

## Organocatalysis

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## N-Heterocyclic Carbene Catalyzed Radical Coupling of Aldehydes with Redox-Active Esters

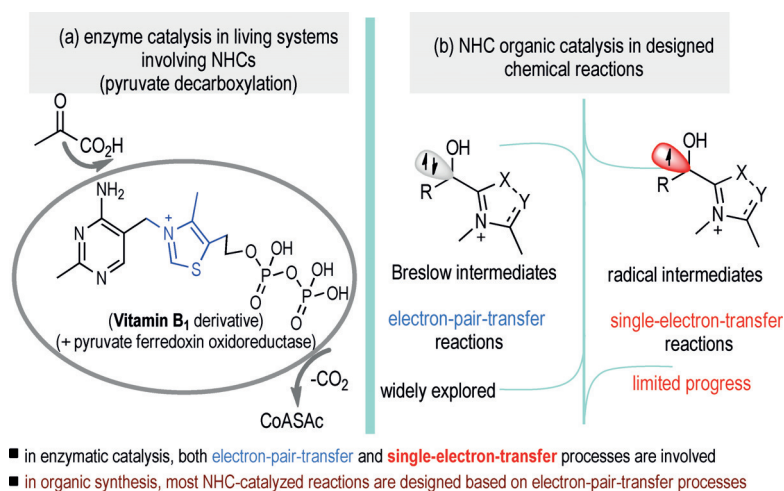
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**Keywords:** ketones · N-heterocyclic carbenes · radical intermediates · redox-active esters · single-electron-transfer reactions

**Abstract:** *N*-Heterocyclic carbene catalyzed radical reactions are challenging and underdeveloped. In a recent study, Ohmiya, Nagao and co-workers found that aldehyde carbonyl carbon centers can be coupled with alkyl radicals under NHC catalysis. An elegant aspect of this study is the use of a redox-active carboxylic ester that behaves as a single-electron oxidant to convert the Breslow intermediate into a radical adduct and concurrently release an alkyl radical intermediate as a reaction partner.

**N**-Heterocyclic carbenes (NHCs) exhibit unique properties in biology and chemistry. In biological systems, thiamine pyrophosphate (a derivative of vitamin B<sub>1</sub>) based NHCs catalyze the oxidative decarboxylation of pyruvate through a redox process enabled by pyruvate ferredoxin oxidoreductase. Approximately half of the steps in this pyruvate decarboxylation process are single electron transfer (SET) radical reactions; the other half are electron-pair-transfer reactions (Figure 1a).<sup>[1]</sup> In synthetic chemistry, thiamine- and related imidazolium- and triazolium-based NHCs have received considerable attention as organocatalysts over the last two decades. Most of the reaction designs in this field, however, are based on electron-pair-transfer processes. Reactions based on SET radical pathways remain challenging and much less developed (Figure 1b).<sup>[2]</sup>

This manuscript aims to give a brief summary on reactions based on NHC-catalyzed radical pathways, and highlight



**Figure 1.** NHC-catalyzed reactions in living systems and organic synthesis.

a recent elegant contribution from Ohmiya, Nagao, and co-workers concerning coupling reactions of aldehyde carbonyl carbon centers with alkyl radicals.<sup>[3]</sup>

The redox properties of the Breslow intermediates formed between NHCs and carbonyl compounds have been intensely studied. For instance, evidence for the formation of a radical intermediate by one-electron oxidation of a Breslow intermediate was reported by Fukuzumi and co-workers in the late 1990s.<sup>[4]</sup> These early studies and the pyruvate decarboxylation chemistry have inspired much of the carbene-catalyzed radical reactions developed to date (Figure 2).<sup>[5–14]</sup>

In 2008, Studer and co-workers converted aldehydes into carboxylic esters through two single-electron oxidation steps by using the (2,2,6,6-tetramethylpiperidin-1-yl)oxy radical (TEMPO) as the oxidant.<sup>[5]</sup> The aldehyde was oxidized to an acyl azolium intermediate, which was subsequently trapped by the reduced form of TEMPO (TEMPOH) to form an ester. In 2014, Chi and co-workers reported a reductive coupling of nitroalkenes under NHC catalysis with aldehydes as the terminal reductants.<sup>[6]</sup> Electron paramagnetic resonance (EPR) analysis and several other mechanistic studies showed that nitroalkene-derived radical anions were formed as key radical intermediates. In 2014 and 2015, the groups of Rovis

