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REVIEW
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Advancements in *N*-heterocyclic carbenes (NHCs) catalysis for benzoin reactions: A comprehensive review from past to present

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Abstract

N-heterocyclic carbenes (NHCs) catalyze benzoin condensation, which is a unique carbon-carbon bond-forming reaction. It entails a coupling reaction between two aldehydes catalyzed by NHCs that produce α-hydroxycarbonyl compounds (acyloins). NHCs have emerged as a potent class of organocatalysts, catalyzing numerous benzoin and benzoin-type reactions. This review provides an overview of the historical development of NHCs and their application in benzoin reactions. Additionally, recent advancements in NHC catalysis, including the use of chiral NHCs, are discussed. This review aims to provide a comprehensive understanding of the current state of NHC catalysis for benzoin reactions and its potential for future developments in synthetic chemistry.

Keywords

acyloin
α-aminocarbonyl compound
benzoin condensation
α-hydroxycarbonyl compound
N-heterocyclic carbene
organocatalysis

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Key findings

- NHCs have emerged as highly stable and reactive catalysts in benzoin reactions due to their ability to activate substrates, form stable intermediates, and accelerate reaction rates.
- The development of chiral NHCs has shown promising results in enantioselective synthesis.
- This review provides a comprehensive and up-to-date understanding of the current state of NHC catalysis for benzoin reactions.

1. Introduction

N-Heterocyclic carbenes (NHCs) are an indispensable class of ligands for transition-metal catalysis due to their resemblance to and superiority over ubiquitous phosphine ligands [1–4]. In addition to their function as ligands, the NHCs serve a crucial role as organocatalysts in a variety of reactions [1, 5–7]. The use of NHCs as organocatalysts has been expanded to include reactions such as the nucleophilic acylation of aryl fluorides [8] and benzylic halides [9, 10], in addition to the well-known benzoin condensation [11–15] and Stetter reaction [16–20]. Figure 1 depicts the most common forms of NHCs.

The most prevalent method for producing NHCs is the deprotonation of imidazolium, triazolium, or thiazolium salts. Depending on the pKa of the salt, free carbenes are typically generated using a base such as triethylamine or potassium *t*-butoxide [10].

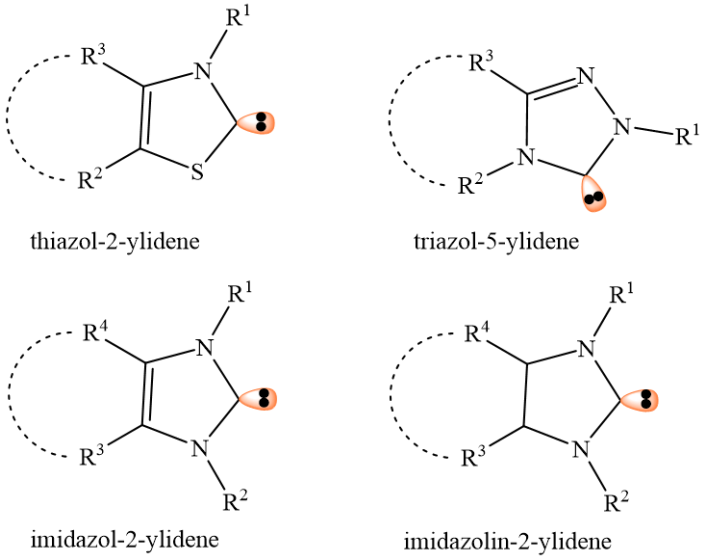


Figure 1 General types of *N*-heterocyclic carbenes (NHCs).

The benzoin condensation (BC) is a coupling reaction between two aldehydes that produces α-hydroxycarbonyl compounds, also known as acyloins. The first methods were only suitable for the conversion of aromatic aldehydes and were developed for classical organic synthesis using cyanide ions. Seventy years after its discovery, however, a thiazolium ion-mediated process (under basic conditions) was developed and reported in the literature [21]. Until now, it has been used with other types of NHCs, including thiazolium, triazolium, and imidazolium catalysts, as shown in Scheme 1.

α-Hydroxycarbonyl compounds, such as benzoin or 2-hydroxy-1,2-diphenylethanone, are essential chemical intermediates. They and have been extensively used as photosensitizers for photosensitive resins, gravure inks, and photocurable coatings, as well as catalysts for the production of polyesters [22–24]. Moreover, one of the most important applications of benzoin is in the synthesis of the antiepileptic drug phenytoin, which suppresses systemic epilepsy and has a positive effect on partial epilepsy [25, 26]. The majority of methods for the preparation of phenytoin involve the oxidation of benzoin to benzil (1,2-diphenyl-1,2-ethanedione or dibenzoyl; $(PhCO)_2$) and the cyclization of benzil with urea, with ethanol and glacial acetic acid serving as solvents in the general procedure. Recently, novel methods for the synthesis of phenytoin, such as liquid-phase heterogeneous synthesis and mechanochemistry, have been developed [27–32].

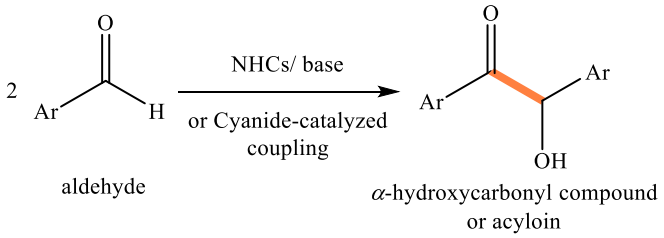
In the following sections, we present in-depth discussions of the numerous types of benzoin condensation catalyzed by NHCs. Various organocatalytic reactions utilizing NHC-derived catalysts have found widespread application as homo-, cross-, and aza-benzoin reactions. This review focuses on advances in benzoin reactions involving NHCs and provides a concise history of research on the biological catalysis of different NHCs in benzoin condensation.

2. Review

2.1. Homo-benzoin condensation

2.1.1. Homo-benzoin condensation Catalyzed by *N*-heterocyclic carbenes

Now, we will explore the development of various benzoin reactions catalyzed by NHCs from the past to the present. In fact, the benzoin reaction involves the umpolung of aldehydes under cyanide ion or *N*-heterocyclic carbene (NHC) catalysis, followed by their capture with the carbon-oxygen double bonds of aldehydes acceptors.

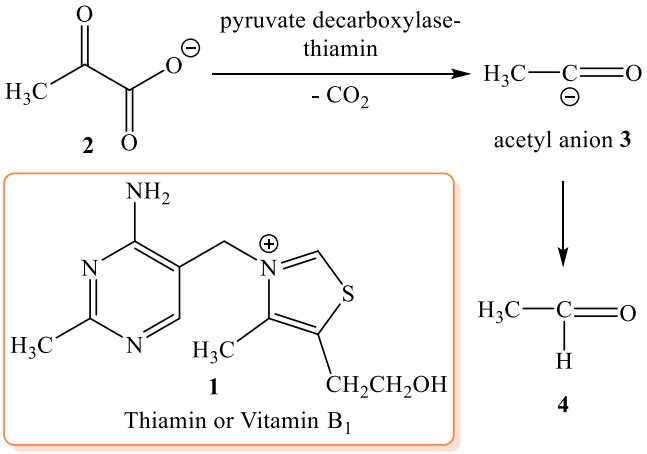


Scheme 1 Benzoin condensation using *N*-heterocyclic carbenes (NHCs) and cyanide as a catalyst.

Although thiamin NHC-catalyzed synthetic reactions appear to be relatively new in organic chemistry and biochemistry, their significance was first recognized during the study of the East Asian vitamin B1 deficiency disease 'kakke' or 'beriberi'. Thiamine (**1**) is a 1,3-thiazolium salt found in rice brans; its diphosphate functions as a coenzyme for decarboxylation of pyruvate in glycolysis to produce acetyl anion equivalent **3**, as shown in Scheme 2. Thiamine deficiency causes nervous system disorders. Vitamin B_1 has been identified as an essential nutrient as a result of extensive efforts to combat disease. During an investigation of the mechanism of thiamin's action [33–37], its catalytic effect on the benzoin reaction was uncovered [38–40].

NHCs had been known to catalyze benzoin condensation prior to the isolation and characterization of the first stabilized carbene [13]. Vitamin B_1 (**1**), represented by its chloride salt, has been identified as a catalyst for the benzoin reaction for more than fifty years and was the first NHC organocatalyst to be discovered. Breslow disclosed in 1958 that thiazol-2-ylidene **5** produced by deprotonation of the precursor thiazolium salt was the active catalyst for the thiamine benzoin reaction [13]. Scheme 3 depicts the hypothesized catalytic cycle analogous to the cyanide-catalyzed benzoin synthesis [41].

Understanding the mechanism of subsequent NHC-catalyzed acyl anion additions is predicated on understanding the mechanism of the benzoin reaction. Aldehyde **6** is initially subjected to nucleophilic attack by NHC **5**, resulting in the formation of thiazolium salt adduct **7**, which undergoes proton transfer to produce intermediate **8**. The NHC part stabilizes the resultant carbanion by accepting electron density, thereby facilitating proton transfer. This enaminol species, **8**, also known as the "Breslow intermediate", is invoked to explain the aldehyde-induced increase in reactivity. A second equivalent of aldehyde **6** is then subjected to a nucleophilic attack by **8** to produce intermediate **9**, followed by the elimination of benzoin (**10**), and original carbene catalyst **5** is regenerated. Notably, each step in this mechanism is reversible, allowing benzoin to be used as an aldehyde source in other NHC-catalyzed reactions.



Scheme 2 Thiamin as a coenzyme for decarboxylation of pyruvate in glycolysis to afford acetyl anion **3**.

