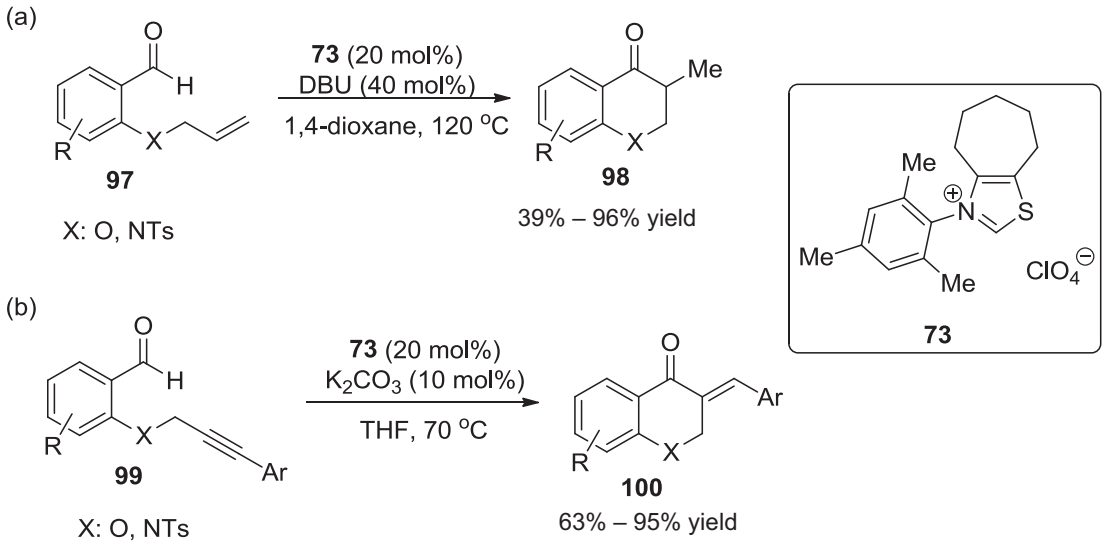
Scheme 20. Selected examples of asymmetric intermolecular Stetter reactions by the Rovis group.

Intermolecular Stetter reactions are significantly limited by the high reactivity of the donor aldehyde, which results in large amounts of self-condensation or benzoin products. This fact hampers the reaction's utility in intermolecular fashion. To bypass this problem, a thiazolium-catalyzed Sila–Stetter reaction has been reported by Scheidt, in which acyl anion equivalents generated from acylsilanes **94** selectively react with the Michael acceptors in an intermolecular fashion to provide 1,4-dicarbonyl products **96** (Scheme 21).[38]



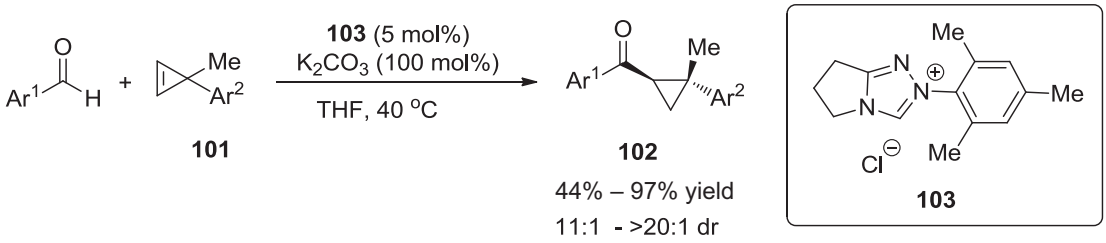
Scheme 21. Thiazolium salt-catalyzed Sila–Stetter reaction.

Recently, the Glorius group reported that *N*-heterocyclic carbenes were shown to powerfully promote the addition of aldehydes to unactivated double bonds.[39] This is an unique example of unactivated double bonds being used as electrophiles in Stetter-type reactions (Scheme 22a). This was shortly followed by the development of NHC-catalyzed hydroacylation of unactivated alkynes to provide unsaturated ketone products **100** (Scheme 22b).[40]



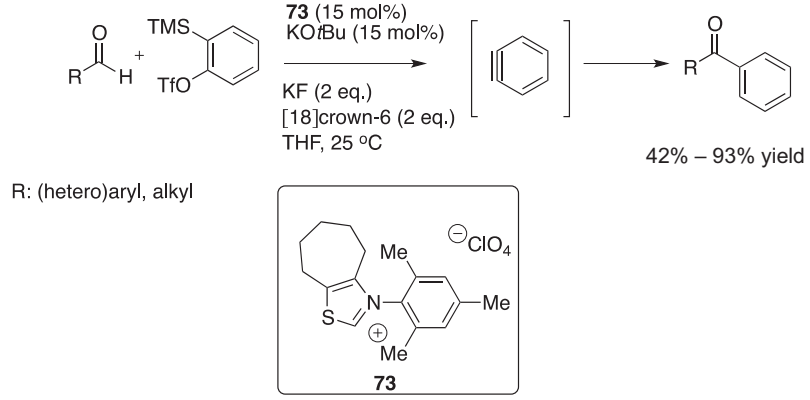
Scheme 22. Intramolecular hydroacylations of unactivated C-C multiple bonds.

