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N-heterocyclic carbene-catalyzed radical reactions

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While N-heterocyclic carbene (NHC) catalyzed electron-pair-transfer processes have been developed into an important tool for synthetically important bond formations during the past decades, the corresponding radical reactions *via* NHC catalysis have only received growing attention in the past six years. Taking into account the advantages NHC-catalyzed radical reactions might bring, such as creating new activation modes that were previously unobtainable, it is worthwhile to provide a conceptual understanding of this emerging area. Therefore, herein we give an overview of NHC-catalyzed radical reactions *via* different synthetic techniques.

N-heterocyclic carbene, radical, one-electron oxidant, photochemistry, electrochemistry

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1 Introduction

Nature has always been regarded as a source of inspiration for synthesis chemists to develop efficient catalysts by mimicking nature's enzyme machinery. Inspired by nature, the last two decades have witnessed the breathtaking speed development of organocatalysis in organic synthesis [1], and quite a number of new transformations have been developed by using several types of small organic molecules, such as amines, thioureas, ketones, and N-heterocyclic carbenes (NHCs) [2]. Among them, NHCs, which can inverse the inherent reactivity of aldehydes, have become one of the most powerful synthetic tools in organic synthesis. A wide range of reactions associated with NHC catalysis *via* electron-pair-transfer processes have been developed (Scheme 1 (a, b)) [3]. The early applications of NHC catalysis were the benzoin and Stetter reactions *via* Breslow intermediates [4]. In 2004, the research groups of Glorius and Bode [5] independently extended this concept to homoenolate equivalents. The ability of NHCs for the generation of azolium enolates was demonstrated by the research groups of Rovis, Bode, Ye and Smith [6]. The [4+2] cycloadditions *via* azolium dienolates were independently reported by Ye *et al*. and Chi *et al*. [7]. The research groups of Castells, Zeitler, Scheidt, Lupton and Studer [3lt,3,8] made important contributions to the development of (α,β-unsaturated) acyl azolium intermediates. Despite its tremendous success, nowadays the development of NHC encounters a "bottleneck" possibly as a result of the limitation of electron-pair-transfer processes; therefore, the development of new activation modes of NHCs is of great importance and highly desirable. Although nature's oxidative decarboxylation of pyruvate to the formation of acetyl-CoA and CO_2 *via* CoA-dependent enzyme (a thiazolium NHC precursor) is thought to proceed *via* single-electron transfer (SET) processes (Scheme 1(c)) [9], it is interesting that the research on NHC-catalyzed radical reactions is mainly limited to the last six years [10]. Considering the fast development and advantages NHC-catalyzed radical reactions might bring, it is necessary and significant to discuss this emerging area. With con-

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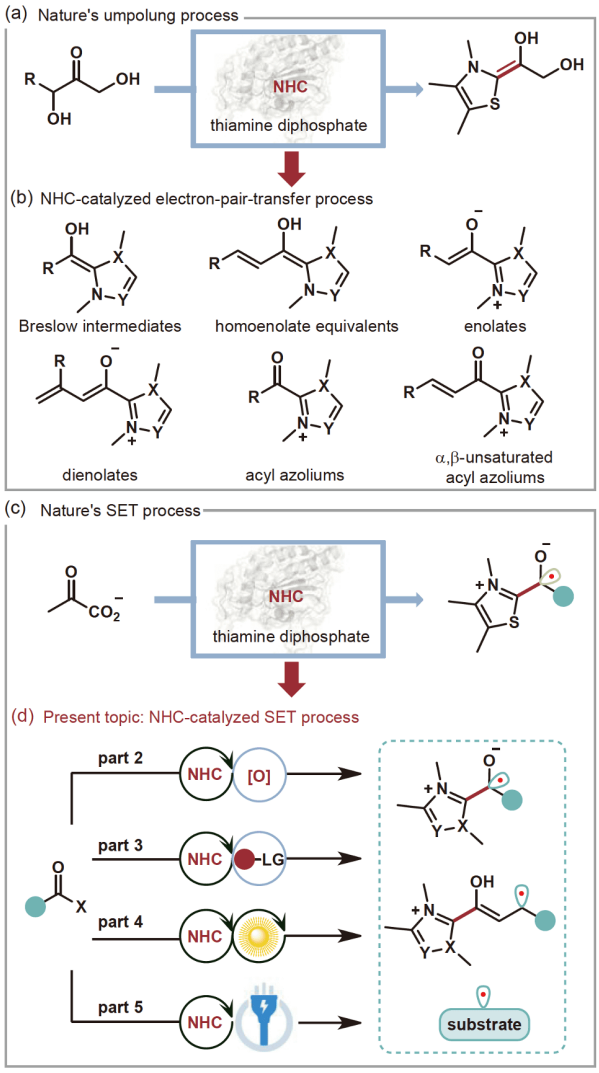


Scheme 1 Overview of NHC-catalyzed reactions (color online).

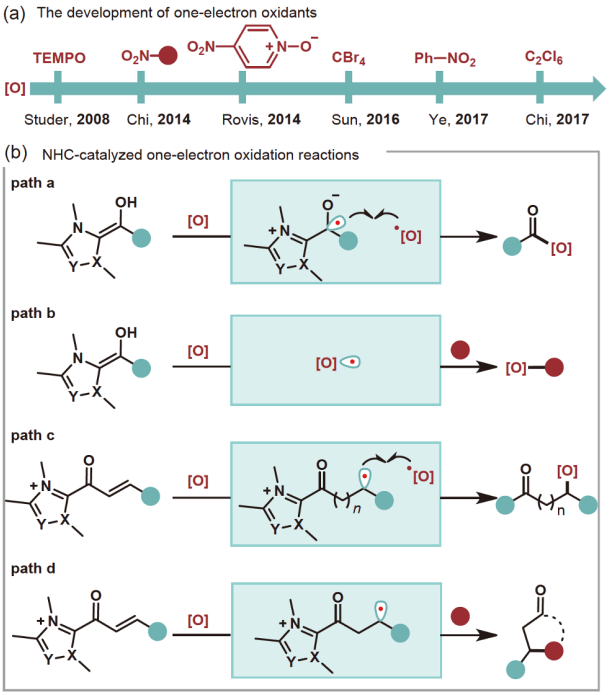
tinuous interest in NHCs, we herein provide an overview of the recent developments of NHC-catalyzed SET processes.

