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N-Heterocyclic Carbene Organocatalytic Reductive β,β-Coupling Reactions of Nitroalkenes via Radical Intermediates

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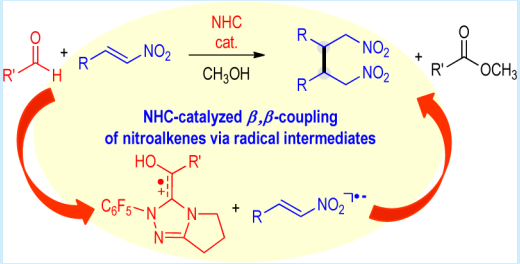
Supporting Information

ABSTRACT: An unprecedented *N*-heterocyclic carbene catalytic reductive β,β-carbon coupling of α,β-nitroalkenes, by using an organic substrate to mimic the one-electron oxidation role of the pyruvate ferredoxin oxidoreductase (PFOR) in living systems, has been developed. The reaction goes through a radical anion intermediate generated under a catalytic redox process. For the first time, the presence of radical anion intermediate in NHC organocatalysis is observed and clearly verified.



Thiamine pyrophosphate (TPP), a thiamine (vitamin B1) derivative and a cofactor of enzymes, catalyzes the oxidative decarboxylation of pyruvate to form acetyl-CoA and CO_2 in living systems.[1] These oxidative catalytic reactions, enabled by pyruvate ferredoxin oxidoreductase (PFOR), are believed to proceed via single-electron transfer (SET)/radical processes.[2,3] In synthetic chemistry, thiamine and related imidazolium and triazolium-based organocatalysts have been explored for a large set of reactions such as Benzoin[4] and Stetter reactions[5] via electron-pair transfer processes. However, a direct mimicking of Nature's radical process for reaction development received rare success.[6] Inspired by the TPP-mediated SET process of decarboxylation, here we report the first organocatalytic biomimetic β-carbon reductive coupling of nitroalkenes. In this reaction, nitroalkene undergoes a one-electron reduction process to form a reactive radical anion intermediate, and aldehyde is used as the reducing agent. The nitroalkene behaves as an oxidant, mimicking the role of PFOR in the TPP-dependent living systems.

The SET enzymatic catalytic pathway that inspired our design is illustrated in Figure 1a. Key steps of this enzymatic reaction include two single-electron oxidation steps that convert the Breslow intermediate (**I**) to a carboxylic acid derivative. The PFOR (briefed as $[Fe_4S_4]^{2+}$ in Figure 1a) serves as an oxidant to remove one electron from the TPP-bound intermediate (**I** and **II**). In small molecule organocatalysis involving *N*-heterocyclic carbenes (NHCs), oxidation of aldehydes (via Breslow intermediates similar to **I**) to carboxylic acids and acid derivatives have been studied by several groups.[7,8] In particular, Studer and co-workers used TEMPO as an oxidant to convert aldehydes to esters presumably through SET redox processes via NHC-bound radical intermediate similar to **II** as illustrated in Figure 1.[6]

We envisioned that the carbene-mediated SET processes could be developed for useful reactions other than the biological oxidative decarboxylation (Figure 1a) and the previously evaluated aldehyde to acid/ester conversions. More specifically, we hypothesized that when an (electron-deficient) alkene is used as a one-electron oxidant (by mimicking the role of PFOR in the living systems), the resulting alkene-derived radical might be modulated for interesting reactions. Nitroalkenes, with electron-deficient carbon−carbon double bonds, are commonly used as Michael acceptors in nucleophilic/electrophilic (electron pair transferring) reactions. A further survey of the literature[9] showed the feasibility of nitroalkenes behaving as a single-electron remover in the presence of metal reductants and under the enzymatic[9c] or electrochemical[9g] reduction environments. We thus chose α,β-unsaturated nitroalkenes (e.g., **2** in Figure 1b) as model substrates to develop NHC-mediated biomimetic coupling reactions via a SET process.

Briefly, an aldehyde molecule (e.g., **1**) may be used as a formal reductant to react with a NHC catalyst to generate Breslow intermediate **I** (Figure 1b). Removal of one electron from the Breslow intermediate **I** by nitroalkene **2** forms a nitroalkene-derived anionic radical intermediate **III**. During the formation of **III**, the Breslow intermediate **I** is oxidized to **II** that then undergoes a subsequent oxidation to form NHC-bound ester intermediate **IV**. The radical intermediates (**III**) combine to form a β,β-reductive coupling product **3** after

