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

Runjiang Song,^[b] Yonggui Robin Chi^{*[a,b]}

Abstract: N-heterocyclic carbene-catalyzed radical reactions are challenging and much less developed. A recent study from Ohmiya and Nagao found that aldehyde carbonyl carbons can couple with alkyl radicals under NHC catalysis. An elegant design in this study is to use a redox-active carboxylic ester that behave as a single-electron oxidant to convert Breslow intermediate to 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 the biological systems, thiamine pyrophosphate (derivative of vitamin B1)-based NHC catalyzes the oxidative decarboxylation of pyruvate via 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).^[1] In synthetic chemistry, thiamine and related imidazolium and triazolium-based NHCs received considerable attentions as organic catalysts in the last two decades. Most of the reaction designs in this field, however, are based on electron-pair-transfer processes. Reactions designed from single-electron-transfer (SET) radical pathways remain challenging and much less developed (Figure 1b).^[2]

This manuscript aims to give a brief summary on reactions designed via NHC-catalyzed radical pathways, and highlight a recent elegant contribution from Ohmiya, Nagao and co-workers concerning coupling reactions of aldehyde carbonyl carbons with alkyl radicals.^[3]

The redox property of Breslow intermediates formed between NHCs and carbonyl compounds was a topic of study. For instance, evidence for the formation of radical intermediate via one-electron oxidation of Breslow intermediate was reported by Fukuzumi in late 1990s.^[4] These earlier studies and the pyruvate decarboxylation chemistry have inspired much of the carbene-catalyzed radical reaction developed to date (Figure 2).^[5-14]

In 2008, through two single-electron oxidation steps, Studer and co-workers converted aldehydes to carboxylic esters by using (2,2,6,6-Tetramethylpiperidin-1-yl)oxy radical (TEMPO) as the oxidant.^[5] The aldehyde is oxidized to the acyl azolium intermediate that is subsequently trapped by the reduced form of

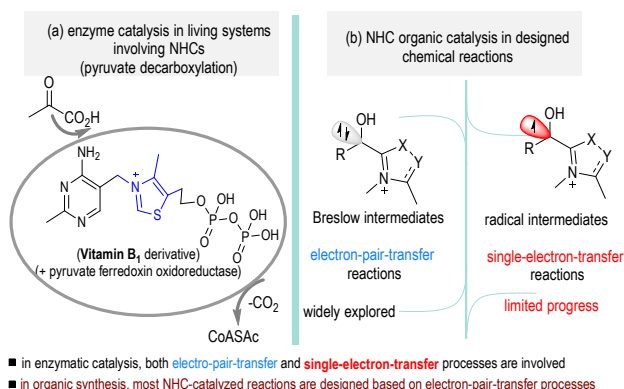


Figure 1. NHC-Catalyzed Reactions in Living Systems and Organic Synthesis.

TEMPO (TEMPOH) to form an ester product. In 2014, Chi reported reductive coupling of nitroalkenes under NHC catalysis by using aldehydes as the terminal reductants.^[6] Electron paramagnetic resonance (EPR) and several other mechanistic studies showed that nitroalkene-derived radical anions are formed as key radical intermediates. During 2014-2015, Rovis and Chi groups independently developed β -carbon hydroxylation reactions of enals via single-electron-transfer oxidations.^[7,8] In these reactions, radical coupling reactions involving the formal enal β -carbon are proposed as the key steps. Similar radical intermediates derived from enals were also later explored for carbon-carbon bond forming reactions by Rovis^[9] and Ye.^[10] In addition to the use of TEMPO and nitroarenes as the SET oxidants, studies from Sun^[11] and Chi^[12] revealed that polyhalides can behave as effective oxidants likely via SET pathways. The Chi lab also developed reductive coupling reactions of nitrobenzyl bromides with ketones, imines, and nitroalkenes by using aldehydes as reductants via SET processes.^[13] Important contributions in this arena of NHC-catalyzed SET reactions also include Rehbein's re-evaluation of benzoin reactions that indicate radical intermediates are involved;^[14] and Bertrand and Martin's careful studies that elucidate 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.^[15]

These radical reactions may provide effective synthetic solutions not readily available with conventional methods. For example, the enal β -hydroxylation reaction^[7,8] allows for quick enantioselective access to chiral tertiary alcohols that are difficult to be prepared via other methods such as asymmetric hydrogenations.

The recent study by Ohmiya, Nagao and co-workers is a significant progress in this field of NHC catalysis via radical pathways. Their study provides a new way to generate reactive radical intermediates in NHC catalysis. It's also interesting to see alkyl radicals can effectively couple with the catalyst-bound aldehyde-derived carbonyl carbon radicals.

[a] Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, People's Republic of China.