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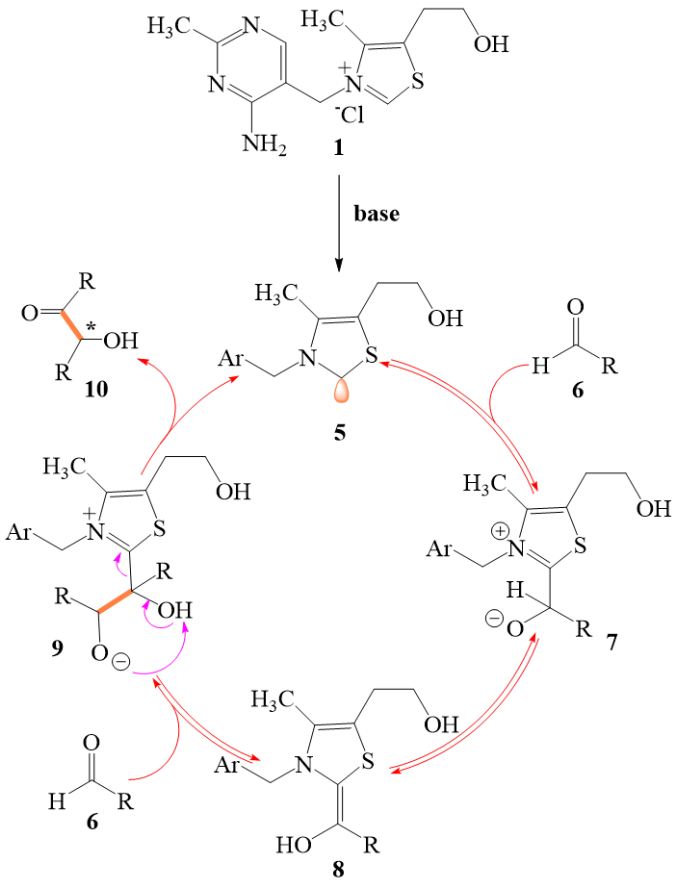

Scheme 3 Catalytic cycle of the benzoin condensation as proposed by Breslow [13].

Benzoin condensation catalyzed by thiazolium salt on a synthetically useful scale was first reported in 1976 by Stetter [42]. Later in 2005, Xu and Xia [43] reported the effective use of *N*-alkyl-substituted imidazolium carbene **11** to promote benzoin condensation. The reactions could be performed under mild conditions but required a high catalyst loading (50 mol.%). Under these conditions, it was discovered that neutral and electron-rich aromatic aldehydes afford high yields of benzoin products, whereas aliphatic aldehydes and electron-deficient aromatic aldehydes result in sluggish reaction times, as illustrated in Table 1.

In later years, Iwamoto and co-workers [44] used 20 mol.% NHC **12** as a precatalyst, which was readily available and endowed with long aliphatic side chains, to promote benzoin condensation under green conditions in an aqueous medium. The improved reactivity was attributed to the formation of micelles in an aqueous medium from the hydrophobic alkyl chains of the NHC catalyst. As shown in Table 1, the reaction with various aromatic and heteroaromatic aldehydes proceeded well, with high yields.

As reported by Seema Bag and colleagues in the same year [45], benzoin reactions have been developed under microwave irradiation using a catalytic amount of thiamine hydrochloride (**1**) (10 mol.%) from various aromatic as well as heteroaromatic aldehydes, affording appreciable yields at a very high rate, as shown in Table 1. In 2008, the same group [46] demonstrated the use of 10 mol.% bis(benzimidazolium) precursor **13** as an improved DBU catalyst for benzoin reactions in water. In this case, NHC precursor catalyst **13** incorporated a long aliphatic bridge between the two imidazolium entities. Table 1 depicts how the aggregation of these units creates a hydrophobic environment in which the two aromatic aldehydes are catalyzed to produce high yields of benzoin products.

Interestingly, *N*,*N*-dimethylbenzimidazolium iodide **14** was used in homo-benzoin reactions under green conditions, as reported by Hahnvajanawong and co-workers in 2013 [47]. The reactions could be conducted in ionic liquid, water, or solvent-free conditions with satisfactory to excellent yields of benzoin-derived products. Table 1 demonstrates that starting heteroaromatic aldehydes in water as a solvent result in extremely low yields of benzoin products. Furthermore, benzimidazolium salt **14** and NaOH employed could be efficiently recovered under all green conditions.

Later in 2014, Phungpis and coworkers [48] reported that the same benzimidazolium salt **14** acted as a catalyst in benzoin reactions involving aromatic aldehydes using the basic ionic liquid [Bmim]OH. Benzoin condensation was performed under [Bmim]OH conditions and proceeded very well with no additional hydroxide base. Using 20 mol.% of *N*,*N*-dimethylbenzimidazolium iodide **14** at 80 °C yielded benzoin products in satisfactory to good yields, as shown in Table 1. Furthermore, the recycled reaction media containing **14** can be reused several times without significant loss of efficiency.

The intermolecular homo-benzoin reaction was studied by Nicholson and colleagues [49] in 2019 using planetary milling. In a planetary mill at 300 rpm for 15 minutes, 4-chlorobenzaldehyde, precatalyst **15**, Cs_2CO_3, and sand (as a grinding auxiliary) were combined to produce homo-benzoin with an isolated yield of 72%. Extending these conditions to a limited number of substrates, however, did not always produce desirable results. Improved product yields were achieved with the addition of isopropanol (IPA) (LAG, Liquid-Assisted Grinding) (Table 1).

Morgan et al. [50] showed in 2023 that microwave heating achieves 88% yield condensation in 5 minutes while consuming only 70 watts of power. The best results were obtained using *N*,*N*′-(2,4,6-trimethylphenyl)imidazo-lium chloride (IMesHCl, **16**) as the catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base (Table 1).

2.1.2. Asymmetric homo-benzoin condensation

The development of numerous thiazolium, imidazolium, and triazolium compounds with a wide range of structural diversity has led to consistent yield and enantioselectivity improvements over the years, as a consequence of benzoin condensation products containing a stereocenter. Extensive research has shown that the most remarkable chiral catalysts are the NHCs derived from 1,2,4-triazole **17**–**19** [51–53], as indicated in Table 2.

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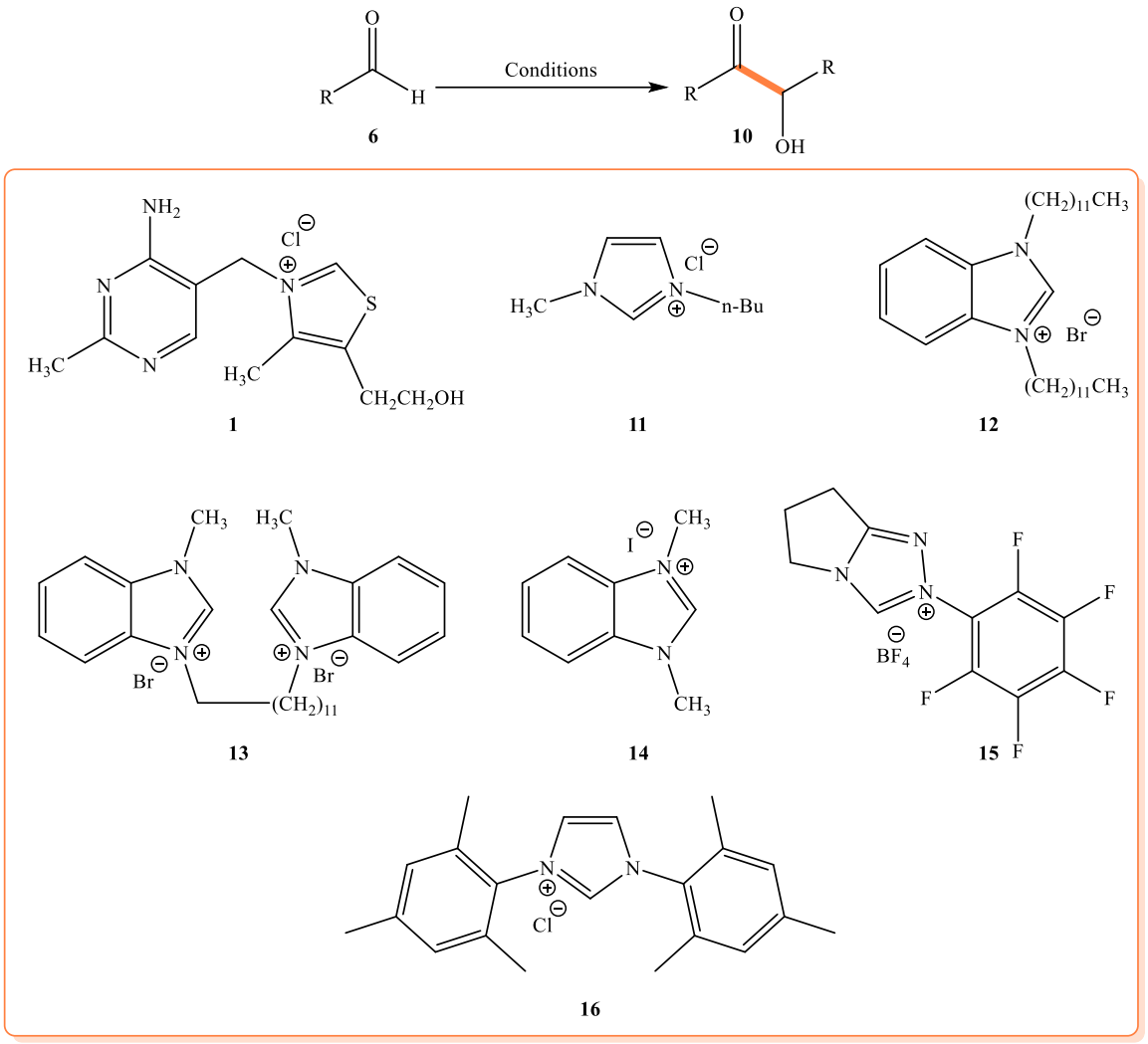

Scheme 4 Homo-benzoin condensation catalyzed by *N*-heterocyclic carbenes (NHC).

Table 1 Homo-benzoin condensation catalyzed by *N*-heterocyclic carbenes (NHC).