To extend the scope of Michael acceptors used in Stetter-type reactions, the Glorius group also investigated cyclopropenes **101**, electron-neutral olefins, as potential electrophiles and reported NHC-catalyzed intermolecular addition of aldehydes to cyclopropenes under mild conditions (Scheme 23).[41] By this methodology, they were able to synthesize acylcyclopropanes **102** with excellent diastereocontrol.



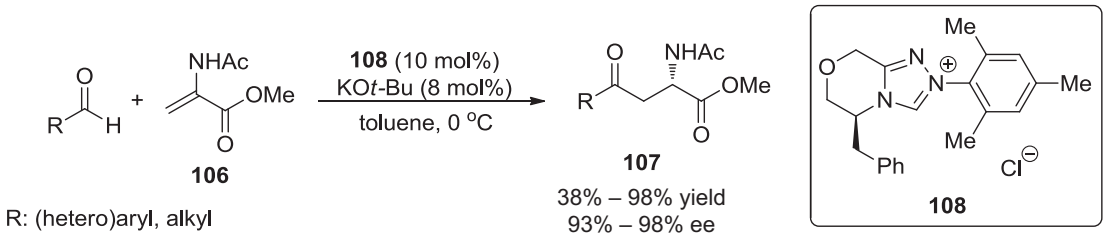
Scheme 23. Hydroacylations of cyclopropenes.

Regarding the recent success in the NHC-catalyzed intermolecular hydroacylation of unactivated alkenes and alkynes, the Glorius group anticipated that arynes, highly reactive intermediates in organic synthesis, could serve as an acceptor for acyl-anion equivalents generated from aldehydes by NHC **73**-catalyzed umpolung reactions.[42] As shown in Scheme 24, the reaction of a wide variety of aldehydes with the arynes generated in situ from 2-trimethylsilylaryl **104** resulted in the formation of the aryl ketones **105** in moderate to excellent yield.



Scheme 24. Addition of aldehydes to arynes.

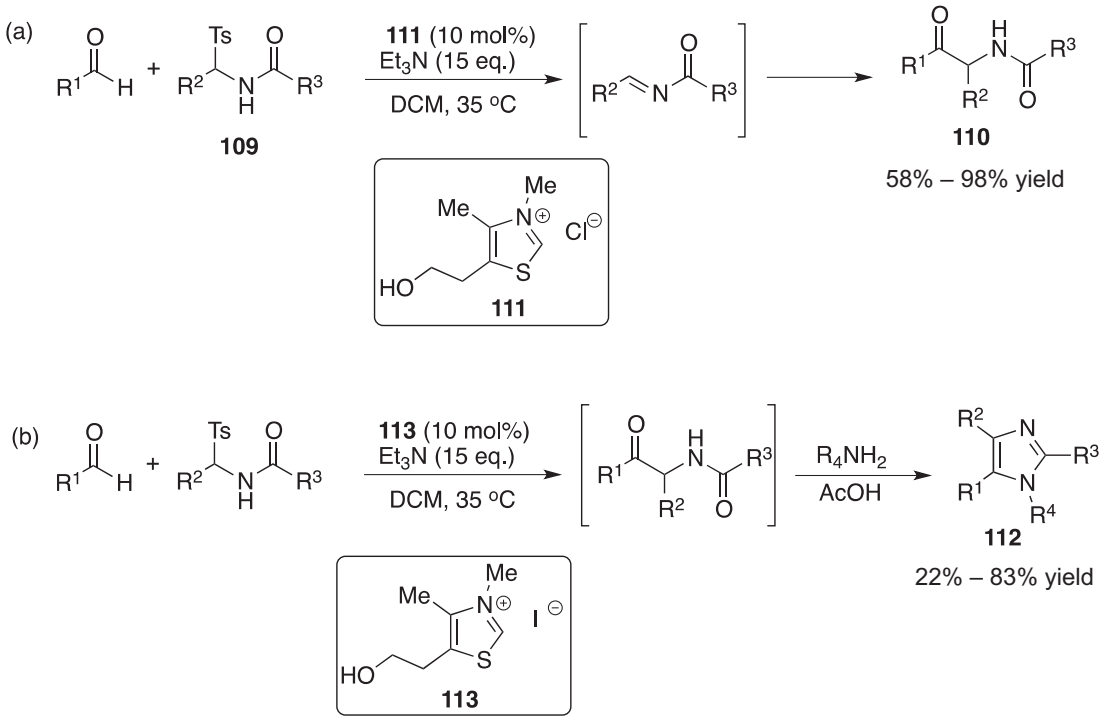
Glorius and co-workers, in a study investigating an asymmetric Stetter reaction that builds up only α-stereocenters, used N-acylamido acrylate **106** as the Michael acceptor in the synthesis of enantioenriched α-amino acid derivatives **107**.[43] As seen in Scheme 25, the mechanism has 2 important steps; the C-C bond formation between the Breslow intermediate and the Michael acceptor as well as an asymmetric protonation are efficiently merged.



