

Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via the Single-Electron-Transfer (SET) Process and Formal 1,4-Addition

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S Supporting Information

ABSTRACT: A carbene-catalyzed reductive 1,4-addition of nitrobenzyl bromides to nitroalkenes is disclosed. The reaction proceeds via a carbene-enabled single-electron-transfer process that generates radicals as key intermediates. The present study expands the potentials of carbene catalysis and offers unusual transformations for common substrates in organic synthesis.



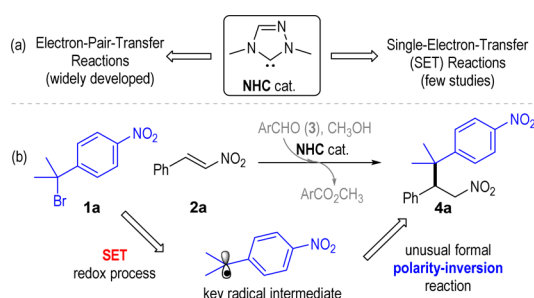
Single-electron-transfer (SET) radical activations provide unique opportunities for unusual transformations not readily accessible from conventional electron-pair reactions (e.g., reactions between nucleophiles and electrophiles).^{1,2} In recent years, *N*-heterocyclic-carbenes (NHCs) as organic catalysts have received considerable attention in synthetic chemistry.³ It is also known that the oxidative decarboxylation of pyruvate to form acetyl-CoA in living systems is mediated by thiamine pyrophosphate (TPP/Vitamin B1) with carbene as the active catalytic site.⁴ This biological reaction catalyzed by Vitamin B1 involves both electron-pair-transfer and SET processes. It is therefore reasonable to expect that in synthetic chemistry, NHCs shall be able to mediate a large set of transformations that include SET radical reactions. Somewhat unfortunately, to date most of the reactions mediated by NHCs are developed based on electron-pair transfers as the key processes (Scheme 1a).³ NHC-mediated SET radical reactions are much less developed. In this challenging direction, Studer's oxidation of aldehydes to esters by using TEMPO as an oxidant is believed to go through a SET process.⁵ Recent mechanistic studies from Rehbein suggest that both radical and electron-pair-transfer pathways operate in the

NHC-mediated benzoin reactions.⁶ Our laboratory reported NHC-mediated reductive self-coupling of nitroalkenes, in which key radical intermediates were verified via EPR (electron paramagnetic resonance) experiments.⁷ Rovis⁸ and our laboratory⁹ independently reported homoenolate-derived radical intermediates for the NHC-mediated β -carbon functionalization of enals. Very recently, we have realized carbene-mediated generation of radical intermediates from nitro-benzyl bromides for formal 1,2-addition to activated ketones.¹⁰

Here we report formal 1,4-addition of nitro-benzyl bromide (**1a**) to nitroalkene (**2a**) via NHC-mediated SET as a key process (Scheme 1b). Aldehyde (**3**) is used as a reductant that transfers one electron to the nitro-benzyl bromide substrate (via a Breslow adduct formed between **3** and NHC catalyst) to eventually form a nitrobenzyl radical as a key intermediate. The reductive 1,4-addition product (**4a**) constitutes a formal polarity inversion¹¹ for the benzylic carbon of **1a**, in which the initially electrophilic benzylic carbon is catalytically converted to a nucleophilic reactive carbon.

Key results of condition optimization using nitrobenzyl bromide **1a** and nitroalkene **2a** as the model substrates are summarized in Table 1. With aryl aldehyde **3** as a formal reductant and CH₃OH as a reagent and solvent, triazolium NHC catalyst **C1** was found to mediate the formation of the 1,4-reductive coupling product **4a** in 81% yield (entry 1).¹³ The *N*-pentafluorobenzyl (C₆F₅) substituent in catalyst **C1** was important for this reaction, as the use of the corresponding *N*-mesityl or *N*-phenyl NHC catalysts led to much poorer yields of **4a** (see Supporting Information (SI)). A few *N*-C₆F₅ substituted triazolium NHC catalysts that could mediate this reaction to give **4a** with 21%–69% yields are shown in entries 2–4. Evaluating

Scheme 1. NHC-Catalyzed 1,4-Addition via SET Process



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Table 1. Condition Optimization

+ ArCHO (3, 0.15 mmol), CH₃OH
 + ArCO₂CH₃ (5)

entry	NHC, mol %	base	solvent (mL)	yield (%) ^a
1	C1, 10	DIEA	CH ₃ OH (1)	81
2	C2, 10	DIEA	CH ₃ OH (1)	21
3	C3, 10	DIEA	CH ₃ OH (1)	55
4	C4, 10	DIEA	CH ₃ OH (1)	69
5	C1, 10	K ₂ CO ₃	CH ₃ OH (1)	53
6	C1, 10	DBU	CH ₃ OH (1)	68
7 ^c	C1, 10	DIEA	toluene (1)	76
8	C1, 10	DIEA	CH ₃ OH (2)	91
9	C1, 5	DIEA	CH ₃ OH (2)	92(87) ^b
10	C1, 1	DIEA	CH ₃ OH (2)	63
11	no NHC	DIEA	CH ₃ OH (2)	no reaction