[b] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg

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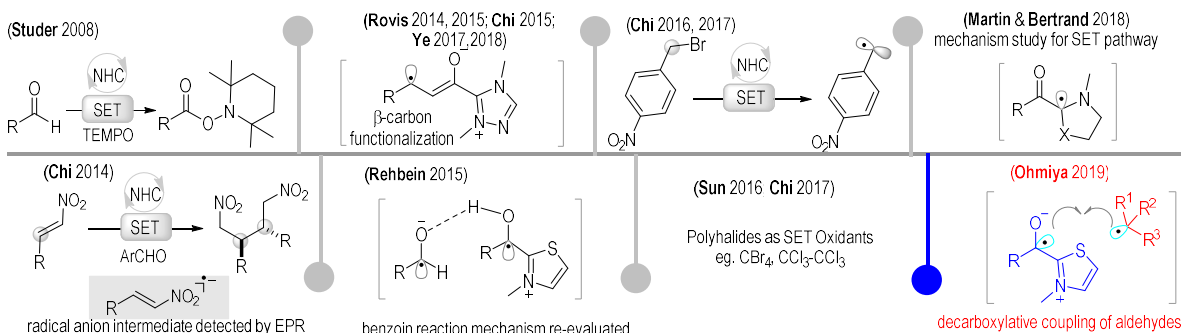


Figure 2. Summary of the NHC-Catalyzed SET Reactions.

Their reactions used aldehydes (e.g. **1a**) and carboxylic esters (e.g. **2a**) as the substrates (Figure 3a). A smart design here is to incorporate a redox-active moiety to 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^+ ion facilitated the electron transfer that oxidized the Breslow intermediate to a radical adduct. This oxidation consists of a decarboxylation step to release CO_2 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 reactions work 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, leading to the incorporation of an acyl group to these functional molecules (Figure 3b). Evidence of radical **IV** formation was offered 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 with regards to both reaction development and mechanistic understanding. Examples of future significant contributions can likely come from the following efforts: identification of new SET oxidants (and reductants), design of new carbene catalysts that provide versatile tuning for the redox potentials of the intermediates, mechanistic studies that include key intermediate characterizations and kinetic studies, and assembling of challenging products including those with sophisticated structures.

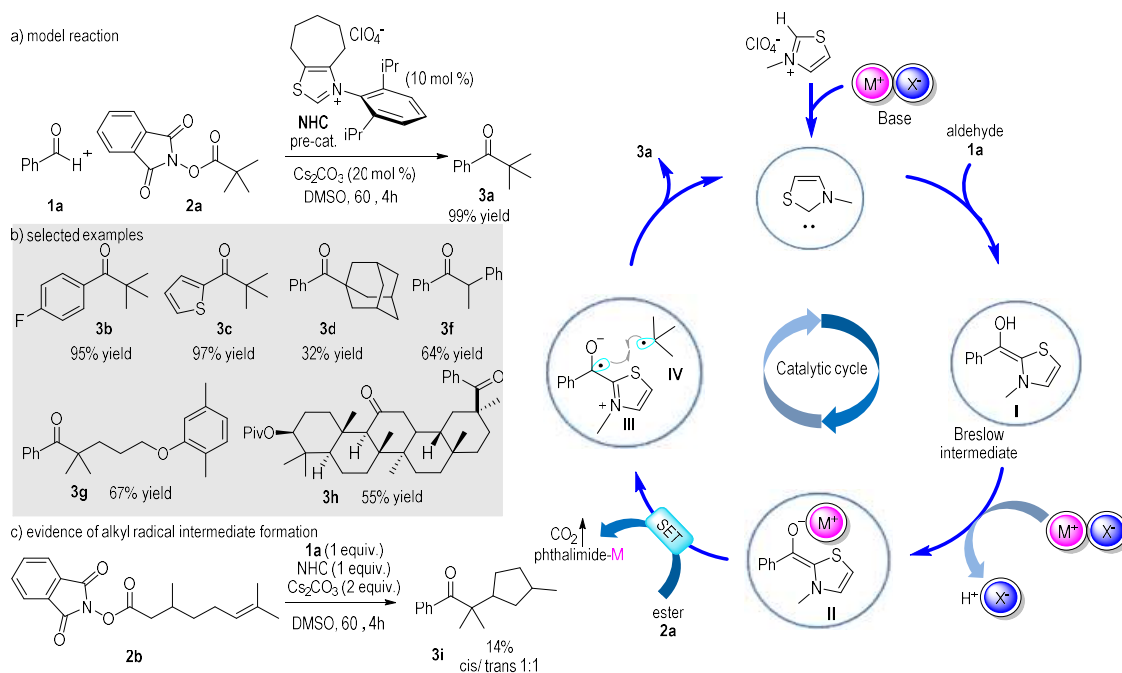


Figure 3. NHC-Catalyzed Decarboxylative Radical Coupling of Aldehydes with Redox Active Esters.

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Keywords: N-heterocyclic carbene • single-electron-transfer reactions • radical intermediates • ketones • redox active ester

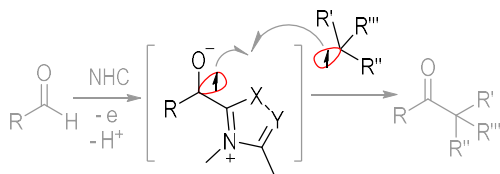
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SET Radical Coupling Reactions

A brief summary on reactions designed via NHC-catalyzed radical pathways is provided, with a particular highlight on a recent contribution from Ohmiya concerning coupling reactions of aldehydes with alkyl radicals.

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