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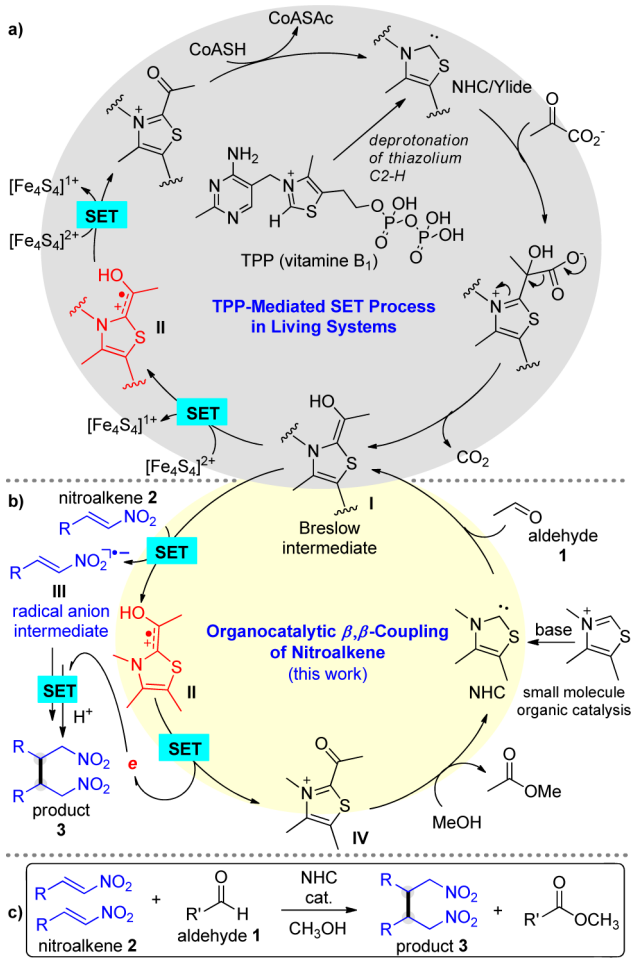


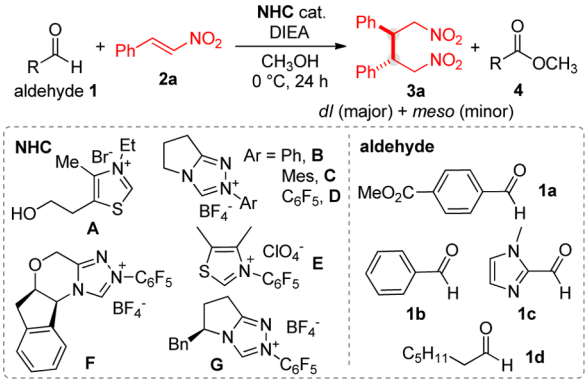
Figure 1. TPP-mediated enzymatic transformation and its biomimetic application in small molecule organocatalysis.

protonation. The NHC-bound ester intermediate **IV** is attacked by a methanol molecule to form an ester, with the generation of the NHC catalyst that can initiate another reaction cycle (Figure 1b). The overall reaction in converting nitroalkene **2** to the *β*,*β*-coupling product **3** is further shown as an equation in Figure 1c.

Key results in searching for suitable NHC catalysts, proper aldehyde reductants, and optimal reaction conditions are shown in Table 1. Since the active catalytic component in Nature's TPP is a thiazolium group, we initially chose thiazolium **A** as a NHC precatalyst. Nitrostyrene **2a** was chosen as a model substrate to develop the proposed coupling reactions. Evaluation of aldehyde reductants revealed that the use of the electron-deficient aryl aldehyde **1a** could lead to an encouraging formation of the proposed nitroalkenes *β*,*β*-coupling product **3a** (Table 1, entry 1).

During this reaction, the aldehyde substrate **1a** was oxidized and trapped by methanol (used as solvent) to form the corresponding ester, as isolated in our experiments. Further evaluations on the NHC catalysts (entries 2−5) showed that triazolium-based catalyst **D** bearing an *N*-C_6F_5 group was effective in mediating the formation of **3a** with 94% yield (entry 4). Chiral triazolium NHC catalysts **F** and **G** could also mediate this reaction, but without any observed enantioselectivity (entries 6−7). The lack of enantioselectivities partially supports the formation of the coupling product **3a** via a radical intermediate (**III**, Figure 1b) that is not covalently bonded to

Table 1. Condition Optimization[a]



entry	NHC	aldehyde	3a yield (%) *dl* + *meso*	3a yield (%) *dl*[b]	3a dr[c]
1	A	**1a**	~5		
2	B	**1a**	10	8	
3	C	**1a**	17	14	
4	**D**	**1a**	**94**	**66**	**71:29**
5	E	**1a**	13	9	
6	F	**1a**	14	12[d]	
7	G	**1a**	85	62[d]	72:28
8	D	**1b**	58	38	70:30
9	D	**1c**	75	51	71:29
10	D	**1d**	<5		