Scheme 25. Synthesis of α-amino acid derivatives via an intermolecular Stetter reaction.

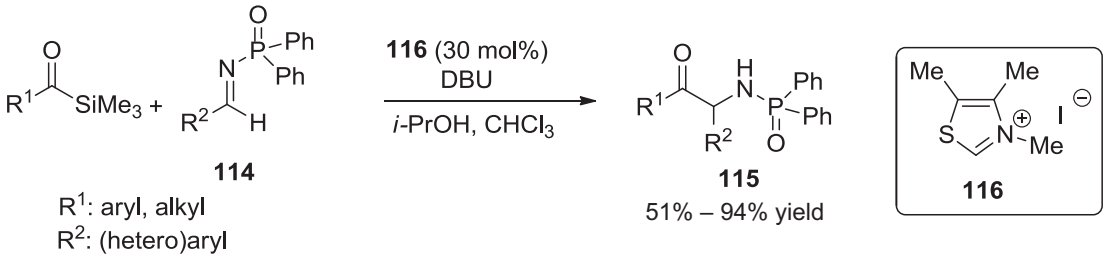
3.3. C=N and other electrophiles

The use of thiazolium-catalyzed reactions to prepare valuable compounds that are the result of an acyl-anion addition reaction has shown general and practical utility in synthetic organic chemistry. The thiazolium-catalyzed acyl anion additions of aldehydes to acyl imines have been much less considered. Murry et al. reported the synthesis of α-amido ketones **110** in a cross-coupling reaction of aldehydes and acyl imine precursor **109**, catalyzed by the thiazolium salts **111** (Scheme 26a).[44a] The acylimine, generated in situ from an aryl sulfonamide **109**, functions as the Michael acceptor. Although not enantioselective, this significant reaction introduced the versatility of the nucleophilic carbenes in the synthesis of valuable targets. Following the same strategy, the Murry group developed a methodology for the synthesis of substituted imidazoles **112** (Scheme 26b).[44b]



Scheme 26. Additions of aldehydes to acyl imines catalyzed by thiazolium salts.

Scheidt and co-workers described a similar strategy for the NHC-catalyzed addition reactions of acylsilanes to readily available imines **114**, which led to an efficient synthesis of valuable α-amino ketones **115** (Scheme 27).[45]

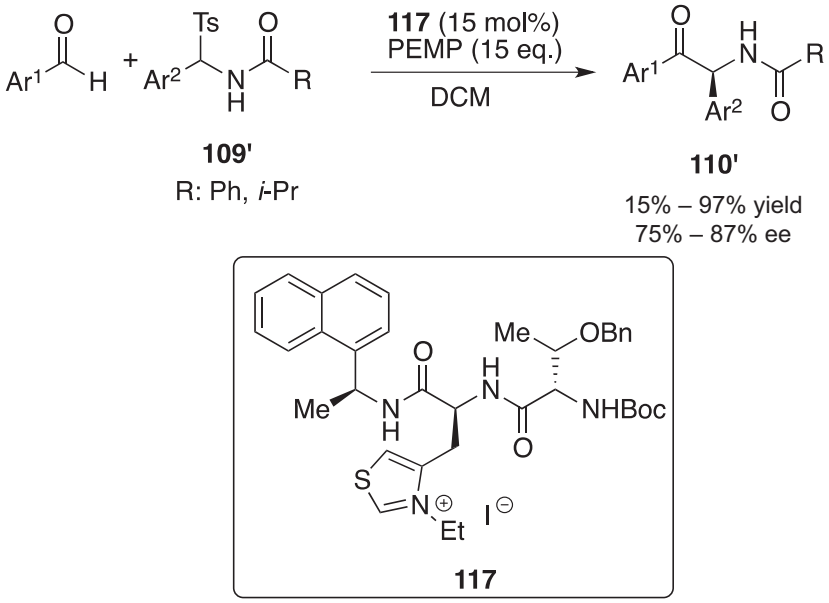


Scheme 27. NHCs catalyzed addition reactions of acylsilanes to imines.

