Carbene-catalysed reductive coupling of nitrobenzyl bromides and activated ketones or imines via single-electron-transfer process

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Benzyl bromides and related molecules are among the most common substrates in organic synthesis. They are typically used as electrophiles in nucleophilic substitution reactions. These molecules can also be activated via single-electron-transfer (SET) process for radical reactions. Representative recent progress includes α-carbon benzylation of ketones and aldehydes via photoredox catalysis. Here we disclose the generation of (nitro)benzyl radicals via N-heterocyclic carbene (NHC) catalysis under reductive conditions. The radical intermediates generated via NHC catalysis undergo formal 1,2-addition with ketones to eventually afford tertiary alcohol products. The overall process constitutes a formal polarity-inversion of benzyl bromide, allowing a direct coupling of two initially electrophilic carbons. Our study provides a new carbene-catalysed reaction mode that should enable unconventional transformation of (nitro)benzyl bromides under mild organocatalytic conditions.
ALKYL HALIDES, SUCH AS BENZYL BROMIDES, ARE READILY AVAILABLE AND INEXPENSIVE RAW MATERIALS IN CHEMICAL SYNTHESIS. DUE TO THE ELECTRONEGATIVE NATURE OF THE HALIDE ATOMS, THESE MOLECULES ARE TYPICALLY USED AS ELECTROPHILES TO REACT WITH NUCLEOPHILIC ATOMS IN SUBSTITUTION REACTIONS. ALKYL HALIDES CAN ALSO BE ACTIVATED TO FORM RADICAL INTERMEDIATES FOR VARIOUS REACTIONS. INSTEAD OF THE USE OF ALKYL HALIDES TO GENERATE RADICAL INTERMEDIATES FOR UNUSUALREACTIONS, WE HAVE FOUND THAT THE PRESENCE OF A NITRO GROUP (IN EITHER SUBSTRATES OR REAGENTS) IS IMPORTANT TO INITIATE A SET PROCESS UNDER NHC CATALYSIS. HERE WE REPORT THAT BENZYL BROMIDES, BEARING A NITRO SUBSTITUENT ON THE BENZENE RING, CAN UNDERGO AN NHC-MEDIATED SET PROCESS USING AN ALDEHYDE AS A FORMAL REDUCTANT. THE CATALytically GENERATED BENZYL RADICAL INTERMEDIATE THEN UNDERGOES A FORMAL 1,2-ADDITION TO A KETONE TO FORM A TERTIARY ALCOHOL. THE OVERALL REACTION IS A FORMAL REDUCTIVE COUPLING OF NITROBENZYL BROMIDE 1 AND KETONE 2. NOTABLY, THE USE OF ALKYL HALIDES TO REACT WITH ANOTHER ELECTROPHILE TYPICALLY NEEDS TO GO THROUGH PRE-FORMED ORGANOMETALLIC REAGENTS (SUCH AS GRIGNARD REAGENTS). CATALYTIC VARIANTS OF THE APPROACHES WITH ORGANOMETALLIC REAGENTS HAVE ALSO BEEN DEVELOPED. HAVEN'T SENSITIVE FUNCTIONAL GROUPS SUCH AS NITRO AND KETONE SUBSTITUENTS OFTEN CANNOT SURVIVE UNDER CONDITIONS WITH ORGANOMETALLIC REAGENTS. IN THE AREA OF ORGANIC CATALYSIS, NHCS HAVE MAINLY BEEN USED IN ELECTRON-PAIR-TRANSFER REACTIONS. DESPITE THE FACT THAT VITAMIN B1 (AN NHC PRECURSOR)-MEDIATED REACTIONS IN BIOLOGICAL SYSTEMS GO THROUGH SET PROCESSES, NHCS-MEDIATED RADICAL REACTIONS IN SYNTHETIC CHEMISTRY ARE MUCH LESS DEVELOPED.