[a]Unless otherwise noted, reactions were carried out at 0 °C using **1** (0.2 mmol), **2a** (0.3 mmol), catalyst (0.02 mmol), DIEA (0.04 mmol), and 2 mL of MeOH. Yields and dr were determined via ^{1}H NMR analysis. [b]Isolated yields of *dl*-**3a**. [c]dr refers to *dl* over *meso*.[10] [d]No enantioselectivity.

the NHC catalyst. We further evaluated the effects of the aldehyde reductant using the optimal NHC catalyst **D** (entries 8−10, also see the Supporting Information for more details). Benzaldehyde **1b** was less effective than the electron-deficient aryl aldehyde **1a**, leading to **3a** with 58% yield. The use of heteroaryl aldehyde **1c** could afford **3a** in 75% yield, and alkyl aldehydes (such as **1d**) were completely ineffective. In addition, we observed significant differences in using different alcohols (see the Supporting Information): the more hindered and less acidic 2-propanol and ethanol were less effective and afforded the reaction products in lower yields.

In these reactions, the diastereomeric ratio (dr) of product **3a** is approximately 2.5:1. *dl*-**3a** is the major isomer that dissolves well in common solvents such as MeOH or CH_2Cl_2. In contrast, *meso*-**3a** is less soluble and tends to precipitate. Similar trends were observed for other coupling products using other *β*-aryl substituted nitroalkenes (Figure 2).

The scope of the *β*,*β*-reductive coupling reactions was then examined. We first studied nitroalkenes with a *β*-aryl substituent using the optimal condition developed above (Table 1, entry 4). The use of nitroalkenes bearing an electron-donating moiety at the *para*-position of the aryl substituent led to high yields of the reductive coupling products **3b** and **3c** (Figure 2). Placing electron-withdrawing groups on the *β*-aryl substituents was also well tolerated (**3d**−**g**), and *β*-naphthyl-substituted nitroalkene worked fine as well (**3h**). These reactions gave moderate values of diastereoselectivity. Heteroaryl (e.g., furyl, thienyl) analogues also worked well, providing products (**3i**−**l**) with high yields. Interestingly, *β*,*β*′-disubstituted *α*,*β*-unsaturated nitroalkene could also work

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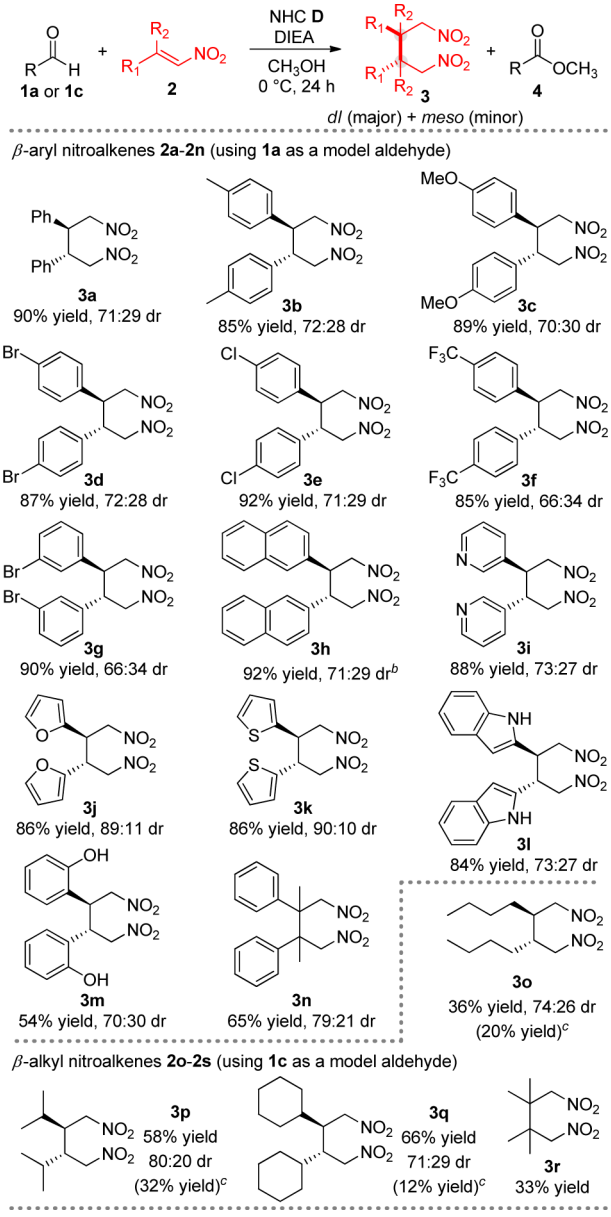


Figure 2. Substrate scope. (a) Unless otherwise noted, yields are isolated total yields; dr (*dl* over *meso*)[11] were determined via ^{1}H NMR analysis. (b) Based on isolated *dl* and *meso*-**3h** (slight dissolves in DMSO). (c) Yields obtained when **1a** was used as the model aldehyde.

under the standard conditions to afford the reductive coupling product **3n** bearing two adjacent quaternary carbon centers. We have tried two different nitroalkenes (e.g., **2b** and **2d**) together in order to synthesize nonsymmetric coupling products but only obtained inseparable complex mixtures.