Entry	NHC	Base	Solvent	*T* (°C)	Time	Additional	Example	Yield (%)
1	**1** (10 mol.%)	–	PG-H_2O	–	20 s	MW (560 W)	15	Up to 82
2	**11** (50 mol.%)	K_2CO_3	CH_2Cl_2	Rt	20 h	–	5	Up to 76
3	**12** (20 mol.%)	various	H_2O	Rt	1–30 h	–	11	Up to 98
4	**13** (10 mol.%)	DBU	H_2O	Rt	1.5–20 h	–	9	Up to 97
5	**14** (10 mol.%)	NaOH	[Bmim]PF_6	80	0.5–8 h	–	4	Up to 83
			H_2O	Rt	0.5–8 h	–	4	Up to 97
			Solvent-free	80	0.5–8 h	–	4	Up to 77
6	**14** (20 mol.%)	[Bmim]OH	[Bmim]OH	80	4–8 h	–	4	Up to 87
7	**15** (10 mol.%)	Cs_2CO_3	IPA	Rt	15 min	Sand, mill (300 rpm)	6	Up to 82
8	**16** (5 mol.%)	DBU	–	–	5 min	MW (70 W)	1	88

For the reaction of asymmetric benzoin condensation reported by Inoue and co-workers in 2009 [52], they used the most effective pentafluorophenyltriazolium **17** as a catalyst and discovered that it promotes homo-coupling of benzaldehyde at a low loading (4 mol.%) to afford benzoin products with a 90% yield and >99%, as shown in Table 2.

In 2016, Rafinski [54] synthesized a series of novel spirocyclic thiazolium salts derived from the readily available and economical compounds (1*R*)-camphor and (1*S*)-fenchone. Successfully utilized in the asymmetric benzoin condensation was a catalyst derived from **20** and dicyclohexylethylamine. Moderate to outstanding yields and acceptable enantioselectivities were obtained for the acyloins (Table 2).

In 2018, Jun Yan and coworkers [55] reported the development of chiral NHC-catalyzed benzoin condensation in water using **21**. This series of transformations produces α-hydroxy ketones with excellent to high yields and enantioselectivities. Table 2 proposes water for the proton transfer in the aqueous asymmetric condensation reaction.

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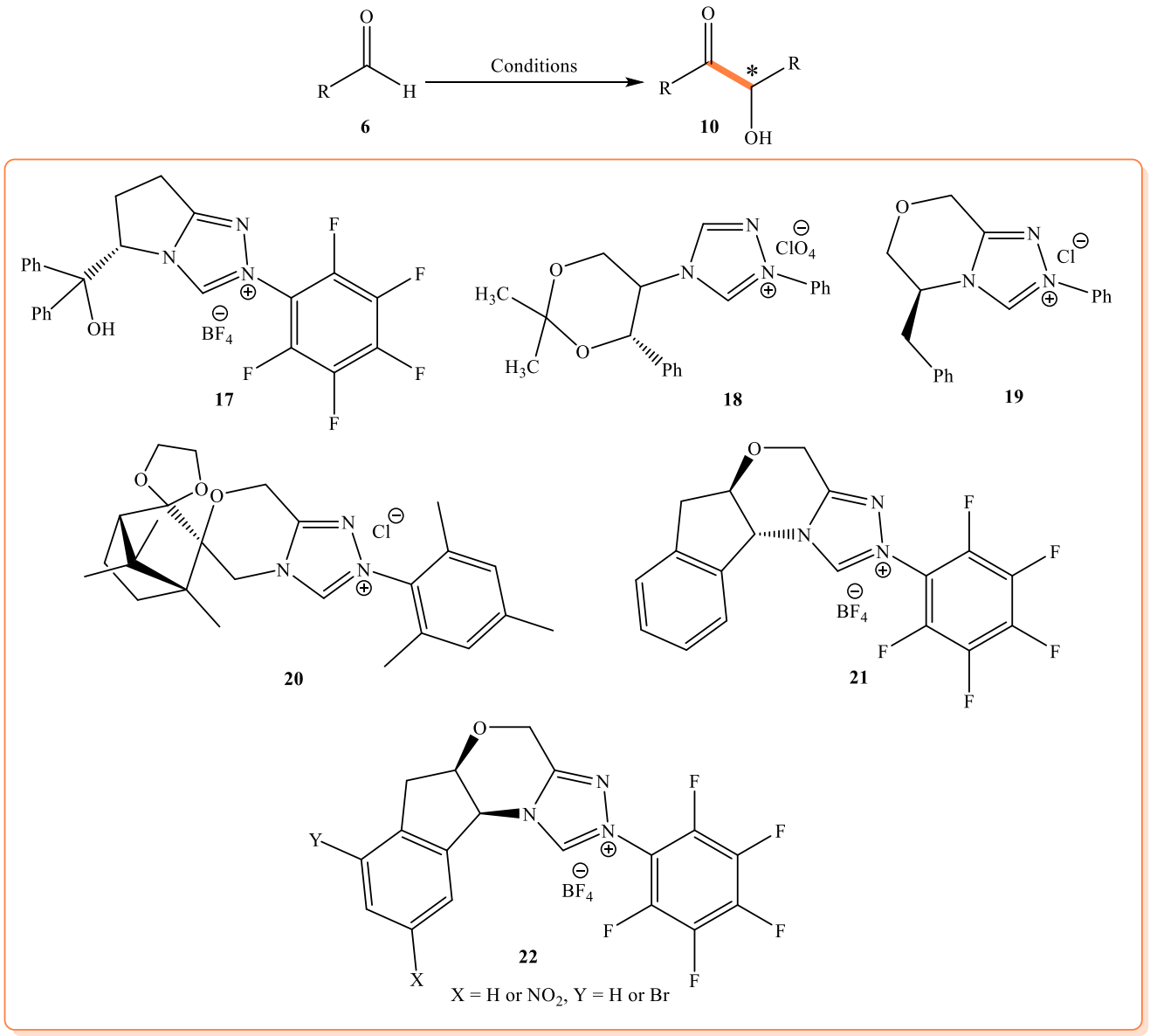

Scheme 5 Asymmetric homo-benzoin condensation.

Table 2 Asymmetric homo-benzoin condensation.

Entry	NHC	Base	Solvent	*T* (°C)	Time	Enantioselective	Example	Yield (%)
1	**17** (4–8 mol.%)	Rb_2CO_3	THF	–20–18	20 h	ee up to >99%	10	Up to 100
2	**18** (1.25 mol.%)	K_2CO_3	THF	rt	60 h	ee up to 86%	8	Up to 72
3	**19** (30 mol.%)	Et_3N	MeOH	rt	18–48 h	ee up to 82%	11	Up to 50
4	**20** (10 mol.%)	DCyEA	THF	rt	24 h	er up to 80:20	5	Up to 92
5	**21** (10 mol.%)	Na_2CO_3	H_2O	rt	vary	er up to 94:6	14	Up to 80
6	**22** (1 mol.%)	Proton sponge	$ClCH_2CH_2Cl$	0	vary	ee up to 96%	14	Up to 100

The remote electronic adjustment of NHC was shown to be effective for the catalytic asymmetric benzoin reaction in 2023 by Inokuma and coworkers [56]. The enantioselectivity of the reaction was improved at the cost of reaction rate by the NHC containing remote electron-withdrawing substituents. In addition to helping keep highly enolizable compounds from being racemized, the presence of distant electron-withdrawing substituents was also useful. Table 2 displays the product yields achieved utilizing NHC **22**.

2.1.3. Polymer-supported *N*-heterocyclic carbenes

Polymer-supported *N*-heterocyclic carbene units that operate as catalytic active species towards NHC-organocatalyzed processes, such as benzoin condensation, were reported in two publications by Garmendia and coworkers in the same year (Scheme 4). After 24 hours and five consecutive catalytic cycles, conversions of benzoin from benzaldehyde utilizing gel-type copolymeric platform **24** were in the range of 65% to 70% [57]. Good

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conversions (70%) were sustained for up to three catalytic cycles in folding single-chain nanoparticles (SCNPs) **25** used in benzoin condensation. Furthermore, the conversions could be improved by as much as 85% when using a 1 mol.% catalyst [58].

In the benzoin condensation of furfural, hybrid catalysts exhibited varying degrees of stability, as reported by Miletto and colleagues in 2022 [59]. The NHC catalyst was composed of a benzimidazole covalently affixed to a variety of mesoporous and hierarchical supports. Anchoring catalyst **28** on the greatest pore of Davisil silica (150 Å) enables the quantitative conversion of furfural, and the hybrid catalyst can be recycled and reused multiple times (Scheme 6).

Polymerization of 2,5-diformylfuran by NHC catalysts results in short oligomers with a low degradation temperature and no visible crystallinity, as demonstrated by Ruelens and colleagues in the same year [60]. The molar mass of polymers is significantly affected by catalyst structure and polymerization time. When NHC **31** was used, a 91% product yield was achieved (Scheme 6).