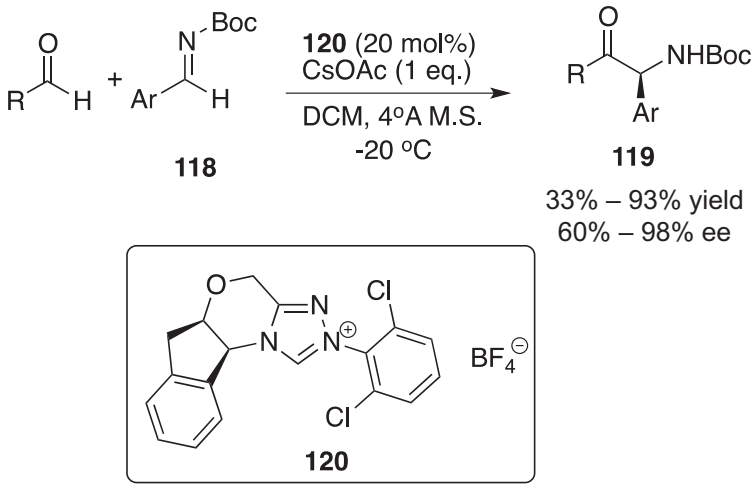
In 2005, Miller and co-workers reported an asymmetric version of cross-aza-benzoin reactions catalyzed by peptide-derived thiazolium salt **117** (Scheme 28).[46] The mechanism of the asymmetric catalysis was explained by the possibility of a bifunctional mechanism. It was thought that covalent catalysis occurs in a chiral pocket that benefits from simultaneous activation of the acyl anion equivalent derived from the aldehyde, with H-bond activation of the N-acylimine component derived from the sulfinamide precursor **109′**.

More recently, a highly enantioselective catalytic asymmetric cross-aza-benzoin reaction of aliphatic aldehydes with *N*-Boc-protected imines **118** was developed by the Rovis group (Scheme 29).[47]

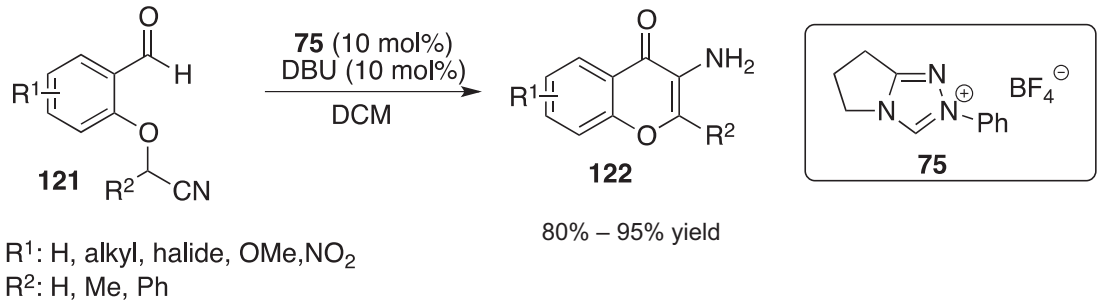
The Liu group, as shown in Scheme 30, launched the synthesis of 3-aminochromones **122** via NHC-catalyzed intramolecular aldehyde-nitrile cross coupling reaction.[48] This methodology is likely the first example of a C-C construction between sp^2 carbon (aldehyde) and sp carbon (nitrile).



Scheme 28. Enantioselective cross-aza-benzoin reactions catalyzed by peptide-derived thiazolium salt.



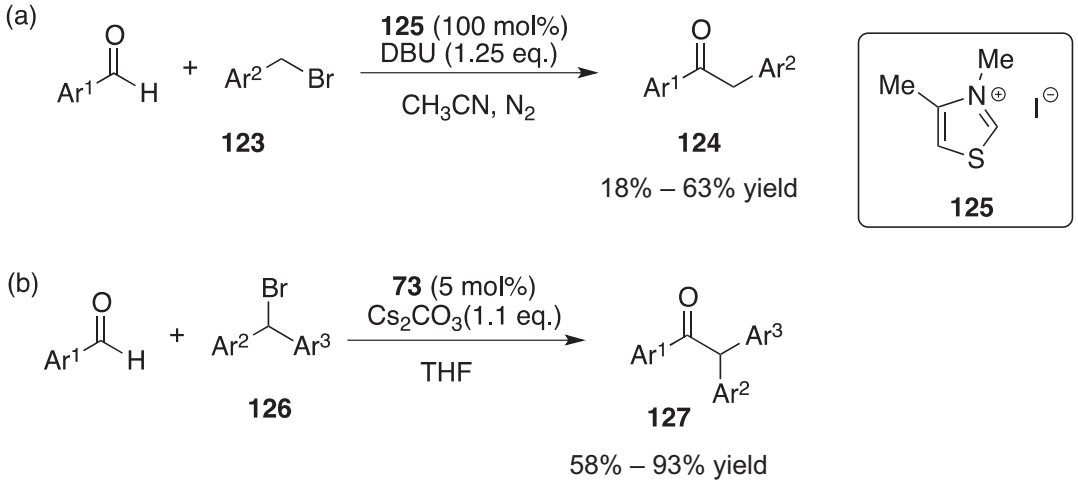
Scheme 29. Enantioselective cross-aza-benzoin reactions of aliphatic aldehydes with *N*-Boc-protected imines.