We then evaluated nitroalkenes with *β*-alkyl substituents. The conditions (e.g., with aldehyde **1a** as a reductant) used for *β*-aryl nitroalkenes were ineffective for the reductive coupling product formations (Figure 2, yields given in parentheses). In these cases (**3o**−**r**), the corresponding Stetter reaction products[12] between aldehyde and nitroalkenes (nitroalkenes behaving as Michael acceptors) were obtained as the major adducts. Fortunately, by using heteroaryl aldehyde **1c** as the reductant, the desired nitroalkenes reductive coupling products (**3o**−**r**) could be obtained in moderate yields. The competing Stetter reactions were still observed, but with much lower yields. For example, in the formation of **3q** (66% yield), the competing Stetter product was formed with 20% yield (in comparison, when aldehyde **1a** was used, **3q** was formed in 12% yield and the corresponding Stetter product was formed in 52% yield.).

To understand the reaction mechanism, we moved to detect and analyze the radical intermediates proposed in our reaction. Fortunately we detected the radical anion derived from *β*-isopropyl nitroethylene **2p** using EPR spectroscopy (Figure 3).

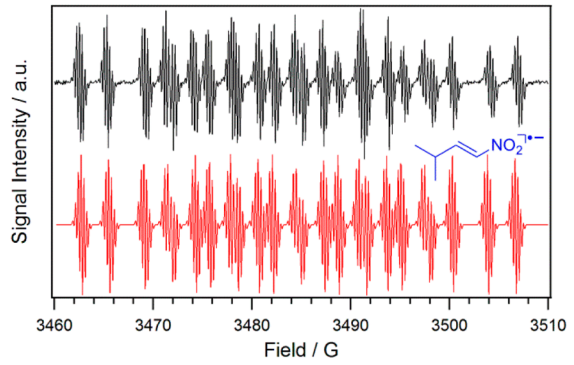
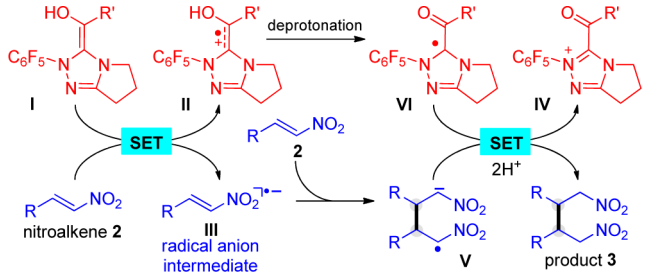


Figure 3. (Black line) EPR spectrum of the anionic radical derived from *β*-isopropyl nitroethylene obtained in methanol at 22(±2) °C. (Red line) Simulated spectrum based on hyperfine coupling constants of 1N = 13.025 G, 1H$_a$ = 8.775 G, 1H$_b$ = 2.80 G, 1H$_c$ = 6.375 G and 6H = 0.275 G, with a line width of 0.15 G.

A postulated pathway is further illustrated in Scheme 1. The catalytically generated radical anion **III** underwent a 1,4-

Scheme 1. Postulated Pathway



addition to a nitroalkene **2** to form intermediate **V**. This intermediate (**V**) underwent another SET reduction process and 2-fold protonations to furnish the nitroalkene dicoupling product **3**. The Breslow intermediate-derived radical cation **II** underwent a deprotonation process and a SET oxidation step to eventually form an acyl azolium intermediate **IV** that was subsequently captured by alcohol. This proposed pathway is consistent with an electrochemical ECE mechanism (electron transfer-chemical reaction-electron transfer) for reductive *β*,*β*-dimerization of activated olefins.[13] Another possible pathway is a direct radical anion combination to form the dicoupling product, which cannot be ruled out at this moment.

In summary, we have developed the first NHC organocatalytic reductive *β*,*β*-coupling reaction of nitroalkenes. The reactions proceed through a SET process mimicking Nature's TPP-mediated oxidative decarboxylation of pyruvates. Nitroalkenes, unlike their frequent use in electron-pair-transfer reactions, participate in the reactions as one-electron acceptors. Aldehydes act as reducing agents. This NHC-catalyzed SET

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procedure is expected to significantly expand the scope of organocatalysis for new reaction developments. Detailed mechanistic studies via experimental and computational approaches are being pursued in our laboratories and will be communicated in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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