This review illustrates the development of NHC-catalyzed radical reactions from the beginning up to the present. Special emphasis are given to the discussion of the radical reactions *via* different synthetic techniques, including one-electron oxidation reactions, functional group transfer reactions, photochemical reactions and electrochemical reactions (Scheme 1(d)). The limitations and advantages of applying these techniques will also be discussed in this review.

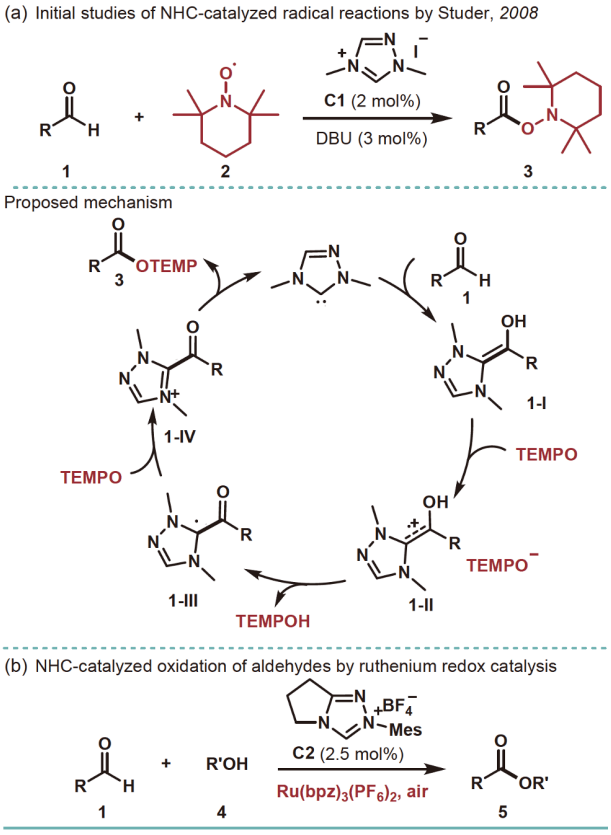
2 NHC-catalyzed one-electron oxidation reactions

Recent studies have demonstrated the ability of NHC catalysis in oxidative radical reactions. In this system, it is usually proposed that the Breslow intermediate was oxidized *via* a one-electron oxidant to initiate a single-electron transfer process [9b,11]. Based on the reaction partners with Breslow intermediate-derived radicals or oxidant-derived radicals, four reaction modes were classified in Scheme 2: (1) the reactions of Breslow intermediate-derived radicals with oxidants; (2) the reactions of oxidant-derived radicals with reaction partners; (3) the reactions of extended Breslow intermediate-derived radicals with oxidants; (4) the reactions of extended Breslow intermediate-derived radicals with reaction partners. The viability of NHC-catalyzed radical reactions was initially demonstrated by Studer and co-workers [12]. They described an efficient NHC-catalyzed oxidation of aldehydes to 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) esters in the presence of TEMPO as the one-electron oxidant. Mechanically, the Breslow intermediate **1-I** is oxidized by TEMPO to give a radical cation **1-II**. The following second one-electron oxidation by TEMPO offers the key acyl azoliums **1-IV** (Scheme 3(a)). Continued efforts by them expanded this chemistry to the oxidation of Breslow intermediate with $Ru(bpz)_3(PF_6)_2$ as the catalyst under air condition (Scheme 3(b)) [13].

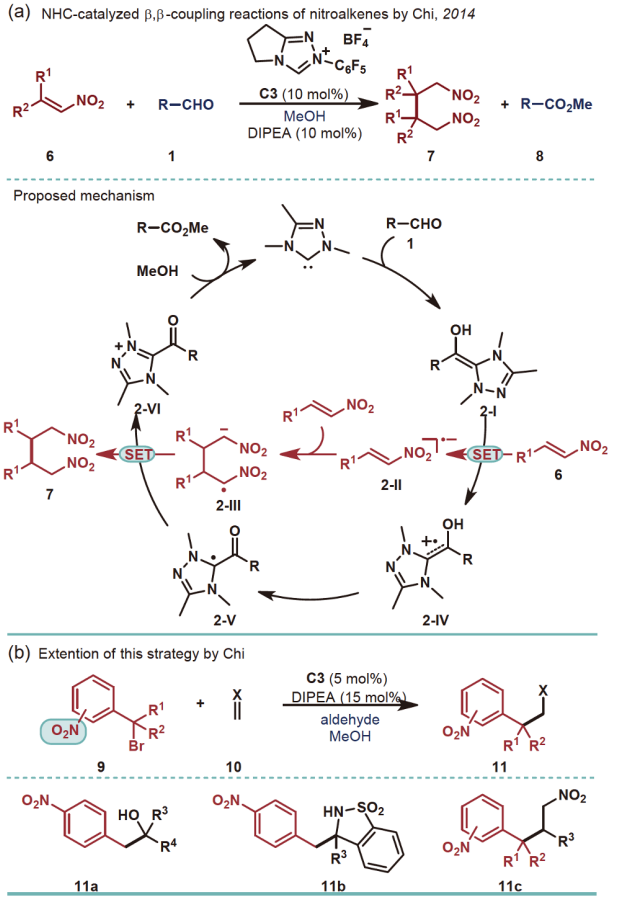
NHC-catalyzed radical processes have become a general concept since 2014. Chi and co-workers [14] reported the β,β-coupling reaction of nitroalkenes in the presence of **C3** as the pre-catalyst and aldehyde as the reductant. In this case, the nitroalkene is reduced to an anion radical **2-II** by the Breslow intermediate **2-I**, which undergoes a 1,4-addition to another nitroalkene, giving the intermediate **2-III**. Subsequent second SET reduction of **2-III** furnishes the final



Scheme 2 Overview of NHC-catalyzed one-electron oxidation reactions (color online).