**Results**

**Reaction optimization.** Key results of initial studies are summarized in Table 1. The 4-nitrobenzyl bromide 1a, and 2,6-unsaturated ketoester 2a were used as model substrates. Optimal conditions for the formation of alcohol product 4a (in 75% isolated yield) were found when triazolium salt 3a was used as an NHC precursor, aryl aldehyde 3a as a reductant, and N,N-diisopropylethylamine as a base (entry 1). The reactions under darkness (the reaction flask was covered with aluminium foil) or normal room lighting conditions gave nearly the same outcomes, indicating that the generation of radical intermediates under our system was not driven by light. Both the NHC catalyst (entry 2) and the aryl aldehyde reductant (entry 3) were required for the reductive coupling reaction to proceed. The nitro group in substrate 1a was critical for this reaction to occur, and its roval or replacement with other substituents (for example, 1b, 1c, or 1d) led to no detectable formation of 4a (entry 4). The substituents on the aryl aldehyde reductant could also affect the reaction efficiency (entries 5, 6). When aryl aldehyde such as 3b and 3c were used as the reductant, 4a was formed in much lower yield. In these cases (entries 4–6), most of the benzyl bromide and the oxidation of aldehydes to carboxylic esters using TEMPO as a single-electron oxidant via NHC catalysis. We developed the dimerisation of nitroalkenes via NHC-mediated generation of radical anion intermediates from nitroalkenes. Rovis and our laboratories independently reported β-hydroxylation of unsaturated aldehydes through SET processes under NHC catalysis. Our present study in catalytically turning (nitro)benzyl bromides to radical intermediates for unusual reaction offers a new reaction mode of NHC catalysis that should provide unique opportunities in chemical synthesis.

**Table 1 | Key results of condition optimizations.**

| Entry | Benzyl bromide | Ar·CHO | NHc | 4a |
|-------|----------------|--------|-----|----|
| 1     | 1a             | 3a     | A   | 78 (75°) |
| 2     | As entry 1, no NHc | ND |
| 3     | As entry 1, no Ar·CHO | ND |
| 4     | As entry 1, benzyl bromide = 1b, 1c or 1d | ND |
| 5     | As entry 1, Ar·CHO = 3b | 36 |
| 6     | As entry 1, Ar·CHO = 3c | 27 |
| 7     | As entry 1, NHc = B | 35 |
| 8     | As entry 1, NHc = C | 29 |
| 9     | As entry 1, NHc = D | 23 |
| 10    | As entry 1, NHc = E | ND |

DIPEA, N,N-diisopropylethylamine; Mes, 1,3,5-trimethylbenzene; ND, not detected.

**Figure 1 | NHC-catalysed reduction coupling of nitrobenzyl bromide with activated carbonyl compounds.** (a) Formation of benzyl radical via photocatalysis or NHC catalysis. (b) Reductive coupling of nitrobenzyl bromides and ketones.
Substrates scope with α-keto esters. With an acceptable condition in hand, we examined the scope of the reductive coupling reaction (Fig. 2). Examples of nitrobenzyl bromides that could react effectively (with ketoester 2a as a model ketone substrate) are given in Fig. 2a. The use of benzyl bromides with the NO2 group at the para (4a) or ortho (4b) position of the benzene ring both worked well, while meta-nitro benzyl bromide could not react to give the proposed reductive coupling product. Placing additional substituents on the para-nitro benzyl bromides (4c, 4d) and ortho-nitro benzyl bromides (4e–j) were all tolerated. For example, having an ester (4f) or ketone (4g) moiety on the ortho-nitrobenzyl bromide did not affect the reaction outcomes. It should be noted that such electrophilic functional groups (for example, esters, ketones) are likely problematic in conventional approaches using organometallic reagents. Secondary and tertiary nitrobenzyl bromides (4k, 4l) are also effective substrates. Examples of ketoester substrates are given in Fig. 2b. Different substituents and substitution patterns on the phenyl ring of unsaturated ketoester 2a were tolerated (4m–r). The phenyl unit of 2a could be replaced with a thiofuran (4s), alkene (4t) or alkylation (4u, 4v) unit. Phenyl ketoester 4v could effectively react with

**Figure 2 | α-Ketoester as substrates and its transformations.** Scope of the reaction (a–b) and synthetic transformation of the reductive coupling product (c). The reactions were performed on 0.1 mmol scale (condition as in Table 1, entry 1). Isolated yields base on ketoesters. **Relative configuration.** MCPBA, 3-chloroperoxybenzoic acid.
nitrobenzyl bromide 1a, while the use of alkyl ketoesters (such as methyl 2-oxobutanoate) did not lead to the proposed products. The carbon–carbon double bond of unsaturated ketoester 2a could be replaced with a carbon–carbon triple bond (4w–z), with little influence on the reaction yields. The reaction, carried out under mild conditions, can be easily scaled up. For example, product 4b could be prepared in gram scale without loss in yield.