Scheme 30. Intramolecular additions of aldehydes to nitriles.

As mentioned above, the NHC-catalyzed C-C bond construction reactions, such as benzoin condensation, aza-benzoin condensation, Stetter reaction, and intramolecular nucleophilic addition of carbonyl anion, have

drawn considerable attention. Another type of umpolung reaction is the nucleophilic substitution towards the carbon–halogen bonds. The major breakthrough came from a finding by the Deng group that benzyl halides **123** (C-heteroatom bonds) could act as an electrophile in NHC-mediated intermolecular nucleophilic acylation of aromatic aldehydes (Scheme 31a).[49] Shortly after, Glorius and co-workers reported the NHC-catalyzed alkylation reaction of aldehydes via the umpolung of aldehydes (Scheme 31b).[50]



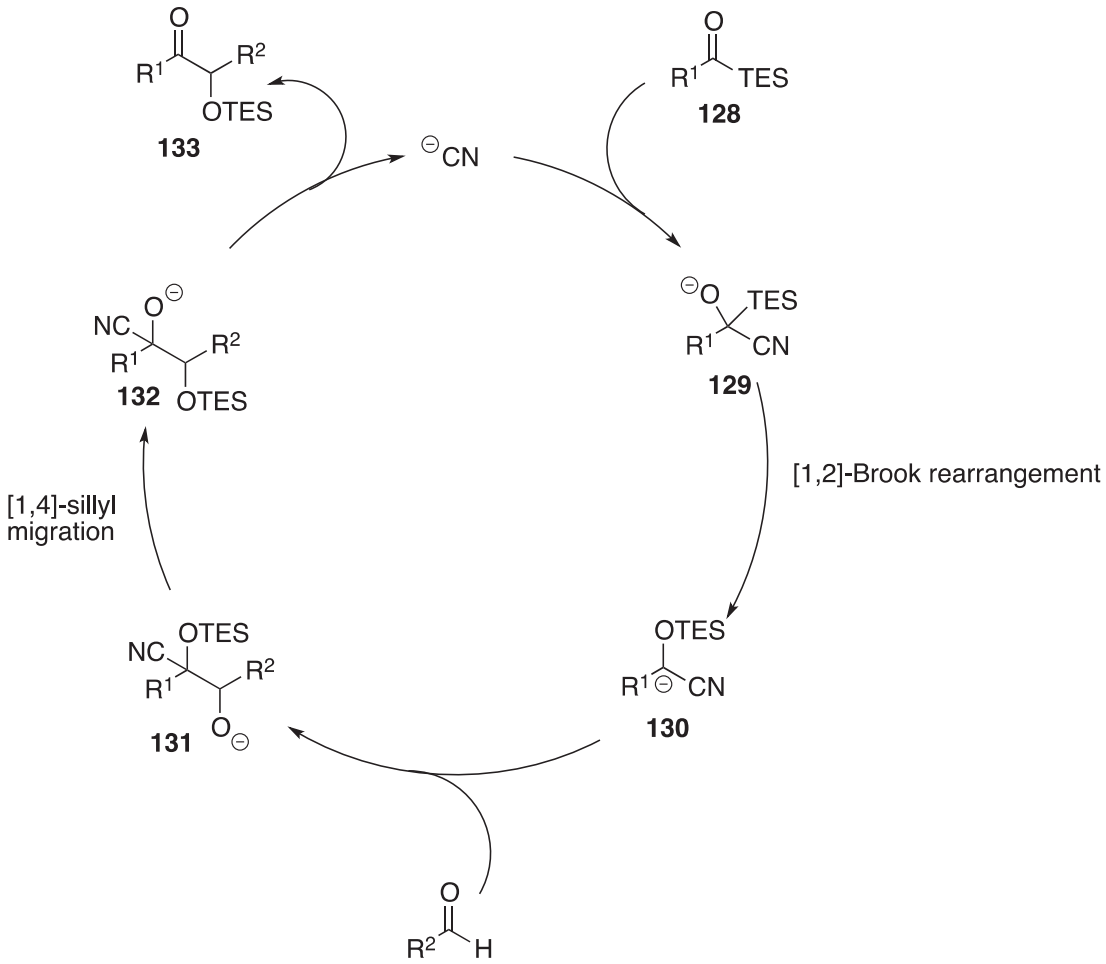
Scheme 31. Alkylation reactions of aldehydes via the umpolung strategy.

4. Cyanide ion catalyzed umpolung reactions

Even though the benzoin reaction has been part of the toolbox of organic chemistry for a long time, employment of this reaction in complex organic synthesis has been restricted due to its inherent drawbacks. Nevertheless, the nature of the benzoin reaction inspires organic chemists to construct practical and easily accessible acyl anion precursors engaging in catalytic C-C bond-forming reactions.