Scheme 3 NHC-catalyzed oxidative esterification of aldehydes by using one-electron oxidants (color online).



Scheme 4 NHC-catalyzed couplings of nitro-containing compounds (color online).

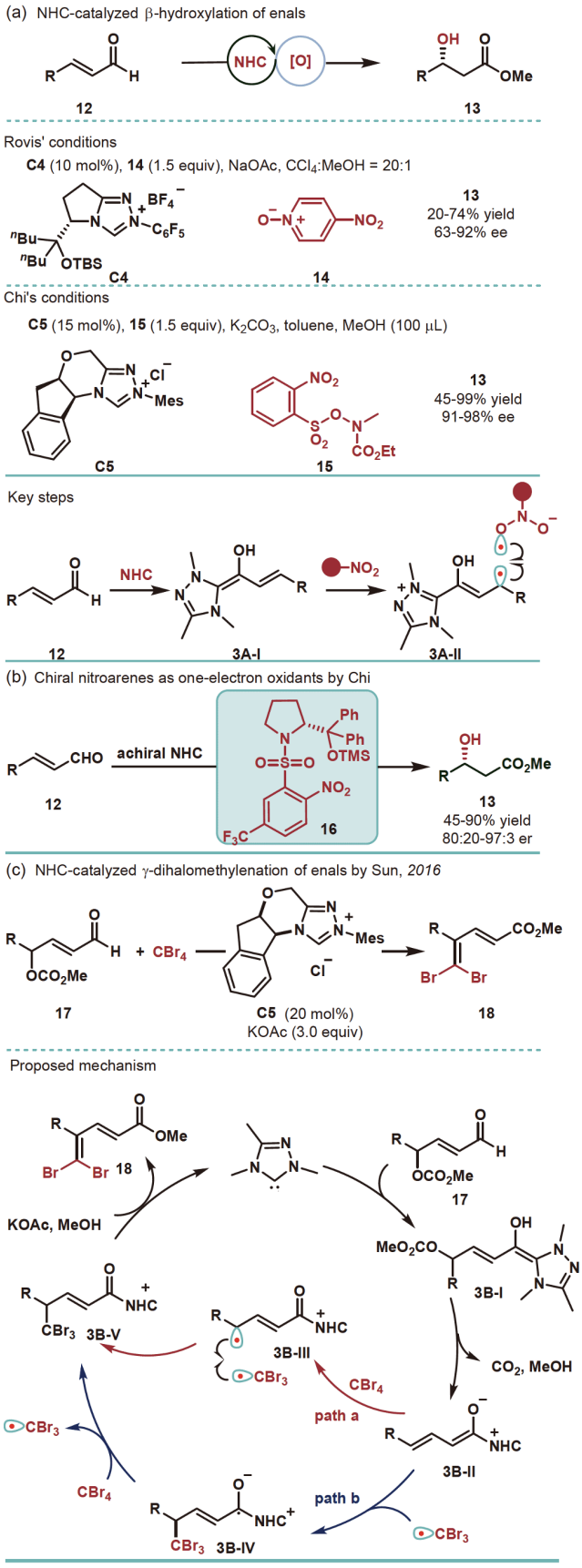
product (Scheme 4(a)). Further efforts by Chi and co-workers [15] resulted in cross-couplings of nitrobenzyl bromides with ketones, imines and nitroalkenes (Scheme 4 (b)).

In a significant addition to this chemistry, the research groups of Rovis and Chi [16] successfully developed an enantioselective version of NHC-catalyzed radical reaction of enals with nitro compounds, providing a direct access to chiral β-hydroxy esters (Scheme 5(a)). In these two cases, the key homoenolic radical species is generated by the oxidation of homoenolate equivalent intermediate in the presence of nitropyridine N-oxide **14** or nitrobenzenesulfonic carbamate **15** as proper oxidants. Recently, Chi and co-workers [17] developed a valuable alternative approach for the synthesis of β-hydroxyl esters by using chiral nitroarene **16** as one-electron oxidant and achiral NHC as the catalyst (Scheme 5 (b)).

In 2016, Sun and co-workers [18] have also offered contributions to the field of cross-coupling of NHC-derived intermediate with one-electron oxidant. They described an interesting NHC-catalyzed γ-dihalomethylenation reaction by employing CBr_4 or $CBrCl_3$ as the one-electron oxidant. This reaction, in the presence of pre-catalyst **C5**, afforded the dihalomethylenated products in generally good yields.

A proposed mechanism for this transformation is provided in Scheme 5(c). The Breslow intermediate **3B-I** is first generated *via* the addition of the NHC to the enal. The generated intermediate **3B-I** then undergoes elimination and deprotonation to form the key azolium dienolate intermediate **3B-II** and releases CO_2 and methanol. This resulting azolium dienolate might undergo two pathways to deliver the final product. In path a, the NHC intermediate-derived radical cation **3B-III** is generated by single-electron oxidation of azolium dienolate by CBr_4, and the following radical-radical recombination of **3B-III** and $Br_3C^{\cdot}$ affords the acyl azolium adduct **3B-V**. In path b, the radical addition of $Br_3C^{\cdot}$ to azolium dienolate generates the radical zwitterion **3B-IV**, which undergoes one-electron oxidation by CBr_4 to give the acyl azolium adduct [18].