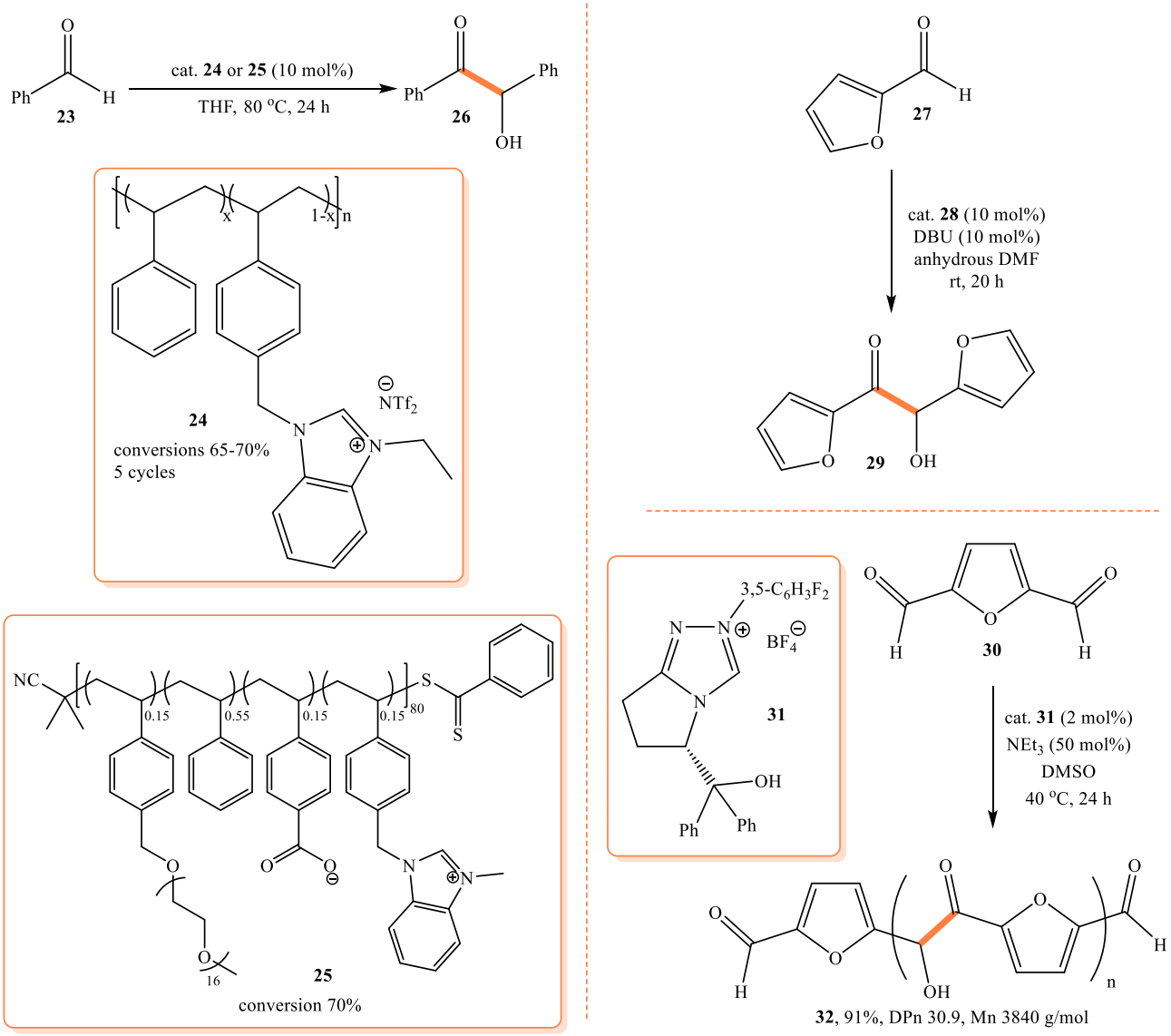
2.2. Cross-benzoin condensation

Cross-coupling between various aldehydes or between aldehydes and ketones is an evident extension of the benzoin condensation. In crossed acyloin condensations, it is common for none of the four possible α-hydroxycarbonyl products to predominate, as depicted in Scheme 7 [21].

2.2.1. Intermolecular cross-benzoin condensation

Inoue and co-workers described the first example in 1985 [61]: the NHC-catalyzed **34** selective cross-benzoin reactions of aliphatic and aromatic aldehydes with formaldehyde led to the formation of α-hydroxycarbonyl compounds, or acyloins. In these reactions, an excellent level of selectivity was observed for the cross-benzoin products as shown in Scheme 6.

In a similar fashion, as reported by Later Kuhl and Glorius [62], α-hydroxycabonyls were synthesized with high yields by using an NHC generated from thiazolium salt **35** (10 mol.%) and DIPEA (10 mol.%) in THF at 60 °C. This reaction is a highly selective cross-benzoin reaction with a broad substrate scope, as illustrated in Scheme 8.



Scheme 6 Polymer-supported *N*-heterocyclic carbenes.

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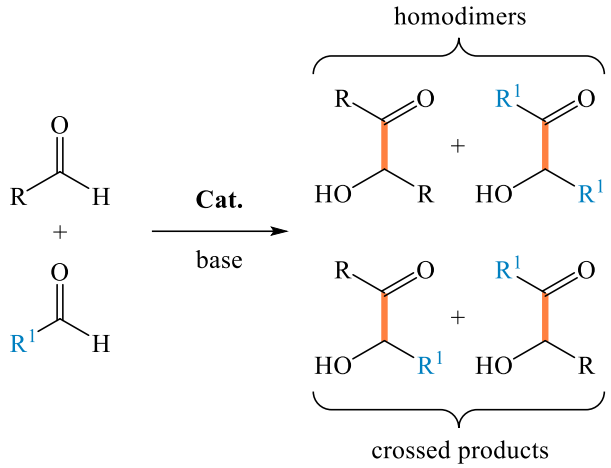

Scheme 7 Four possible products from a crossed intermolecular benzoin condensation.

The choice of electrophile is crucial for intermolecular crossed acyloin condensation. Selectivity was achieved, as depicted in Scheme 8–10, when the electrophilic reaction partners were α-ketoesters (**37**) and trifluoromethyl ketones (**39**) [63–65].

In 2011, Yang and coworkers [66] developed an intermolecular cross-coupling of aromatic aldehydes with acetaldehyde by demonstrating an intriguing divergence in reactivity controlled by the catalysts, namely, thiazolium salt **44** and triazolium salt **15**. In this reaction, the carbene derived from thiazolium facilitated the formation of the Breslow intermediate from aromatic aldehyde, followed by coupling with acetaldehyde. As depicted in Schemes 8–10, the triazolium-derived carbene prefers to activate acetaldehyde to generate the corresponding acyl anion equivalent before coupling with aromatic aldehydes. Connon, Zeitler, and coworkers reported the use of thiazolium and triazolium precatalysts for selective cross-benzoin reactions, which may be cited as an example of these reactions [21].

In 2011, Glorius and coworkers [67] introduced a number of thiazolium NHC precatalysts with sterically bulky aryl groups on the nitrogen and varying backbone substitutions. 10 mol.% of NHC **48** exhibited high levels of reactivity and selectivity during intermolecular cross-benzoin condensation, yielding a library of asymmetrically substituted benzoins. Schemes 8–10 requires the presence of an ortho-substituent on the electrophilic aromatic aldehyde (which inhibits the direct addition of NHC to these aldehydes).

Yang and coworkers [68] reported in 2014 the NHC-catalyzed chemoselective intermolecular cross-benzoin condensation of aliphatic and aromatic aldehydes employing 10 mol.% of **15**. The chemoselectivity was attained by utilizing a large excess of aliphatic aldehyde (1:15 molar ratio). In contrast to the earlier problem, directing groups of aromatic aldehydes were not necessary for high levels of selectivity. In order to recycle the excess aliphatic aldehydes used to achieve selectivity, post-workup catalytic reactions were employed.

Scheme 8–10 demonstrates that recycling in this reaction can be repeated up to five times without altering the product yield or chemoselectivity.

Using morpholinone- and piperidinone-derived triazolium precatalysts, cross-benzoin condensation of aliphatic and aromatic aldehydes can occur chemoselectively and efficiently. In 2014, Michel Gravel and colleagues [69] reported that using a load of just **54** at 5 mol.% for cross-benzoin condensation smooth reactions and selective benzoin reactions were observed with a wide range of linear and branched aliphatic aldehydes as well as aromatic aldehydes, as depicted in Scheme 8–10. Specifically, aliphatic aldehydes served as acyl anion equivalents, resulting in the formation of α-hydroxycarbonyls (acyloins) products.

In 2016, Haghshenas and Gravel [70] reported that the use of α-amino aldehydes in NHC-catalyzed cross-benzoin reactions using the same catalyst (**15**) produces chemoselectivity via steric hindrance and electronic activation. As depicted in Schemes 8–10, the method produces the desired compounds with good yields and good diastereomeric ratios for a variety of aldehydes. In addition, a concise total synthesis of D-arabino-phytosphingosine requires the developed method as a crucial phase.

Two distinct aromatic aldehydes can undergo highly chemoselective cross-benzoin condensation, according to the work of Delany and Connon in 2018 [71]. To achieve high coupling yields, it was necessary to use a new triazolium salt (**58**) in combination with a base (potassium carbonate). This allowed for the coupling of both ortho- and non-substituted aromatic aldehydes (Schemes 8–10).

In subsequent years, Ji et al. [72] established the intermolecular cross-benzoin reaction of aliphatic aldehydes with isatins; the reaction is catalyzed by the *N*-pentafluorophenyl-substituted triazolium salt (**61**), which is produced from morpholinone. In a highly chemoselective manner, as depicted in Scheme 6, gram-scale 3-acyl-3-hydroxyoxindoles with an extensive range of substituents are formed.

In the same year, a highly chemoselective intermolecular cross-benzoin reaction involving aldehydes and isatins was developed by Xu and coworkers [73] using **64** and $NaHCO_3$ as bases. Good to excellent enantioselectivities can be achieved in the production of 3-substituted 3-hydroxyoxindoles with moderate to good yields (Scheme 8).

Recently, Delany and Connon [74] examined the asymmetric intermolecular cross-benzoin condensation of two distinct aromatic aldehydes utilizing chiral NHC **67**. When the steric and electron-withdrawing properties of the *N*-aryl ring were increased, the chemistry became more chemoselective, efficient, and enantioselective. As demonstrated by quenching the reaction at various intervals and deuterium incorporation tests involving the product, *in situ* product racemization (except for benzoin itself) complicates this. After optimizing the process using an *o*-substituted benzaldehyde, moderate to good yields of crossed-benzoins with moderate to remarkable enantioselectivity were obtained (Scheme 8).