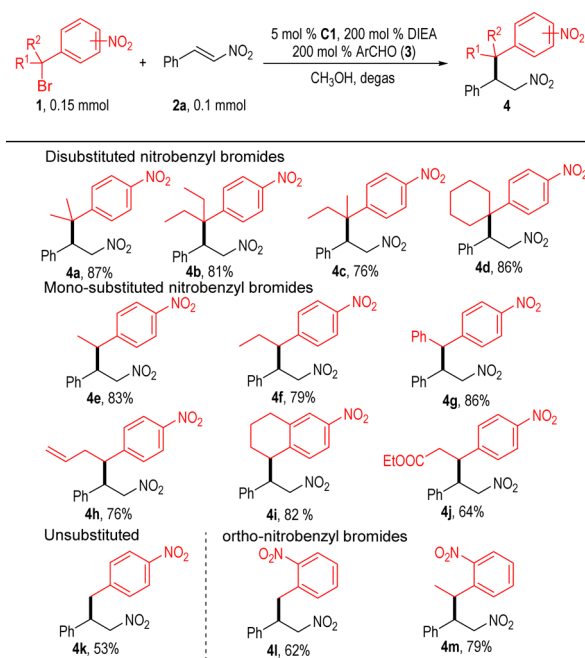
^aYield (based on 2a) was estimated via ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^bIsolated yield in parentheses. ^c10 equiv CH₃OH was used.

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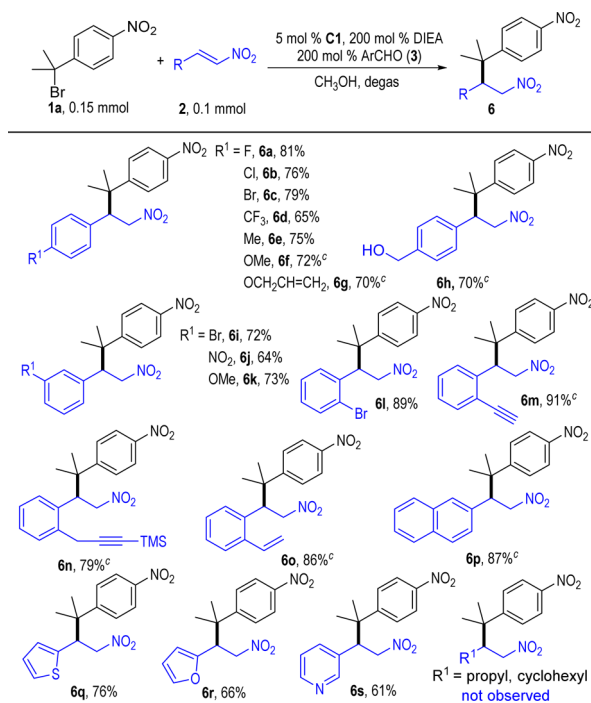
the effects of bases showed that DIEA was an optimal choice (entries 1, 5, 6; see SI). Toluene could also be used as a solvent (entry 7). We then found that the reaction yield could be improved when the reaction concentration was reduced (entry 8). The loading of the NHC catalyst could be reduced to 5 mol %, affording product 4a in 87% yield (entry 9). The use of 1 mol % NHC catalyst could still afford 4a in 61% yield (entry 10). The NHC catalyst was required to enable the SET process for the reaction to proceed, as no product (4a) could be obtained when NHC was absent (entry 11).

With acceptable conditions in hand, we next evaluated the generality of this reaction. We first studied the scope of the nitrobenzyl bromides by using nitro-styrene 2a as a model substrate (Scheme 2). *para*-Nitrobenzyl bromide with two substituents on the benzylic carbon worked very effectively, giving the corresponding 1,4-addition products (4a–d) in 76–87% yields. Nitrobenzyl bromide with one substituent on the benzylic carbon was then studied (4e–j). The substituent could be alkyl (4e, f), aryl (4g), and allyl (4h) units. The carboxylic ester group (e.g., 4j) could also be tolerated. The simplest *p*-nitrobenzyl bromide reacted as well, leading to 4k in 53% yield. The nitro group could be placed on the ortho-position of the benzyl ring (4l, m) without affecting the reaction outcomes. The relatively low yields for 4k and 4l are likely due to the relatively low stability of benzyl radicals bearing no substituents on the benzylic carbon.¹⁴