The reactions detailed so far typically generate the desired products through pathways a, b and c, while the cross-couplings of NHC intermediate-derived radicals though phathway d have been less explored (Scheme 2(b)). An early example of these cross-couplings was reported by Rovis and co-workers [19] in 2015. During the investigation of NHC-catalyzed β-hydroxylation of enals, they found that the cyclopentanones could be obtained as the major products when the reaction was performed in a non-nucleophilic solvent. By



Scheme 5 NHC-catalyzed couplings of extended Breslow intermediate-derived radicals with oxidants (color online).

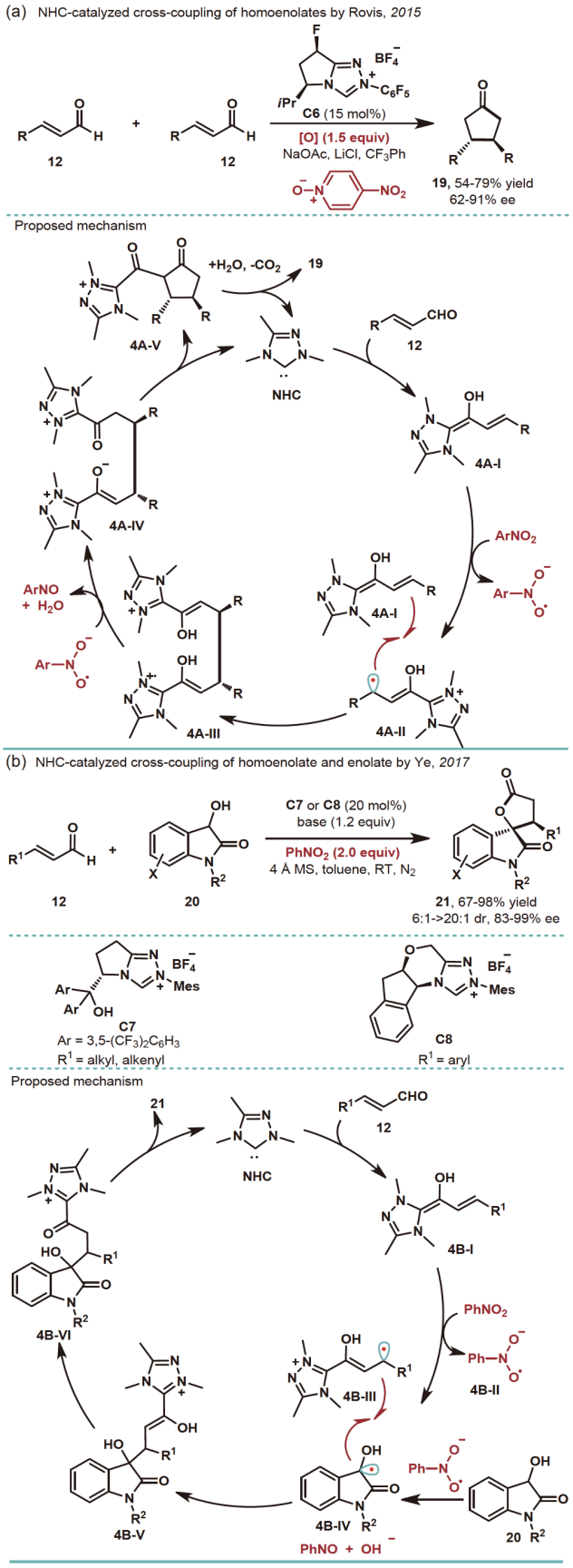
using CF_3Ph as the solvent and **C6** as the pre-catalyst, the 3,4-disubstituted cyclopentanone derivatives were obtained in good yields and enantioselectivities. The reaction is proposed to proceed by the radical addition of homoenolic radical species **4A-II** to homoenolate equivalent intermediate **4A-I**. The subsequent second one-electron oxidation provides the acyl azolium intermediate, which is attacked by the enolate **4A-IV** to give the adduct **4A-V**. The final hydrolysis and decarboxylation processes lead to the desired products (Scheme 6(a)).

In 2017, Ye and co-workers [20] further contributed to this field with the development of cross-coupling reactions of homoenolate and enolate. Various enals underwent cross-coupling with dioxindoles to provide spirooxindole-γ-lactones in good yields with high to excellent diastereo- and enantioselectivities. Compared with the classical one-pair electron processes [21], the challenging aliphatic alkyl enals were also compatible and gave the desired products in high diastereo- and enantioselectivities by using the newly developed strategy in the presence of **C7** as the pre-catalyst. Based on the control experiments and electron paramagnetic resonance (EPR) studies, the cross-coupling of homoenolic radical and isatin radical is proposed. The homoenolic radical **4B-III** is generated *via* one-electron oxidation of homoenolate equivalent intermediate in the presence of nitrobenzene as the oxidant. Then the isatin radical is formed *via* hydrogen atom abstraction of dioxindole. Subsequent cross-coupling of these two radicals affords the adduct **4B-V**. The following tautomerization and lactonization provide the final product **21** (Scheme 6(b)). Additionally, this method was also extended for the synthesis of a wide range of spirocyclic oxindole-γ-lactones bearing two contiguous tetrasubstituted stereocenters, which were difficult to achieve *via* traditional methods [22].

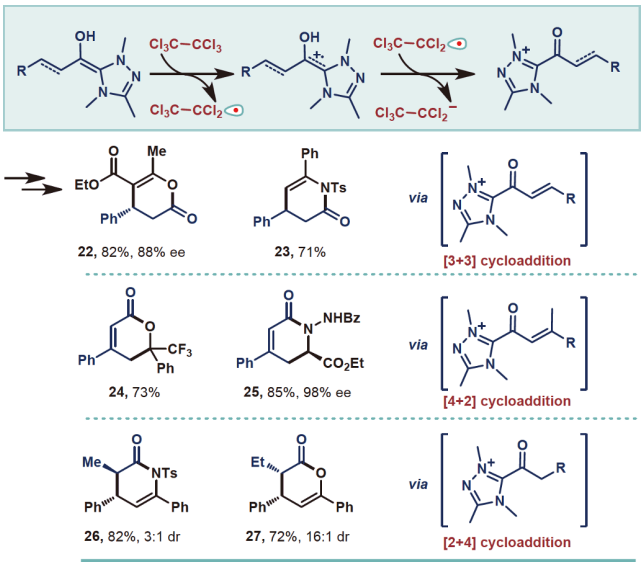
To expand the applications of NHC-catalyzed radical processes, Chi and co-workers [23] explored polyhalides as efficient and mild one-electron oxidants for various transformations of enals, such as [3+3] cycloadditions of enals with 1,3-dicarbonyls and imines; [4+2] cycloadditions of enals with trifluoromethyl ketones and hydrazones and [2+4] cycloadditions of aliphatic aldehydes with α,β-unsaturated imines and ketones. Notably, this strategy was also successful in asymmetric catalysis, affording the desired products in good yields and high enantioselectivities (Scheme 7).