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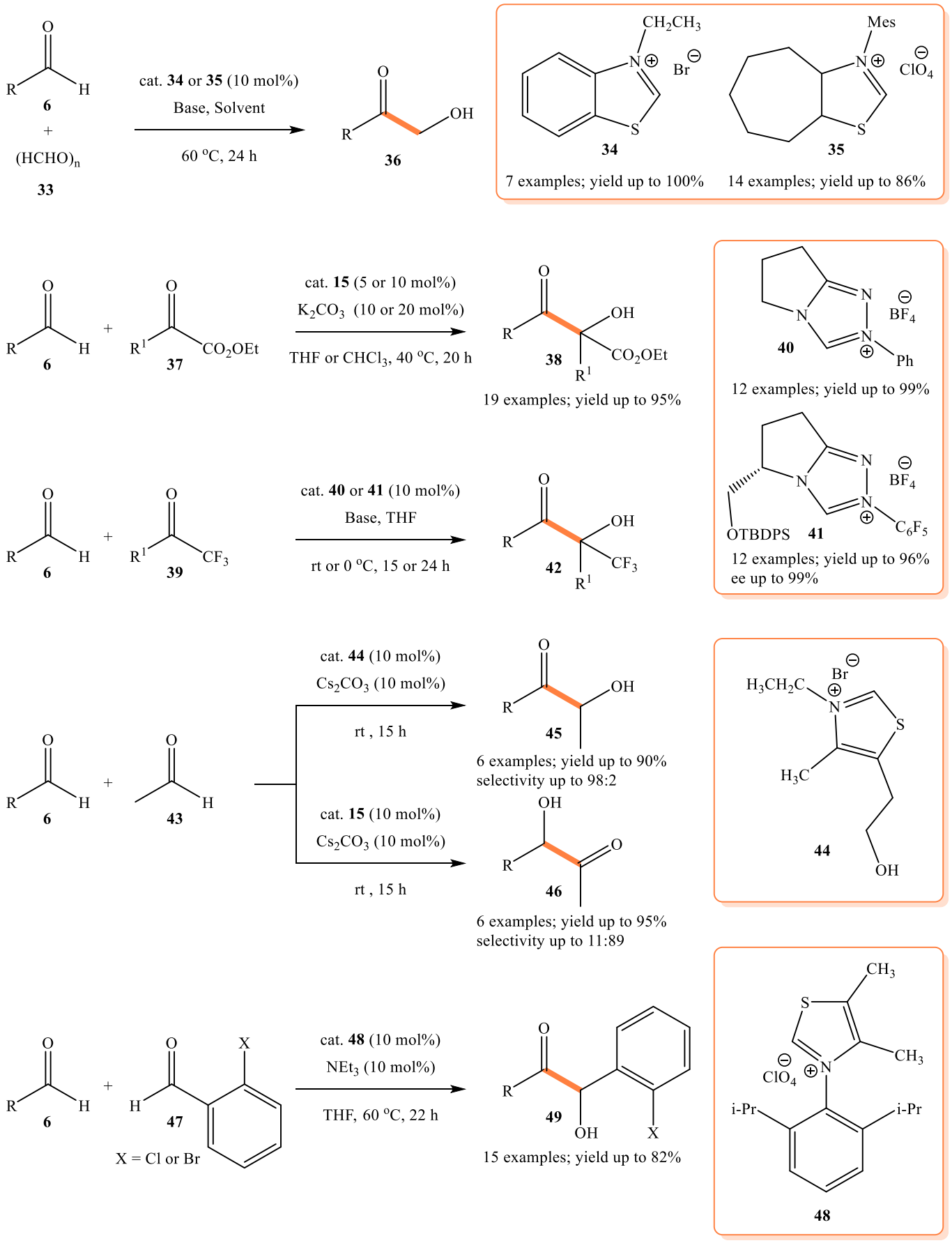

Scheme 8 Intermolecular cross-benzoin condensation.

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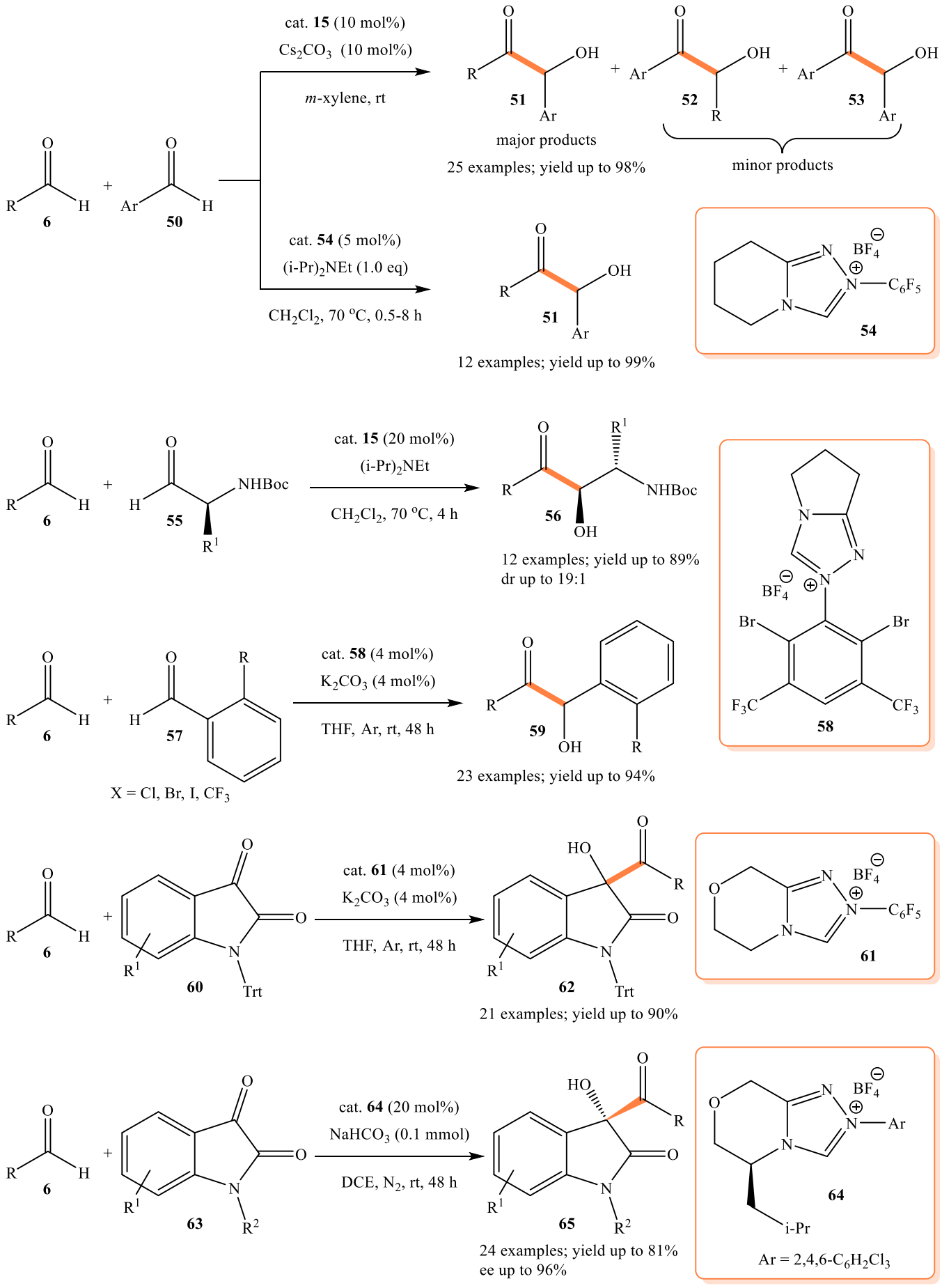

Scheme 9 Intermolecular cross-benzoin condensation (continued).

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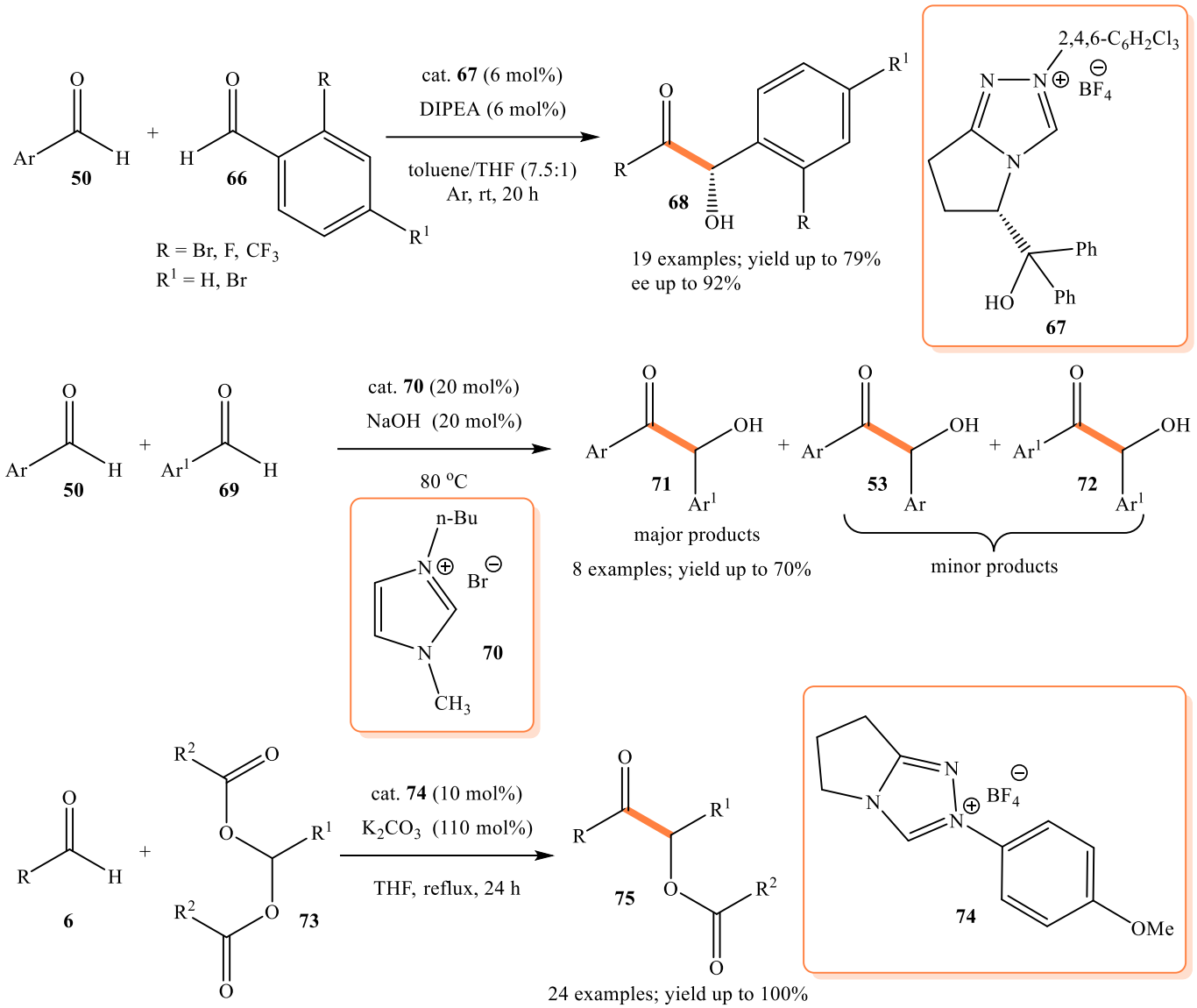

Scheme 10 Intermolecular cross-benzoin condensation (continued).