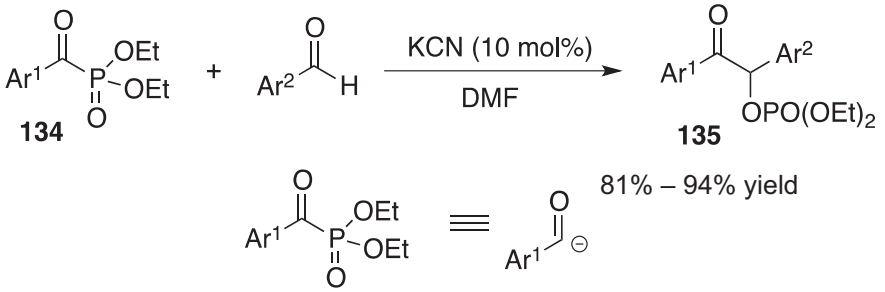
Recently, cyanide ion promoted silyl benzoin reactions have been reported in which acylsilanes **128** generate acyl anion equivalents that selectively react with the aldehydes in an intermolecular fashion to provide unsymmetrical silyl ether protected benzoin compounds like **133** with good regioselectivity.[51] As shown in Scheme 32, the proposed mechanism of the reaction is basically the same as the classical benzoin condensation catalyzed by the cyanide ion. The cross silyl benzoin reaction relies on the generation of an acyl anion equivalent **130** by addition of cyanide to an acylsilane **128** followed by [1,2]-Brook rearrangement. On the other hand, Johnson later demonstrated that the counter ion (M^+) in MCN catalysis is highly critical, and that one lanthanum tricyanide ($La(CN)_3$) was identified as the optimal catalysts after screening of various metal cyanides.[52]

Acyl silanes are not only useful acyl anion precursors but also good catalysts to achieve regioselective benzoin-type products in one step. Nowadays, cyanide-catalyzed silyl benzoin reactions play a prominent and practical role in cross-benzoin condensation reactions. It is a well-established method utilizing catalytic generation of acyl anion equivalents. Nevertheless, the major limitation of the acylsilane chemistry is its complexity and the difficult availability of the starting acylsilanes.[53]



Scheme 32. Synthesis of unsymmetrically protected benzoin compounds regioselectively.

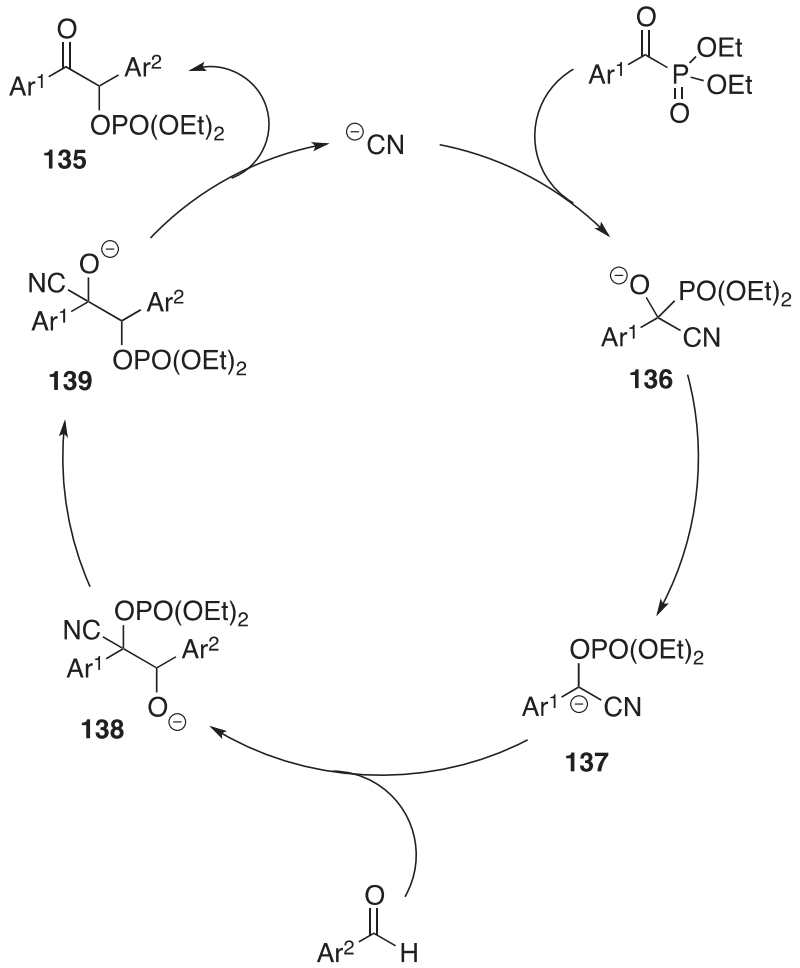
Demir et al. have reported that acylphosphonates **134** are new generation of potent acyl anion precursors. These precursors undergo nucleophile-promoted phosphonate phosphate rearrangement to afford the corresponding acyl anion equivalents as reactive intermediates (Scheme 33).[54]



Scheme 33. Synthesis of protected crossed benzoin derivatives from acylphosphonates and aldehydes.