3 NHC-catalyzed functional group transfer reactions

Although significant progress has been made in NHC-catalyzed radical reactions in the presence of one-electron oxidants, in addition to safety problems, the utility of superstoichiometric amounts of oxidants inevitably produces



Scheme 6 NHC-catalyzed couplings of extended Breslow intermediate derived radicals with reaction partners (color online).

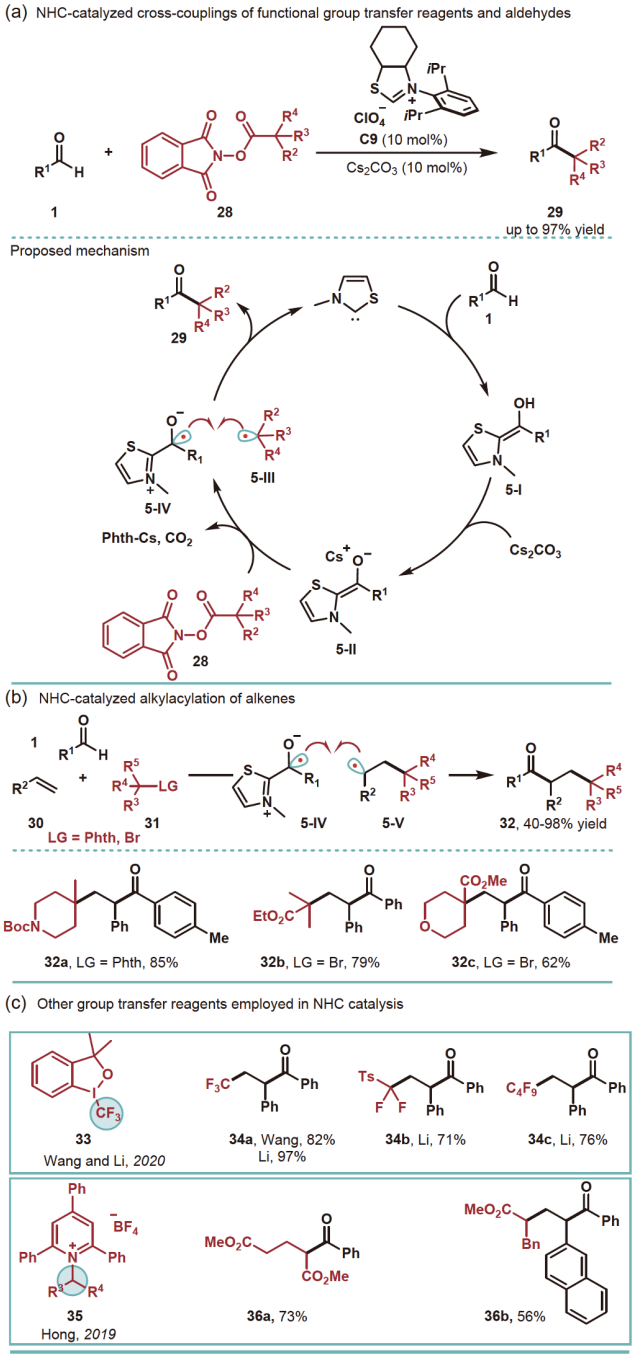


Scheme 7 NHC-catalyzed radical reactions by using polyhalides as one-electron oxidants by Chi (color online).

excess waste. Thus, the development of new types of NHC-catalyzed radical reactions without oxidants is still highly desirable.

During the last few years, transition metal and photocatalyzed radical reactions of redox-active scaffold-derived functional group transfer reagents have witnessed great achievements and offered a number of new transformations [24]. A recently developed NHC-catalyzed SET process of functional group transfer reagents offers a valuable alternative for the NHC-catalyzed radical reactions in the absence of a stoichiometric oxidant (Scheme 1(b)). One of the first applications of this concept was realized by Ohmiya and co-workers [25] in 2019, where the decarboxylative coupling of aryl aldehydes and *N*-(acyloxy)phthalimides (NHPI esters) for the synthesis of aryl alkyl ketones using pre-catalyst **C9** was reported (Scheme 8(a)). Regarding the mechanism, it is postulated that the addition of the NHC to the aldehydes, followed by deprotonation, leads to the key intermediate **5-II**, which undergoes a SET process with NHPI esters to give the Breslow intermediate-derived radical **5-IV** and alkyl radical **5-III**. Subsequent cross-coupling of these two radicals provides the desired products **29** and releases the NHC catalyst.

As evidence for the rapidly growing interest in NHC-catalyzed transformations of functional group transfer reagents, the research groups of Ohmiya and others have been active in exploring further applications of this concept. Ohmiya and co-workers [26] have expanded this strategy for the synthesis of functionalized ketone derivatives using aldehydes, alkenes and functional group transfer reagents as reaction partners (Scheme 8(b)). Similar to this strategy, the research groups of Wang [27] and Li [28] employed fluoroalkyl sources such as Togni reagents as one electron redox-triggered functional group transfer reagents for tri-



Scheme 8 NHC-catalyzed radical reactions of functional group transfer reagents (color online).

fluoromethylation reactions. This protocol provided an efficient way for the construction of fluoro-compounds and the late-stage modification of drug skeletons. Very recently, Hong and co-workers [29] developed an NHC-catalyzed deaminative coupling reaction of Katritzky salts and aldehydes. This reaction relies on the same mechanism as the previously discussed in Ohmiya's report, but was enabled by the use of Katritzky salts as alkyl radical precursors (Scheme 8(c)).