As reported in 2021 by Phungpis and coworkers [75], for cross-benzoin reactions at room temperature, 1-butyl-3-methylimidazolium bromide ([Bmim][Br]) acted as a catalyst, and a NaOH-based solvent was used. 20 mol.% 1-butyl-3-methylimidazolium salt **70** can improve the performance of cross-benzoin condensation and provide the desired cross-benzoin products with satisfactory yields. Scheme 6 demonstrates that homo-benzoin condensation also occurred as a side reaction with minor yields.

In the same year, Onodera and coworkers [76] developed a synthetic method (Scheme 6) for the selective preparation of *O*-acetyl cross-benzoins by using acylals as aldehyde equivalents in NHC-catalyzed reactions involving bicyclic triazolium salts **74** as precatalysts and potassium carbonate as a base in THF at reflux temperature.

2.2.2. Intramolecular cross-benzoin condensation

A number of intramolecular cross-aldehyde-ketone benzoin condensations have been carried out. In 2003, Suzuki and colleagues [15] described a case in their facile preanthraquinones synthesis. As depicted in Scheme 7, aldehyde **76** reacts intramolecularly with a ketone in the presence of thiazolium salt **44** and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to produce desired hydroxyl-ketone **77** in high yields.

Subsequently, the groups of Ender [77] and Takikawa [78] independently reported an asymmetric variant of the intramolecular crossed benzoin reaction. As shown in Scheme 7, Enders uses chiral lactam-derived triazolium salt **79**, whereas Suzuki employs chiral aminoindanol-derived triazolium salt **80** developed by Rovis and coworkers [79]. Notably, both Enders and Suzuki observe a significant decrease in enantioselectivity between the six-membered and five-membered cyclization precursors. Enders also developed another intramolecular crossed aldehyde-ketone benzoin condensation of simple dicarbonyl systems in 2004 [80], as shown in Scheme 7. This method produces high yields of five- and six-membered cyclic acyloins using thiazolium salt **44** as a precatalyst.

Ender group [81] reported in 2006 that intramolecular benzoin reactions of oxoalkoxybenzoic aldehyde **84** catalyzed by chiral NHCs (**79**, **85**, **86**) produce chiral hydroxychromanone products **80**, as depicted in Scheme 7. The acyl

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anion intermediate can serve as a carbon nucleophile for the nucleophilic substitution, and the reaction of tosylates **88** produces annulated chromanone **90** and dihydrobenzofuranone **91** [82], as depicted in Scheme 11.

Kankala and coworkers [83] reported that the intramolecular cross-benzoin condensation of chalcones derived from *o*-phthalaldehydes **92** was catalyzed by NHC derived from *N*-tert-butyl-substituted imidazolium salt **93** (10 mol.%) and DBU base. The reaction proceeded rapidly in 20 minutes at room temperature to give good yields of tertiary alcohols **94** derived from naphthalenone in the range of 75–94%, as shown in Schemes 11–13.

The NHC-catalyzed intramolecular benzoin condensation of carbohydrate-derived dialdehydes has been applied to the synthesis of carbocyclic sugars. In 2014, Stockton and colleagues [84] investigated the diastereoselective benzoin condensation of manno- and galacto-configured dialdehydes **95**, **97** or **100**, which were promoted by triazolium carbene precatalysts **15, 21**, or **40** in 20 mol.% with 15 mol.% of NEt_3 or DBU to produce single inosose stereoisomers **96**, **98**, **99**, **101**, or **102** in high yields, as depicted in Scheme 11. Good yields of allo- and epi-inositol were derived from the stereospecific reduction and deprotection of inosose derivatives.

Similarly, Kang and colleagues [85] established a highly site-selective cross-benzoin-type cyclization of asymmetrical dialdoses (**97**) to produce inosose derivatives (**104** or **105**). As shown in Schemes 11–13, the selection of NHCs and protective groups is crucial for controlling the site- and face-selectivity of the cyclization. Good yields of chirally protected derivatives of epi-, muco-, and myo-inositol can be derived from the resulting inososes.

In 2016, Shirke et al. [86] described a rapid and facile method for preparing dihydrobenzofuranones **108**, which can be readily converted into previously unidentified benzofuran derivatives. Schemes 11–13 depicts the synthesis of benzofurans from commercially available 3-furan carboxaldehydes via sequential bismuth(III) chloride-catalyzed furfurylation and a NHC-promoted intramolecular cross-benzoin condensation reaction.

The intramolecular cross-benzoin reaction of tethered ketone-aldehyde substrates yielded α-hydroxychromanone **110** products in good yields, as depicted in Schemes 11–13. This was accomplished by Nicholson and co-workers [49] using the same planetary milling conditions as previously described for homo-benzoin condensation.

NHC-catalyzed intramolecular benzoin condensation-oxidation using **107** and DBU in one pot has recently been developed and described by Satyam and colleagues [87] as a means to synthesize various cyclic 1,2-diketones incorporated in dibenzo-fused seven-membered heterocycles **112** under ambient conditions and in good to excellent yields, as depicted in Scheme 11.

In a recent study, Liu and coworkers [88] developed a desymmetric organocatalyzed method for the synthesis of siliconstereogenic silacycles with optical activity. This catalytic process is effective in the presence of a chiral NHC **114** catalyst for the synthesis of enantiomerically enriched dibenzo[b,f]silepin-10-ones containing 1,4-carbon- and siliconstereogenic centers from a wide range of silicon-centered diaromatic aldehydes (Schemes 11–13). The current intramolecular benzoin process can be easily scaled up to the gram scale, and the products can be refined into a variety of useful compounds.

2.3. Aza-benzoin condensation

In these reactions, the aldehyde-derived Breslow intermediate is subjected to nucleophilic attack by the NHC reacting with an aza electrophile. Imines with an electron-withdrawing *N*-substituent are the most commonly used aza electrophiles for preparing α-aminocarbonyl compounds. Conveniently, this section also discusses the NHC-mediated addition of aldehyde-derived acyl anions to nitroso compounds, which results in the formation of hydroxamic acid derivatives.

In the NHC-catalyzed aza-benzoin condensation, acylimines serve as electrophiles to react with aldehydes. Murry and coworkers [89] reported that the acylimine generated in situ by the action of a base on sulfonylamide derivative **116** was reactive. In the meantime, the aldehyde is converted into the Breslow intermediate by 10 mol.% of thiazolium **107**-derived NHC. As shown in Scheme 14, the combination of these two reactive intermediates produced α-aminocarbonyls **117** in outstanding yields.

Under thermodynamic control, inactivated imines are also capable of cross-coupling with aromatic aldehydes. As depicted in Scheme 14, this coupling is effectively catalyzed by 20 mol.% of thiazolium salt **107** in the presence of triethylamine in ethanol at 70 °C to give high yields of α-aminocarbonyl products **119**, as reported by Li and co-workers [90].

Thiazolium salt **107** catalyzes the cross-aza-benzoin reaction of phthalaldehyde with imines, leading to the formation of *cis*-2-amino-3-hydroxyindanones **122**, as reported by Sun and colleagues in 2011 [91]. Scheme 14 depicts the generation of the imine electrophile in situ from α-sulfo-*N*-Boc amine **121**. Following the initial cross-aza-benzoin reaction of one of the aldehyde functionalities with the imine, an intramolecular aldol reaction generates the indanone framework.

A report by the DiRocco group in 2012 [92] describes the use of 20 mol.% chiral triazolium salt **124** as an efficient catalyst for the enantioselective cross-aza-benzoin reaction between aliphatic aldehydes and *N*-Boc-protected imines. As shown in Scheme 14, the aldehydes serve as the acyl donors in this reaction, while the imines act as the receptors. NHC was added to highly electrophilic *N*-Boc imines, resulting in the formation of corresponding aza-Breslow intermediates; however, the reaction is reversible under the reaction conditions, and, most importantly, the chirally pure aminocarbonyl products formed in this reaction are valuable building blocks in organic synthesis.

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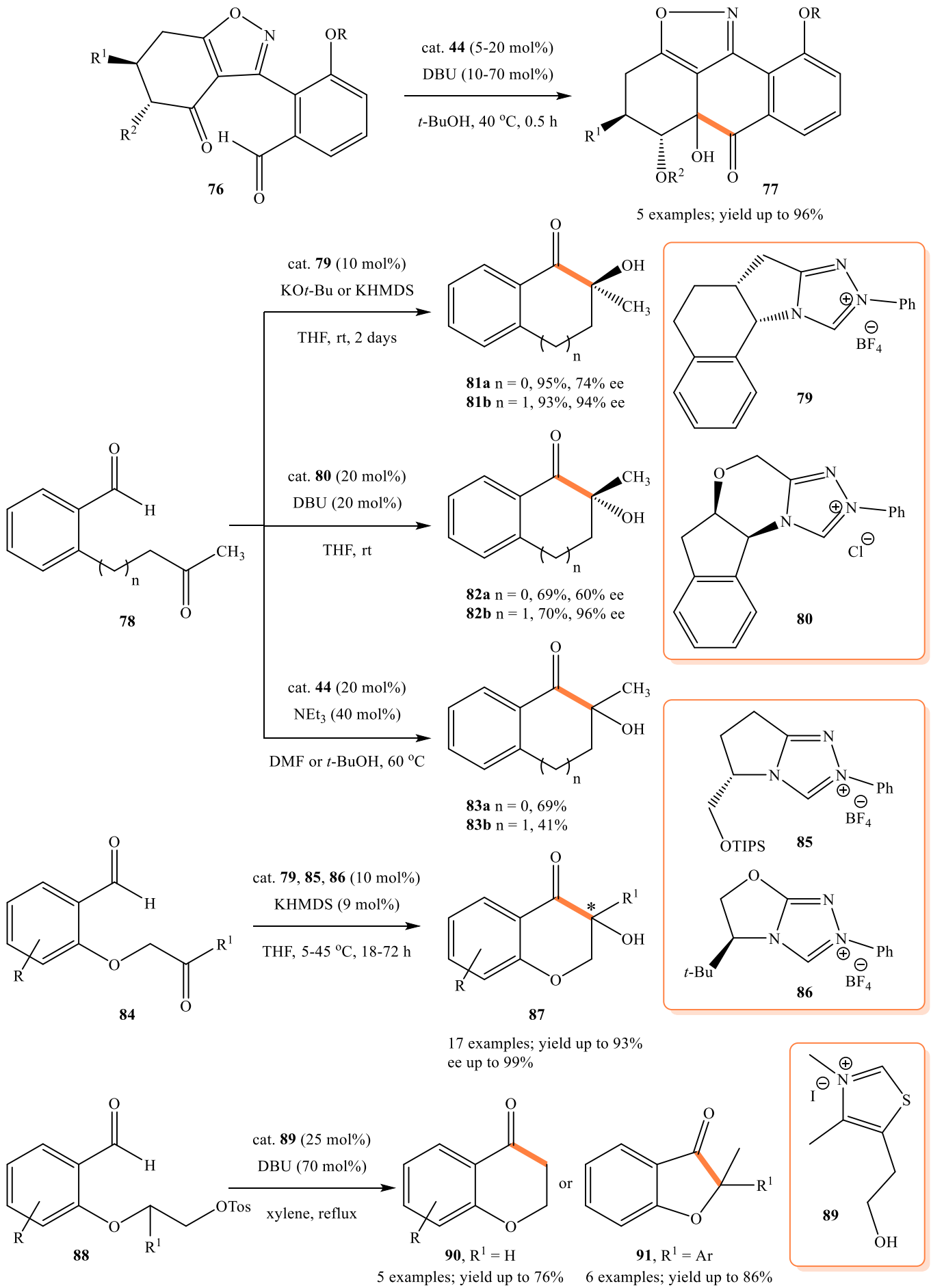