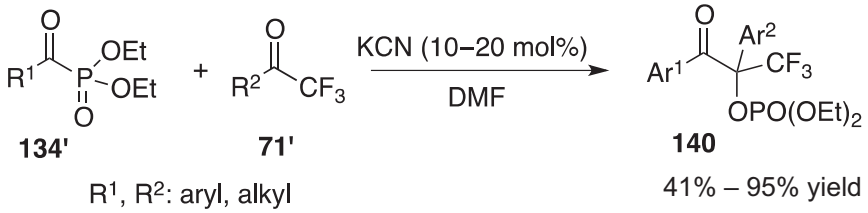
The proposed mechanism, shown in Scheme 34, resembles the benzoin reaction mechanism and its congeners. Cyanide ion promoted rearrangement affords the critical acyl anion equivalent **137**, which reacts with aldehyde to give the intermediate adduct **138**. This adduct undergoes a [1,4]-*O*,*O*-phosphate migration, leading

to retrocyanates as usual to give the desired benzoin product **135**. This method provides a highly practical and flexible access to all isomers of cross benzoin except for R^1 = alkyl and R^2 = alkyl combination. Beside this exception, the introduced method had no drawbacks for the synthesis of cross-unsymmetrical benzoins.



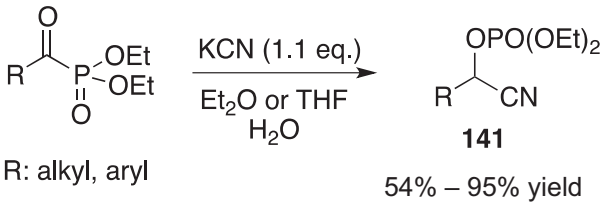
Scheme 34. Mechanism of cross-benzoin reaction of acyl anions from acylphosphonates.

One of the challenges in this area (organic synthesis) is the aldehyde–ketone acyloin reaction due to the low electrophilic and enolizable nature of ketones. Intermolecular catalyzed addition of aldehydes to ketones has not been reported so far and remains a challenging reaction. Although catalyzed intramolecular coupling reactions of aldehydes and ketones have been studied,[32] corresponding intermolecular catalytic couplings remained unsolved until recent examples from the Demir research group. In their study, the first catalytic intermolecular aldehyde–ketone coupling via acylphosphonate was developed (Scheme 35).[55] They studied the reaction of benzoylphosphonates **134′** with potent electrophile 2,2,2-trifluoroacetophenones **71′**, which provided the expected aldehyde–ketone coupling products **140**. The proposed mechanism proceeds through similar steps with the cross-benzoin reactions that are mediated with acylsilanes and acylphosphonates. Independently, in the same year, the Johnson group reported that lanthanum tricyanide efficiently catalyzes a benzoin-type coupling between acyl silanes and ketones.[56] The reaction works well for a number of aryl-alkyl and alkyl-alkyl ketones, greatly expands the scope of suitable ketones that can engage in benzoin-type reactions with acyl anion equivalents, and is operationally simple to perform.



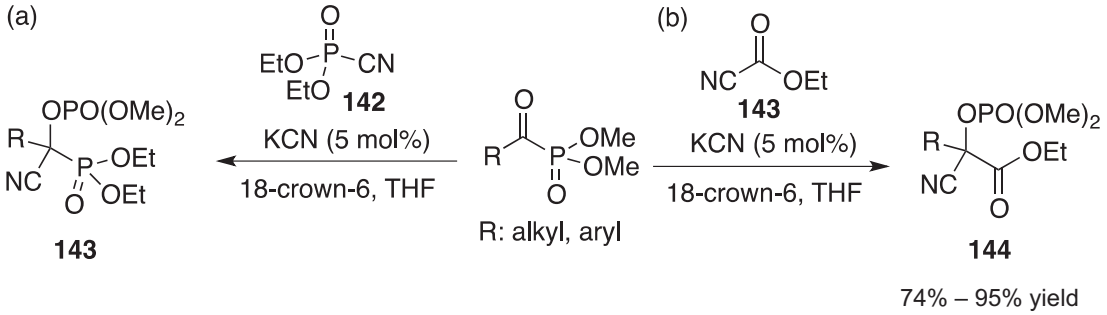
Scheme 35. Catalytic intermolecular aldehyde–ketone couplings.

Demir et al. showed that protonation of acyl anion equivalents **137** from acylphosphonates provided cyanohydrin *O*-phosphates in high yields (Scheme 36).[57] The acylphosphonates react with the cyanide ion in DMF, resulting in acyl anion intermediate **137**. Protonation of **137** leads to cyanohydrin *O*-phosphates **141**, which is equivalent to an aldehyde under the appropriate hydrolysis conditions. This study seems to be an example for the direct reduction of carboxylic acids to aldehydes under aqueous conditions.