The reductive coupling adduct from our reactions can be readily converted to other functional molecules (Fig. 2c). For example, reduction of the NO$_2$ group in 4b followed by an intramolecular ester-to-amide exchange could give lactam 4b-1 that bears a quinolone core widely found in natural products and bioactive molecules.$^{35}$ The alkene in allylic alcohol 4b could be easily converted to epoxide 4b-2 in 87% yield with excellent stereo-selectivity (only one diastereoisomer was obtained). The hydroxyl group in 4b could undergo a formal 1,3-migration under acidic conditions to form γ-hydroxy α, β-unsaturated ester 4b-3 in 81% yield.

**Substrates scope with isatins.** To further expand the scope of our reductive coupling reactions, we next examined isatin derivatives as ketone substrates to react with the nitrobenzyl bromides (Fig. 3). To our delight, the standard conditions used above for the ketoester substrates (Table 1, entry 1) worked effectively for the isatin substrates without any further optimization. The reaction yields here were slightly higher than those reactions using ketoesters. Nitrobenzyl bromides with different substituents and substitution patterns were well tolerated, giving the desired alcohol products in 68–81% yields (7a–j, Fig. 3a). The substituents on the isatin had little effect on the reaction yields (7k–t, Fig. 3b). The isatin without an N-substituent (7u) reacted effectively as well. Further synthetic transformations of the reductive coupling products can provide a shortcut to functional molecules (Fig. 3c). For example, reduction and cyclization of 7u followed by a facile methylation gave neocyptoplepine 7u-2, a natural product isolated from the bark of the roots of *Cryptolepis sanguinolenta*.$^{36,37}$ Neocyptoplepine and its analogs exhibit a strong antiplasmodial activity against *Plasmodium falciparum* chloroquine-resistant strains.$^{38}$

**Substrates scope with imines.** Imines as reaction partners also worked effectively under our catalytic condition (Fig. 4). The results further illustrated the broad applicability of our NHC-mediated SET approach.
Discussion

To understand the reaction pathway (as postulated in Fig. 5f), we analysed the side reactions and performed multiple control experiments (Fig. 5, additional control experiments see Supplementary Methods). Under the standard conditions (Table 1, entry 1), a debromination product (10a) of nitrobenzyl bromide 1a was observed in 42% yield (Fig. 5a); the yield of 10a is based on ketone ester 2a-the limiting reagent. This side product (10a) likely come from a further reduction of nitrobenzyl radical intermediate B2 (Fig. 5a). Specifically, the reduction of B2 formed a nitrobenzyl anion that underwent spontaneous protonation in CH3OH as the solvent and proton source to form 10a. The nitrotoluene substrate 10a could not react with our ketone substrate 2a (Fig. 5b,c), suggesting that the formation of 4a in our catalytic reaction likely came from a nucleophilic addition of nitrobenzyl anion to the ketone substrate. A possible reduction39 of the ketone substrate 2a to form α-hydroxyl ester 11a was not observed. To rule out the possibility that 9a was formed in situ and quickly reacted with the bromide substrate 1a. We prepared 11a and evaluated its reaction with 1a (Fig. 5d). No formation of 4a was observed under various conditions (Fig. 5d).

We have also measured the reduction potential of compounds 1a, 2a and 6a via cyclic voltammetry (see Supplementary Method and Supplementary Fig. 13). The experiments showed that compound 1a (E^red = −1.18 V vs) has a higher reduction potential than compounds 2a (E^red = −1.47 V vs) and 6a (E^red = −1.38 V vs). The results suggested that most likely 1a is easier to be reduced, supporting our mechanistic proposal (Fig. 5f) that the SET process first occurs on nitrobenzyl bromide 1a. Finally, the addition of radical trapping agent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to our reaction diminished the yield of 4a (Fig. 5e). A radical–radical coupling product 12a between TEMPO and nitrobenzyl radical B2 was observed in 7% yield (Fig. 5e). Similar observations in trapping of benzyl radical intermediates with TEMPO under photocatalysis were reported by Melchiorre39 and Meggers41, respectively.