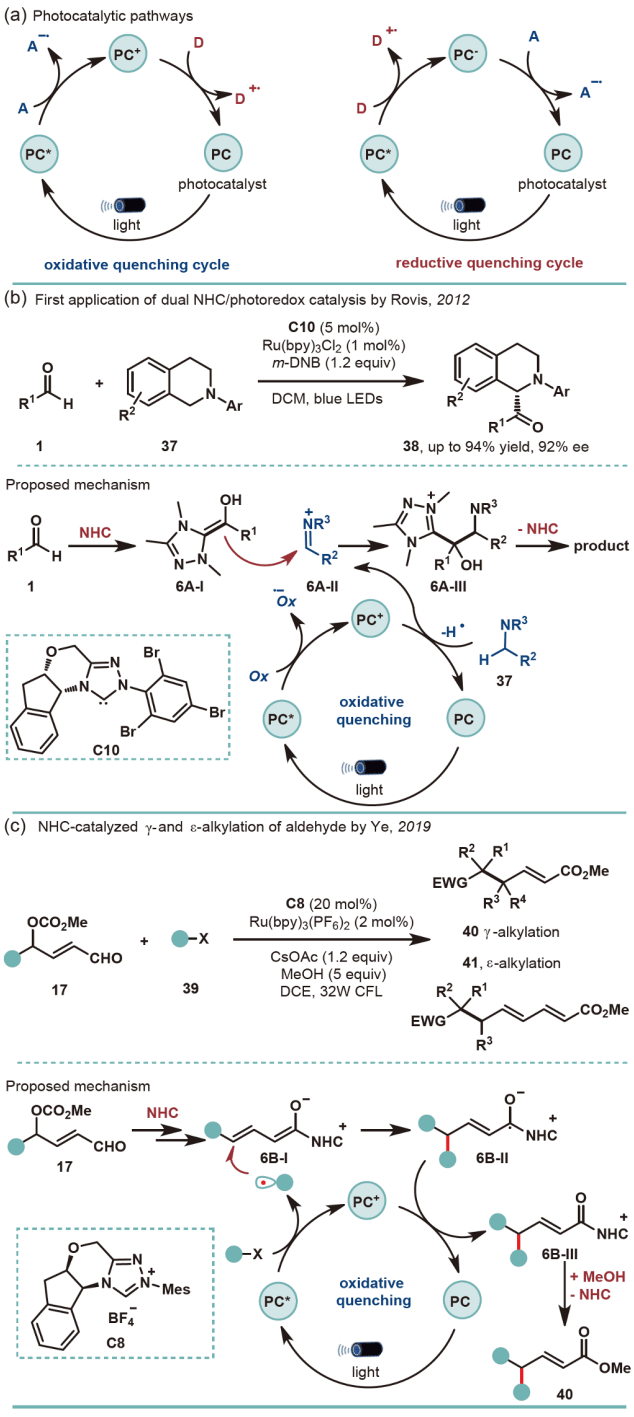
4 Dual NHC/photo-catalyzed reactions

In the cases of above NHC-catalyzed radical reactions, the radicals are generally generated through the oxidation of NHC-derived intermediates. Recently, photochemistry has become a powerful synthetic technique to generate radicals for a broad range of unconventional transformations [30]. Mechanistically, the excited state photocatalyst is quenched *via* either an oxidative or a reductive SET to generate the radicals with the reaction partners (Scheme 9(a)). One of the first examples demonstrating the applications of dual NHC/photoredox catalysis was introduced by Rovis and co-workers [31] in 2012, where the photoinduced one-electron oxidation of a tertiary amine **37** generates the iminium ion intermediate **6A-II**. Subsequent addition of the Breslow intermediate affords adduct **6A-III**, which gives the desired product and regenerates the catalyst (Scheme 9(b)).