Scheme 36. Protonation of acyl anion equivalents.

Based on these initial studies, the Demir group extended the "acyl anion concept" to include other classes of electrophiles, as shown in Scheme 37.[58,59]



Scheme 37. Cyanide ion promoted addition of acyl phosphonates to (a) diethylcyanophosphonate **142** and (b) ethyl cyanoformate **143**.

It has long been known that cyanide ion catalyzes the cleavage of benzil to benzaldehyde and the ester of benzoic acid.[60] Later, Kwart and Beavsky investigated the mechanism and kinetics of the reaction, and demonstrated the highly nucleophilic intermediacy of **146** (Figure 4).[61] Although **146** could be generated efficiently under aprotic conditions, utilizing it to obtain unsymmetrical benzoin has only been exemplified with furfural and it was not well developed or understood whether it is useful for unsymmetrical benzoin synthesis. Finally, Demir and co-workers focused on understanding the nature of **146** and its derivatives together with its possible utilization for the synthesis of unsymmetrical benzoin.[62]

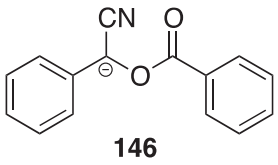
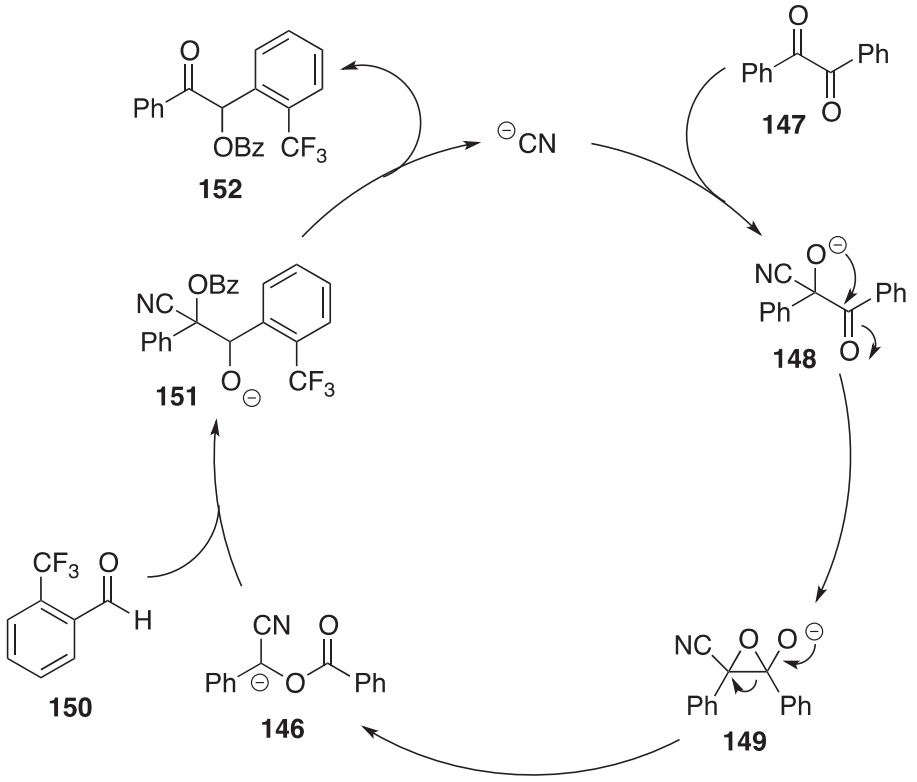


Figure 4. Acyl anion equivalent generated from benzil and cyanide ion.

In their research, the Demir group treated a solution of benzil **147** and a potentially competent electrophile, 2-trifluoromethylbenzaldehyde **150**, in DMF with KCN for the synthesis of unsymmetrical benzoins. Product of benzoyl protected form of cross benzoin **152** was obtained as expected, in agreement with the mechanisms proposed by Kuebrich et al., as shown in Scheme 38.



Scheme 38. Mechanism of cross-benzoin reaction of benzil and *o*-trifluoromethyl benzaldehyde.

5. Conclusions and outlook

In this mini-review article we have highlighted the umpolung strategy, accepted as a powerful alternative synthetic approach to traditional C-C bond forming methods. In this regard, the article has mainly involved the investigations of catalytic methods in acyl anion equivalents' generations in the history of organic synthesis from benzoin condensation discovered in 1832 to the present day. We have tried to detail the advances in 3 major fields, comprising enzyme, *N*-heterocyclic carbene (NHC), and cyanide ion catalyzed umpolung reactions. Some of the issues still need to be addressed. We hope that this mini-review will be of interest to the scientific community and will result in further research to address some of the challenges in the future.

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