We then evaluated the scope of the nitroalkenes by using 1a as a model nitrobenzyl bromide substrate (Scheme 3). By placing various substituents on the 4-position of the phenyl ring of the nitrostyrene, increasing the amount of 1a and aldehyde 3 from 1.5 to 2.0 equiv was necessary for complete conversion of the nitroalkene substrates (6f–g). The presence of an unprotected alcohol in the substrate did not affect the reaction yield (6h). Installing various substituents at the meta- or ortho-positions on the phenyl ring of the nitrostyrene substrates led to desired

Scheme 2. Examples of Nitrobenzyl Bromides^{a,b,c}

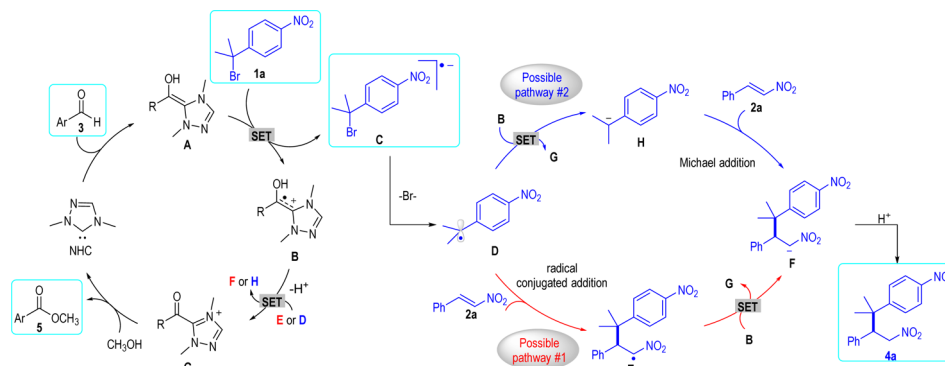
^aReaction conditions same as those in Table 1, entry 9. ^bIsolated yield. ^cFor 4c, 4e–4j, 4m, dr between 1.1:1 and 1.2:1, determined via ¹H NMR.

Scheme 3. Examples of Nitroalkenes^{a,b}

^aReaction condition as in Table 1, entry 9. ^bIsolated yield. ^c0.2 mmol of 1a, 0.2 mmol of 3 were used.

products with satisfactory yields as well (6i–o); substrates with ortho-unsaturated substituents did not give any cyclization products (6m–o). Finally, the phenyl ring of 2a could be replaced with naphthyl or heteroaryl groups (6p–b). The use of β -alkyl nitroalkene substrates examined in our studies did not

Scheme 4. Proposed Reaction Pathways

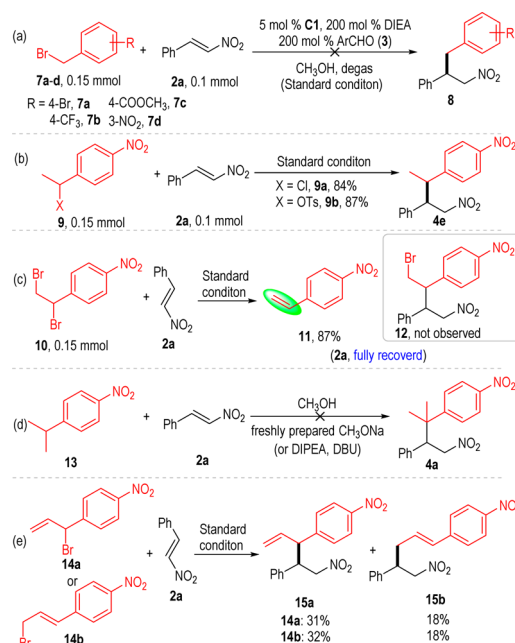


lead to desired products. In these cases, the nitrobenzyl bromides were reduced, and the nitroalkene largely remained unchanged.

The plausible pathways leading to the formation of the formal 1,4-addition product were illustrated in Scheme 4. Reduction of nitrobenzyl bromide **1a** by Breslow intermediate **A** leads to radical cation intermediate **B** and benzyl bromide-derived radical anion intermediate **C**. The release of a Br^- from radical anion **C** leads to benzylic radical intermediate **D**. In one possible pathway (possible pathway #1), 1,4-addition of the benzylic radical (**D**) to nitroalkene **2a** leads to radical intermediate **E**. Similar 1,4-addition of a carbon-centered radical to a Michael acceptor is a known process.¹⁵ This radical intermediate (**E**) undergoes one further SET reduction to form anion intermediate **F**. Protonation of **F** leads to final product **4a**. During this SET redox process (**E** to **F**), the Breslow intermediate-derived radical cation intermediate **B** is further oxidized to azolium ester intermediate **G** that is then trapped by CH_3OH to form ester **5**. Alternatively (possible pathway #2), the benzylic radical intermediate **D** may be further reduced to the corresponding benzylic anion intermediate **H**. A nucleophilic addition (electron-pair reaction) of **H** to nitroalkene **2a** furnishes intermediate **F** that is then converted to **4a** after protonation.