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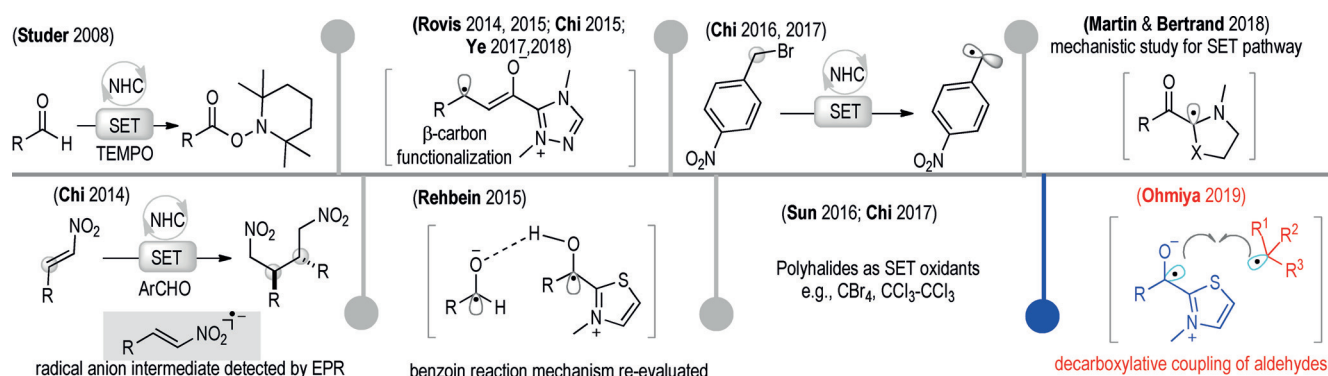


Figure 2. Summary of NHC-catalyzed SET reactions.

and Chi independently developed  $\beta$ -carbon hydroxylation reactions of enals by SET oxidation.<sup>[7,8]</sup> Radical coupling reactions involving the formal enal  $\beta$ -carbon center were proposed as the key steps. Similar radical intermediates derived from enals were also later explored for carbon-carbon bond-forming reactions by the groups of Rovis<sup>[9]</sup> and Ye.<sup>[10]</sup> In addition to the use of TEMPO and nitroarenes as the SET oxidants, studies by the groups of Sun<sup>[11]</sup> and Chi<sup>[12]</sup> revealed that polyhalides can behave as effective oxidants likely through SET pathways. The Chi group also developed reductive coupling reactions of nitrobenzyl bromides with ketones, imines, and nitroalkenes by using aldehydes as reductants in SET processes.<sup>[13]</sup> Important contributions in this arena of NHC-catalyzed SET reactions also include Rehbein's re-evaluation of benzoin reactions that indicated

the involvement of radical intermediates,<sup>[14]</sup> and the careful studies of Bertrand, Martin, and co-workers that elucidated the characteristics of the NHC-bound radical intermediates and the reaction pathways in the single-electron oxidation of aldehydes and enals, especially with mild oxidants.<sup>[15]</sup>

These radical reactions may provide effective synthetic solutions that are not readily available with conventional methods. For example, the enal  $\beta$ -hydroxylation reaction<sup>[7,8]</sup> provides quick enantioselective access to chiral tertiary alcohols that are difficult to be prepared by other methods such as asymmetric hydrogenation.

The recent study by Ohmiya, Nagao, and co-workers constitutes significant progress in this field of NHC catalysis through radical pathways. Their study provides a new way to generate reactive radical intermediates in NHC catalysis. In