A postulated reaction pathway is illustrated in Fig. 5f. Aldehyde reagent 3 reacts with the NHC catalyst to form a Breslow intermediate40 A1 that then serves as a single-electron reductant to convert nitrobenzyl bromide 1a into radical anion intermediate B1. Breslow intermediate A1 is oxidized to a radical cation intermediate31 A2 in this process. The leaving of a bromide anion (Br^-) from B1 affords nitrobenzyl radical intermediate B2. On the one hand, addition of radical intermediate B2 to ketone41–44 substrate 2 forms radical intermediate B3. Subsequent reduction of B3 by Breslow intermediate-derived radical cation A2 forms B4, which can then be protonated to form alcohol product 4. The oxidized A2 becomes azolium ester intermediate A3 that can then be trapped by CH3OH to form ester 5 with regeneration of the NHC catalyst. Alternatively, reduction of radical intermediate B2 to form intermediate B5 with an anionic benzylic carbon may occur. Nucleophilic addition of B5 to ketone substrate 2 can also lead to product 4. At this point, this ionic pathway (via intermediate B5) cannot be ruled out. In the overall process, the initially electrophilic nitrobenzyl bromide is catalytically activated to directly react with another electrophilic substrate (the ketone substrate).

In summary, we have developed a new organic catalytic method for the generation of nitrobenzyl radical intermediates from nitrobenzyl bromides under mild conditions. The catalytically formed radical intermediates react with ketones, resulting in a formal reductive coupling of initially electrophilic nitrobenzyl bromides and ketones. The products from our catalytic reactions can be readily transformed to functional molecules and natural products. Our study provides a new reaction mode that can likely allow for unique design in organic synthesis. It may also encourage further adventures in developing novel organocatalytic activations by single-electron-transfer processes. Mechanistic studies and additional development of this reaction mode for challenging substrates are in progress.

Methods

General strategy of reduce coupling reactions. To a reaction tube equipped with a stirrer bar were added NHC catalyst salt A (0.005 mmol), aldehyde 3 (0.15 mmol), ketone (2, 6 or 8, 0.1 mmol), and benzyl bromide 1 (0.15 mmol). The tube was sealed, evacuated and purged, and a solution of N,N-disopropylethylamine (0.15 mmol, 19.4 mg, 25 μl) in methanol (1.0 ml) was added. The reaction was stirred for 8h. The solvent was removed in vacuo and the residue was purified by flash column chromatography.
**Figure 5 | Experiments to elucidate the reaction mechanism and possible reaction pathways.** (a) The experiment indicates that the α-ketoester has no effect for the generation of nitrobenzyl radical. (b) The result suggests that the 1,2-addition product unlikely come from 4-nitro toluene in the current reaction system. (c) The coupling product could not be produced in the presence of NaOMe. (d) The final product could not be obtained via the alkylation of α-hydroxy ester. (e) The result indicates that the nitro benzyl radical is existent in current reaction system. (f) The nitrobenzyl radical B2 could be formed via oxidation of Breslow intermediate A1 and leaving of bromide anion from B1. Subsequently, the carbon-carbon bond can be formed via 1,2-addition of nitrobenzyl radical intermediate B3 or ionic intermediate B5 to carbonyl compounds.

**Data availability.** For 1H, 13C NMR and high-performance liquid chromatography spectra of compounds in this manuscript, see Supplementary Figs 1–129. For Oak Ridge thermal ellipsoid plot (ORTEP) of products 4w and 7l, see Supplementary Information. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (4w: CCDC 1451838; 7l: CCDC 1451840). These data could be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Author contributions

B.-S.L. and Y.W. contributed equally to this work. B.-S.L. proposed the reductive coupling reactions of benzyl bromides with ketones, and performed most of the experiments; Y.W. initially proposed NH6-mediated generation of nitrobenzyl radicals; R.S.I.P. performed part of the experiments; R.D.W. carried out EPR studies attempting to understand the reaction mechanism; Y.Z., Y.S. and B.-A.S. participated in designing part of the experiments; Y.R.C. conceptualized and directed the project, and drafted the manuscript with the assistance from all co-authors. All authors contributed to discussions.
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