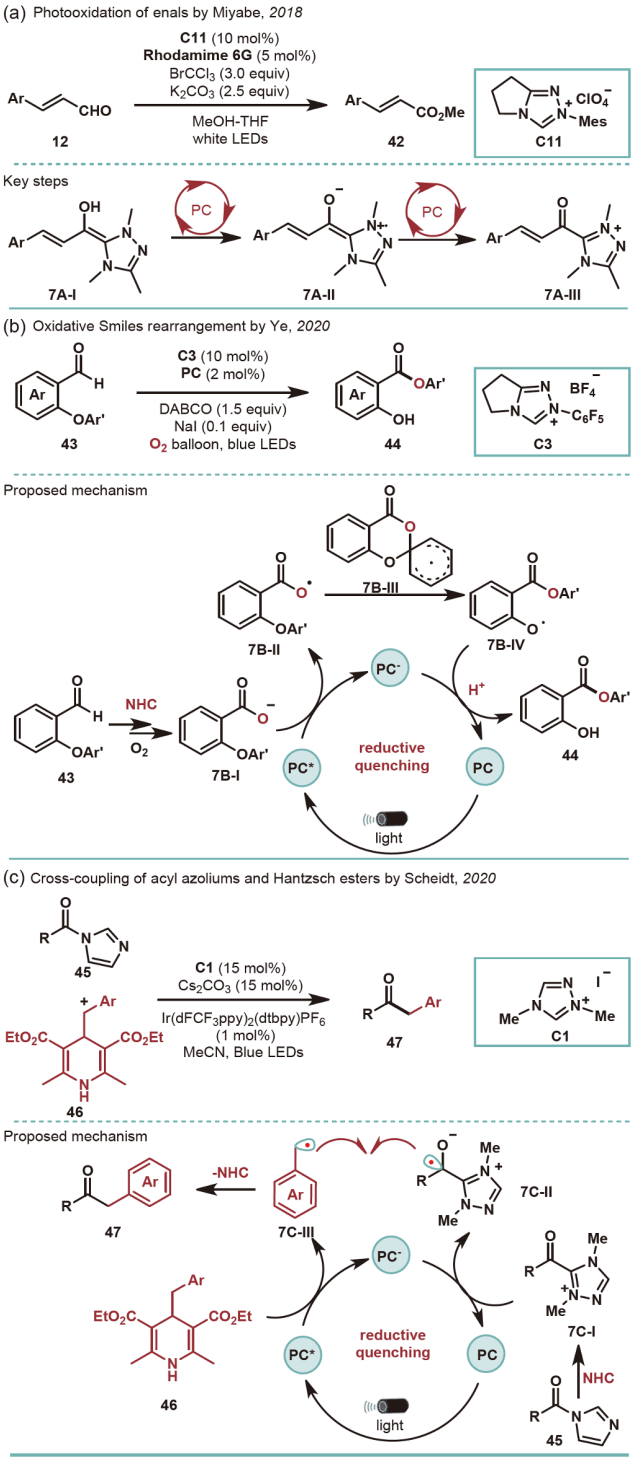
Further elegant NHC/photo dual catalyzed reactions have also been developed *via* the combination of dienolates and alkyl radicals. In 2016, Sun and co-workers [18] reported an example of the radical addition of carbon-centered trihalomethyl radical to dienolate intermediate. Recently, an impressively broad expanse of dual NHC/photoredox catalysis for the coupling of alkyl radicals and di/tri-enolates has been developed by Ye and co-workers [32], where alkylation reactions of enals with alkyl halides went well in the presence of **C10** as the pre-catalyst and $Ru(bpy)_3(PF_6)_2$ as the photocatalyst, affording the γ-multisubstituted-α,β-unsaturated esters and ε-multisubstituted-α,β-γ,δ-diunsaturated esters in moderate to good yields (Scheme 9(c)). This method allows a quick entry to vicinal all-carbon quaternary centers. Similar to this strategy, they further realized the ring-opening and γ-alkylation of cyclopropane enals.

Besides these achievements, the combination of reductive quenching and NHC catalysis has also been explored recently by several groups, where a photoactivated catalyst undergoes a one-electron reduction with a radical precursor. Employing dual NHC/photoredox catalysis, Miyabe and co-workers [33] realized the photocatalytic oxidation of enals to the corresponding esters. They found that the electron-rich Breslow intermediate **7A-I** could be easily oxidized by photocatalysts (Scheme 10(a)).

A nice example of oxidative Smiles rearrangement *via* reductive quenching was reported by Ye and co-workers [34]. The reaction worked well for various *O*-aryl salicylaldehydes with both electron-withdrawing and electron-rich aryls as migrating groups in the presence of **C3** as the pre-catalyst and 9-mesityl-10-methylacridin-10-ium perchlorate ($Mes\text{-}Acr\text{-}Me^{+}ClO_4^{-}$) as the photocatalyst, affording the desired aryl salicylates in good yields. The proposed reaction mechanism includes the formation of carboxylate anion *via* the reaction of *O*-aryl salicylaldehydes and NHC. Subsequent one-electron oxidation *via* excited photocatalyst



Scheme 9 NHC-catalyzed photochemical reactions *via* oxidative quenching (color online).



Scheme 10 NHC-catalyzed photochemical reactions *via* reductive quenching (color online).

gives the carboxyl radical **7B-II**. The radical Smiles rearrangement *via* spirocyclic intermediate delivers the radical **7B-IV**. Finally, the photocatalyst reengages the radical **7B-IV** to return the ground state photocatalyst and give the carboxylate anion **44** (Scheme 10(b)).

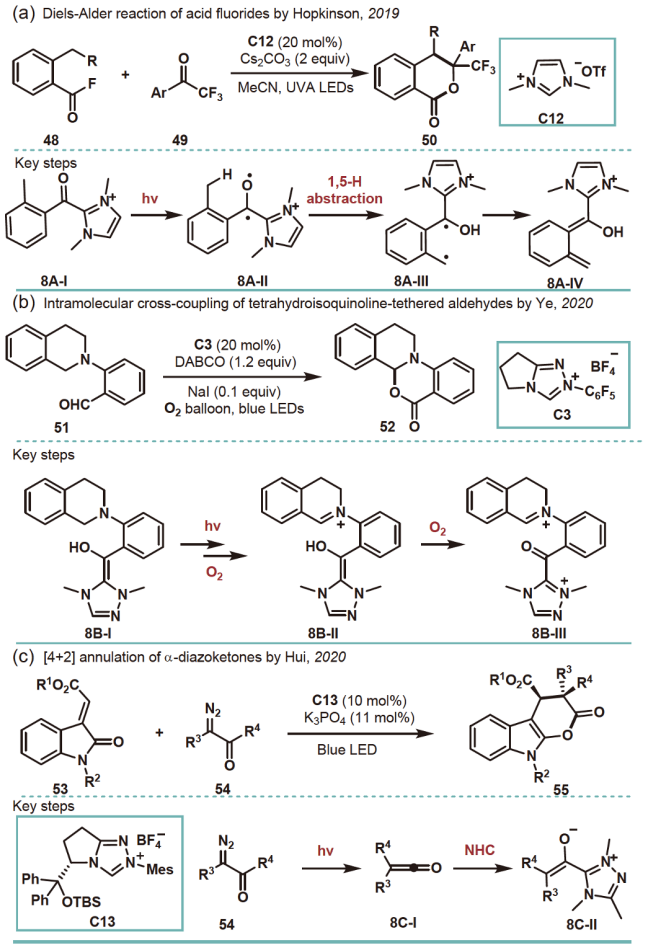
Very recently, Scheidt and co-workers [35] reported another nice example of NHC/photo dual catalyzed coupling reaction of acyl azoliums and Hantzsch esters, giving the corresponding ketones in moderate to good yields. The protocol was further utilized in one-step late-stage functionalization of pharmaceutical compounds. Mechanically, the Hantzsch ester is oxidized by excited-state photocatalyst to generate alkyl radical **7C-III**, and the acyl triazolium is reduced by reduced state photocatalyst to give the

azolium radical **7C-II**. Final radical-radical coupling affords the desired product and releases the NHC catalyst (Scheme 10(c)).