To further understand the reaction pathways, we performed multiple experiments (Scheme 5). The nitro (NO_2) group on the benzyl bromide is required for the NHC-mediated generation of radical intermediates (**C** and **D**, Scheme 4), as replacing the NO_2 group with other electron-withdrawing units (such as Br , CF_3 , COOMe , **7a–c**) led to no formation of the corresponding reductive coupling product **8** (Scheme 5a). Placing the nitro group on the meta-position of the benzyl bromide also led to no reaction (**7d**). Replacing the bromide (Br) with other leaving groups (such as Cl , OTs , **9a–b**) led to an identical product with similar yields (Scheme 5b), suggesting that the leaving group (Br , Cl , or OTs) has little influence on the SET process that transfers one electron from Breslow intermediate **A** (e.g., to **1a**) to form the radical anion intermediate (e.g., **C**). Similar leaving groups have been used in the electrochemical process for benzylic radical formations.¹⁶ In our earlier studies of NHC-mediated self-couplings of nitroalkenes,⁷ the formation of a nitroalkene-derived radical anion initiates the subsequent coupling reactions. In the present work, our experiments suggest that it is *not* the addition of nitroalkene-derived radical anion to nitrobenzyl bromide that leads the formation of **4a**. For example, when dibromoethyl-4-nitrobenzene (**10**) was used to replace **1a** as the substrate, the corresponding reductive coupling product **12** was not formed (Scheme 5c). These results (Scheme 5c) suggest that, in our present catalytic reaction (Table 1), addition of a nitroalkene-derived radical anion to nitrobenzyl bromide

Scheme 5. Control Experiments for Mechanistic Insights



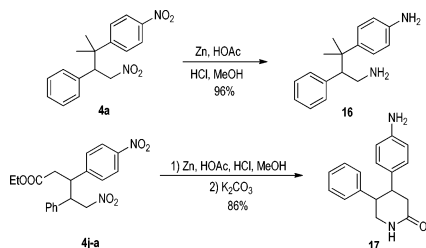
unlikely occurred. Additional discussions on this mechanistic aspect are provided in the SI.

We also performed experiments to evaluate the feasibility of possible pathway #2 (Scheme 5). The use of **13** to react with **2a** in the presence of various bases failed to produce **4a** (Scheme 5d). This observation (Scheme 5d) suggests that, under our condition with CH_3OH as the solvent, the ionic pathway (addition of **H** to nitrostyrene **2a**, Scheme 4, possible pathway #2) is likely unfavorable. When 4-nitrobenzyl bromide **14a** or **14b** was used as the substrate, identical results were obtained with the formation of product **15a** and **15b** in 32% and 18% yields respectively (Scheme 5e). In particular, **15a** derived from a secondary carbon was formed in a higher yield than **15b** that was formed from the corresponding primary carbon. These results (Scheme 5e) suggest that the reaction likely goes through the radical pathway (possible pathway #1, Scheme 4), although the ionic pathway (possible pathway #2) cannot be completely ruled out. Moreover, there is a third possibility of direct coupling of two radicals.¹⁷ Although we cannot completely exclude this possibility, we feel this pathway is unlikely, because the result of using **10** as a nitrobenzyl bromide (Scheme 5c), and in all our reactions of reaction scope study, the nitroalkene reductive self-coupling products⁷ were not observed, suggesting that a

nitroalkene-derived radical anion intermediate was not formed in significant concentration in our reactions.

The reductive coupling products from our reactions could undergo further transformations by using simple conditions. For example, **4a** could be reduced to the corresponding diamine **16** in 96% yield (Scheme 6). Catalytic reaction product **4j-a** (one

Scheme 6. Synthetic Transformations of our Products



diastereomer) could be converted to lactam **17** in 86% yield. Structures such as **17** are widely found as core structures in biological active alkaloids and pharmaceuticals.¹⁸

In summary, we have developed an unusual reductive coupling of nitrobenzyl bromides and nitroalkenes. The reaction proceeds through an NHC catalyst-enabled SET that generates a benzylic radical intermediate as the key process. A formal 1,4-addition of the benzylic carbon to the nitroalkene furnishes the final product. In this overall process, the initially electrophilic benzylic carbon of the benzyl bromide is catalytically converted to a nucleophilic reactive carbon. Our catalytic reaction is carried out under mild conditions, with different functional groups being well tolerated. We expect this study to encourage further advances in carbene-catalyzed radical reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03792.

Experimental procedures and spectral data for all new compounds; crystallographic data for **4a** (PDF)

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Notes

The authors declare no competing financial interest.

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