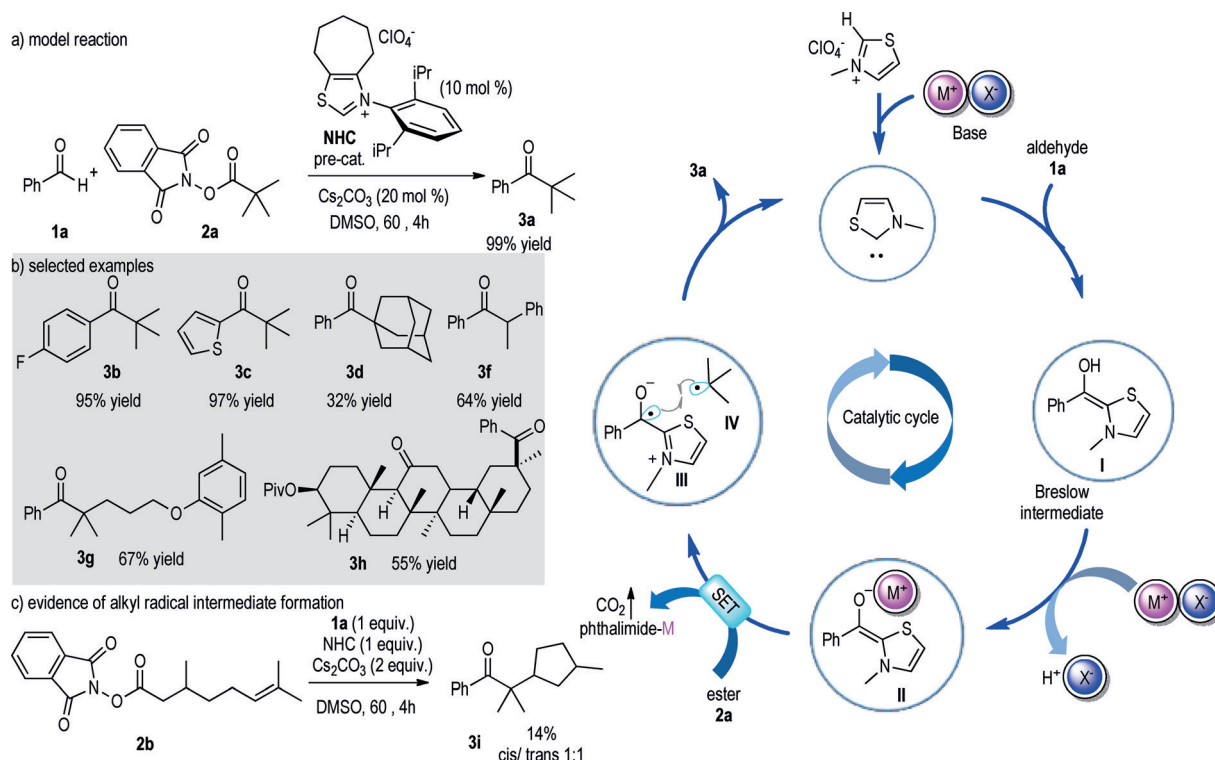


Figure 3. NHC-catalyzed decarboxylative radical coupling of aldehydes with redox-active esters.

addition, it was found that alkyl radicals can be effectively coupled with catalyst-bound aldehyde-derived carbonyl carbon radicals.

In particular, the authors employed aldehydes (e.g., **1a**) and carboxylic esters (e.g., **2a**) as the substrates (Figure 3a). A key element was the incorporation of a redox-active moiety into the carboxylic ester. Under the mild assistance of a Lewis acid, SET oxidation of the Breslow intermediate **I** (in the enolate form as illustrated by **II**) by the redox ester occurred effectively. The authors proposed that activation of the phthalimide moiety of the ester by the Lewis acidic Cs<sup>+</sup> ion facilitated the electron transfer that oxidized the Breslow intermediate to a radical adduct. This oxidation entails a decarboxylation step to release CO<sub>2</sub> and form two radical intermediates: the aldehyde-derived ketyl radical **III** and the carboxylic-ester-derived alkyl radical **IV**. Coupling of the two intermediates affords ketone **3a** as the product. The reaction works well for aryl aldehydes and tertiary or secondary alkyl carboxylic esters that can form stable carbon radicals. Esters derived from pharmaceuticals and natural products are effective substrates as well, enabling the incorporation of an acyl group into these functional molecules (Figure 3b). Evidence for the formation of radical **IV** was obtained by using an ester (e.g., **2b**) bearing an alkene moiety as the substrate (Figure 3c).

In summary, carbene-catalyzed radical reactions provide unique solutions for organic synthesis. This area is still in its infancy with limited progress in terms of both reaction development and mechanistic understanding. Future significant contributions might likely result from the following efforts: identification of new SET oxidants (and reductants), design of new carbene catalysts that enable the versatile tuning of the redox potentials of the intermediates, mechanistic studies that include key intermediate characterization and kinetic studies, and assembly of challenging products including those with sophisticated structures.

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## Conflict of interest

The authors declare no conflict of interest.

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