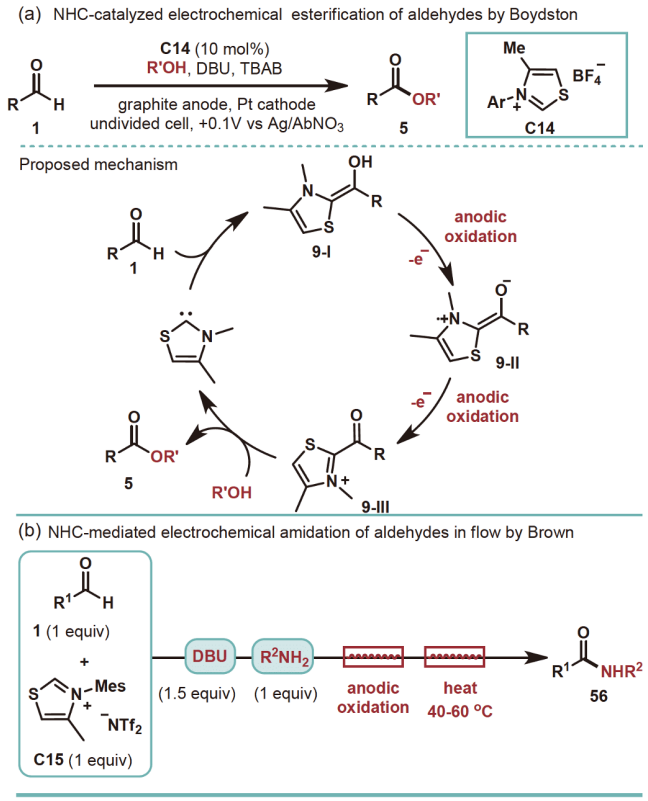
As a complement to the previously described dual NHC/photoredox catalysis, Hopkinson and co-workers [36] developed an interesting [4+2] annulation of *o*-toluoyl fluorides with trifluoroacetophenones in the absence of photocatalyst under ultraviolet A (UVA) irradiation. Based on the control experiments and time-dependent density functional theory (TD-DFT) calculations, they proposed that the biradical intermediate **8A-IV** is generated from the acyl azoliums under UVA irradiation (Scheme 11(a)). Very recently, Ye and co-workers [37] developed an elegant NHC catalyzed intramolecular cross dehydrogenative coupling of tetrahydroisoquinoline-tethered aldehydes in the presence of molecular oxygen as the oxidant and **C3** as the pre-catalyst under blue light irradiation without using photocatalyst (Scheme 11(b)). Shortly after these studies, Hui and co-workers [38] developed an efficient stereoselective [4+2] annulation of 3-alkylenyloxindoes **53** and α-diazoketones **54** for the synthesis of tetrahydropyrano[2,3-*b*]-indoles **55** in good yields with excellent diastereo- and enantioselectivities. This approach involves steps of the generation of ketenes **8C-I** from α-diazoketones under light irradiation and the following [4+2] annulation of enolate with 3-alkylenyloxindoes (Scheme 11(c)).

5 NHC-catalyzed electrochemical reactions of aldehydes

Recently, the novel ability of electrochemistry has been demonstrated for various classical transformations [39]. Interestingly, the electrochemical strategy is far less explored in NHC catalysis. One of the first examples using this strategy was reported by Boydston and co-workers [40], who described the cross-coupling of aldehydes and alcohols under undivided electrolytic conditions. This approach involves steps of anodic oxidation of the Breslow intermediate and esterification of acyl azolium (Scheme 12(a)). They further expanded the reaction partners to thiols for the synthesis of thioesters [41]. Employing a flow reaction system, Brown and co-workers [42] realized the anodic oxidative amidation of aldehydes in the presence of a stoichiometric amount of NHC as the catalyst. This method was tolerable with a wide range of functional groups, affording the desired products in high yields (Scheme 12(b)).



Scheme 11 NHC-catalyzed photochemical reactions without using photocatalysts (color online).



Scheme 12 NHC-catalyzed electrochemical reactions of aldehydes (color online).

6 Conclusions

NHC-catalyzed radical reactions provide an efficient strategy for various transformations. Taking the advances of the development of synthetic techniques especially electro- and photochemistry, this method has become more environmentally friendly for new transformations in the absence of oxidants. The newly developed environmentally friendly techniques, which enable chemists to address the issues that are not readily available with conventional methods, will be one of the future directions in modern organic synthesis.

An important step in NHC-catalyzed radical reactions is to generate the radicals, there are four reaction protocols used in these reactions: (1) traditional strategy—one electron oxidants are employed for the generation of NHC intermediate-derived radicals; (2) functional group transfer reagents—NHC-catalyzed generation of radicals based on a redox-active scaffold; (3) photochemistry—a photoredox catalyst is used for the generation of NHC intermediate-derived radicals and alkyl radicals; (4) electrochemistry—direct anodic oxidation is used for the generation of NHC intermediate-derived radicals. Despite this progress, NHC-catalyzed photo- and electrochemical transformations are still in their infancy. In the case of radical reactions catalyzed by NHC, future contributions might result from the efforts of integrating electrosynthesis and NHC catalysis and the development of asymmetric approaches.

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Conflict of interest The authors declare no conflict of interest.

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