Scheme 11 Intramolecular cross-benzoin condensation.

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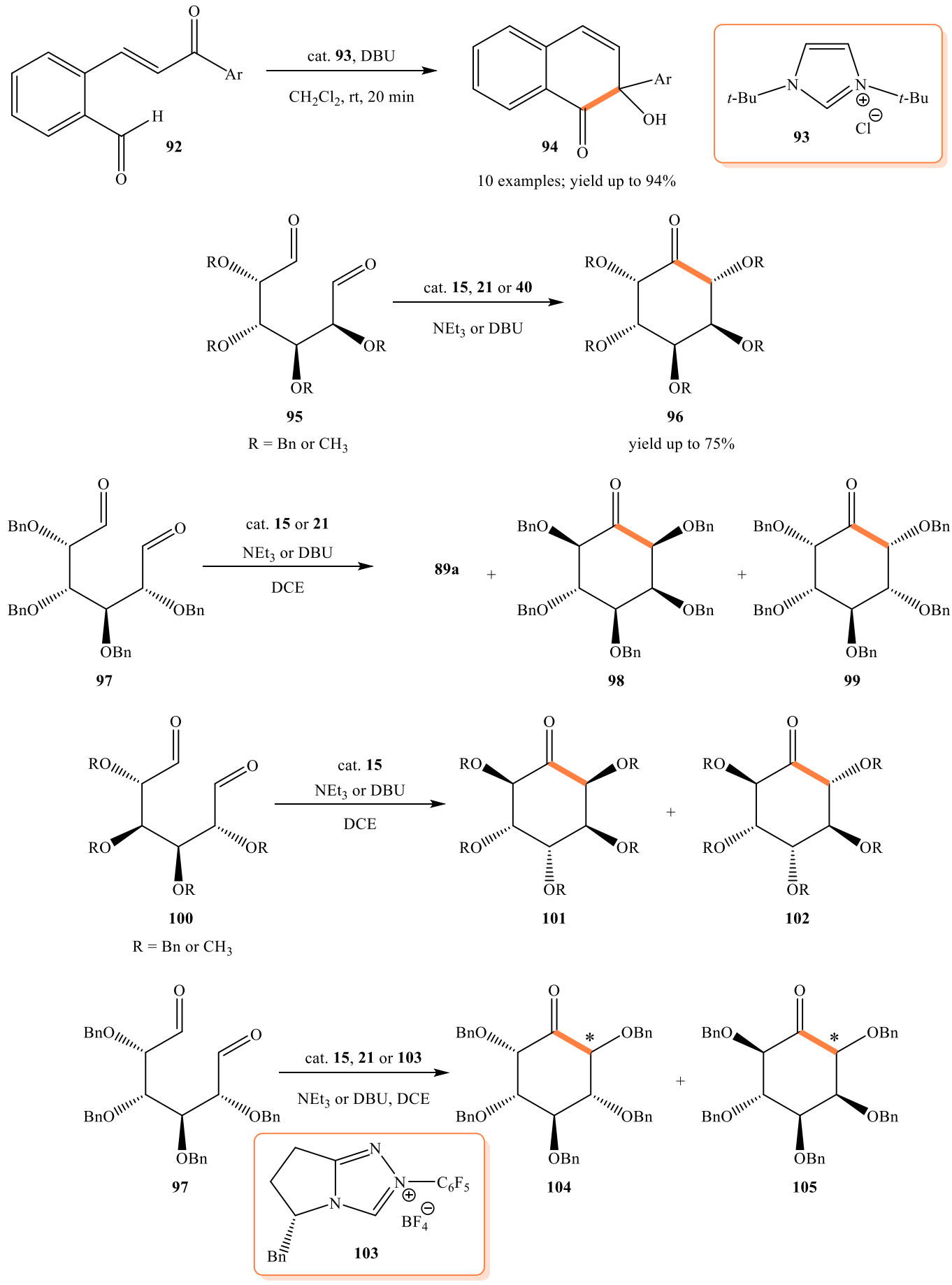

Scheme 12 Intramolecular cross-benzoin condensation (continued).

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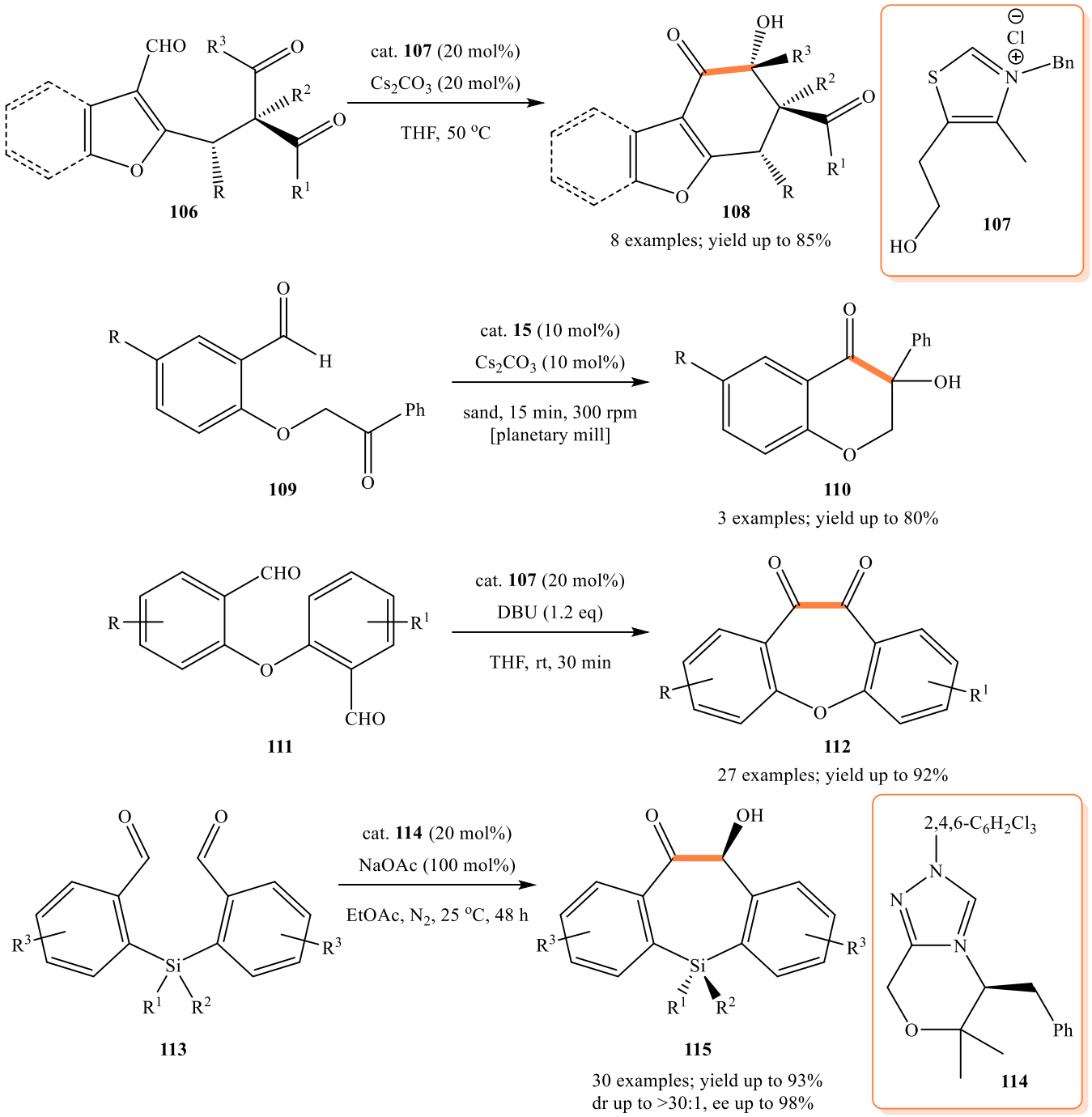

Scheme 13 Intramolecular cross-benzoin condensation (continued).

The cross-aza-benzoin reaction between aldehydes and *N*-PMP-imino esters **126** was very well promoted by the NHC generated from bicyclic pentafluorotriazolium salt **15** to afford products of α-amino-β-keto esters **127** in good yield, as investigated by Uno and colleagues in 2012 [93]. Scheme 8 depicts their findings. Importantly, under the optimized reaction conditions, a variety of functional groups can be tolerated. In 2012, Sun and coworkers [94] utilized nitrosoarenes as the electrophilic component in several NHC-bound aldehyde reactions. During these reactions, acyl anions are added to the nitrogen atom of the nitroso compound. The reaction of *o*-vinylarylaldehydes with nitrosoarenes, catalyzed by triazolium salt **130**, led to the formation of functionalized 2,3-benzoxazin-4-ones **131**. The initial intermolecular aza-benzoin reaction is followed by an intramolecular oxa-Michael reaction, as depicted in Scheme 8, yielding the observed product.

In addition, as reported by Hahnvajanawong and coworkers in 2016 [95], the cross-coupling of aromatic aldehydes with unactivated imines was catalyzed by benzimidazolium salt **14** as an efficient green catalyst to afford satisfactory yields of α-aminocarbonyls (Scheme 8). Condensation of benzoin and further oxidation of the resulting acyloins occurred as byproducts of this reaction.

Intermolecular cross-coupling between enamides and aldehydes was documented in 2016 by Wu and coworkers [96] using *N*-heterocyclic carbene (NHC) as the catalyst.

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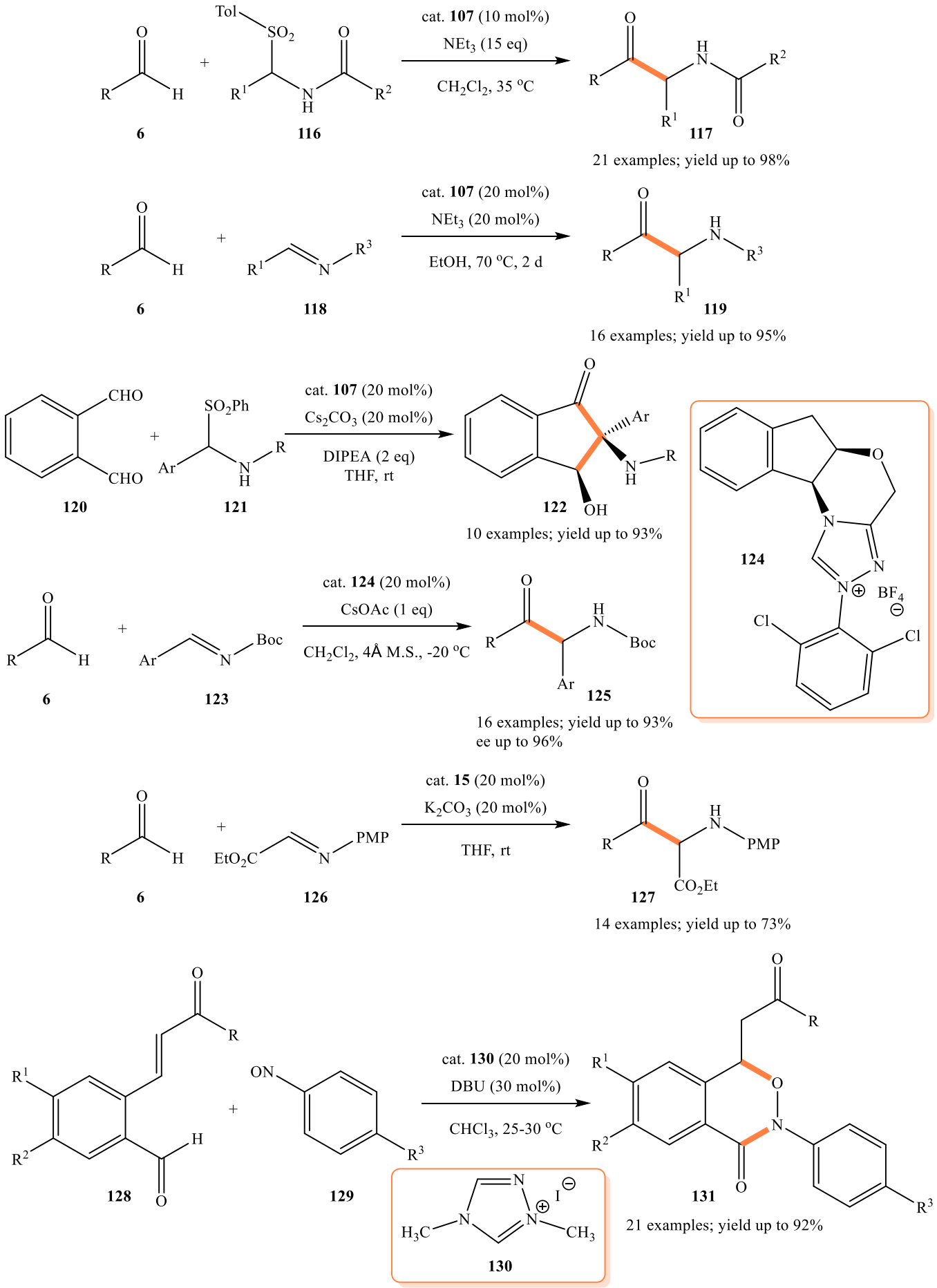

Scheme 14 Aza-benzoin condensation.

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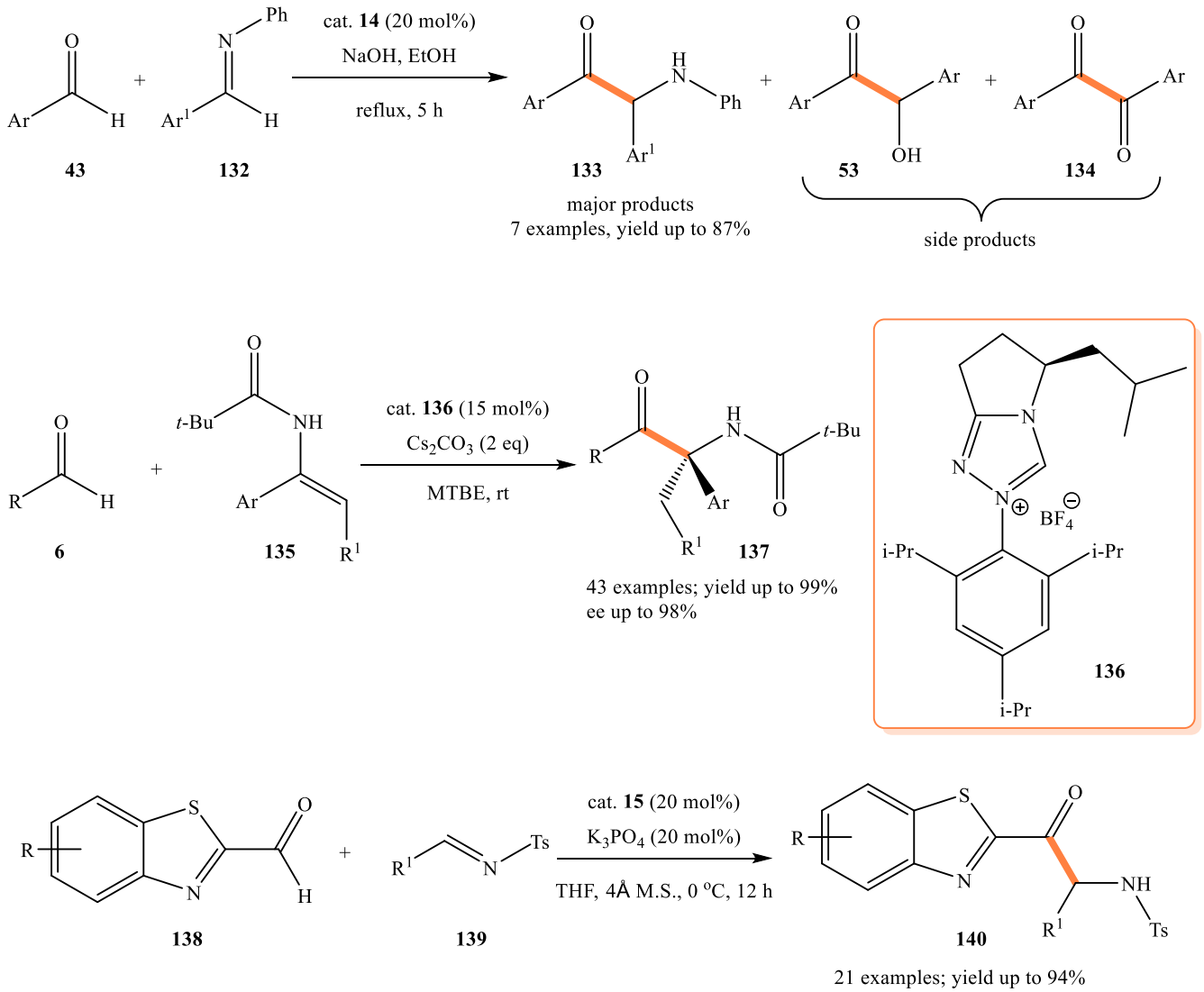

Scheme 15 Aza-benzoin condensation (continued).

High-yielding and enantioselective *N*-protected amines containing a quaternary carbon center can be obtained by exposing enamides to aldehydes in the presence of an NHC catalyst (**136**), as shown in Scheme 14.

The aza-benzoin reaction between benzothiazole-2-carboxaldehydes **138** and *N*-sulfonylimines **139** was recently reported by Li et al. in 2021 [97]. Under mild conditions, a-aminoketone products with a variety of substituents and substitution patterns can be produced in good to excellent yields. A 78% yield can be achieved by performing the aza-benzoin reaction on a gram scale (Scheme 14).

3. Conclusions

The benzoin condensation (BC) is a coupling reaction between two aldehydes. This reaction was formerly catalyzed by cyanide but is now catalyzed by thiazolium salts or *N*-heterocyclic carbenes (NHCs). The products of this reaction (BC) are α-hydroxycarbonyl compounds, also known as acyloins, and α-aminocarbonyl compounds if there is a cross-coupling between aldehydes and nitrogen imines. This comprehensive review highlighted the significant developments in *N*-heterocyclic carbene (NHC) catalysis for benzoin reactions. The development of NHCs as catalysts has shown remarkable progress in recent years, with the ability to activate substrates, form stable intermediates, and accelerate reaction rates. Enantioselective synthesis has also shown great potential with the use of chiral NHCs. A variety of NHCs are also described as catalysts for diverse benzoin reactions, including homo-benzoin, inter- and intramolecular cross-benzoin, and aza-benzoin condensation. Overall, this review provides valuable insights into the historical development and current advances of NHC catalysis for benzoin reactions. It serves as an important resource for researchers and chemists working in the field of synthetic chemistry and identifies important areas for future research and development.

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Writing – review & editing: B.P., P.N., K.W.

• Conflict of interest

The authors declare no conflict of interest.

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