Nickel-Catalyzed Site- and Stereoselective Reductive Alkylalkynylation of Alkynes

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Development of a catalytic multicomponent reaction by orthogonal activation of readily available substrates for the streamlined difunctionalization of alkynes is a compelling objective in organic chemistry. Alkyne carboalkynylation, in particular, offers a direct entry to valuable 1,3-enynes with different substitution patterns. Here, we show that the synthesis of stereodefined 1,3-enynes featuring a trisubstituted olefin is achieved by merging alkynes, alkynyl bromides and redox-active N-(acyloxy)phthalimides through nickel-catalyzed reductive alkylalkynylation. Products are generated in up to 89% yield as single regio- and E isomers. Transformations are tolerant of diverse functional groups and the resulting 1,3-enynes are amenable to further elaboration to synthetically useful building blocks. With olefin-tethered N-(acyloxy)phthalimides, a cascade radical addition/cyclization/alkynylation process can be implemented to obtain 1,5-enynes. The present study underscores the crucial role of redox-active esters as superior alkyl group donors compared to haloalkanes in reductive alkyne dicarbofunctionalizations.

Aliphatic carboxylic acids are abundant feedstock chemicals that have found extensive utility in chemical synthesis.¹-² With recent advances in cross-coupling chemistry, these readily available organic molecules which were once regarded as non-traditional cross-partners, have emerged as convenient alkyl donors in catalytic decarboxylative C–C bond forming transformations, either via the innate carboxyl groups³-¹⁰ or their activated ester derivatives.¹¹-²³ These developments are further driven by the much wider commercial availability of alkyl carboxylic acids as compared to conventional alkyl halides or alkylmetal reagents.¹²,²²,²⁴ A related class of reactions that utilize N-(acyloxy)phthalimides (or NHPI esters) involve decarboxylative alkyl additions to alkynes²⁵ or alkenes.²⁶-³⁷ Intrigued by previous studies, we speculated if alkyl NHPI esters could be exploited in three-component processes by merging with an alkyne and an alkynyl halide to deliver synthetically valuable acyclic 1,3-enyne motifs, conjugated entities commonly embedded within natural products, pharmaceuticals, agrochemicals and materials.³⁸-⁴²

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Various routes to architecturally analogous 1,3-enynes that contain a trisubstituted alkene moiety\textsuperscript{43-54} have been developed, but the majority focused on two-component systems involving coupling reactions of elaborated alkynes/alkenes as starting materials.\textsuperscript{43,47-48,51-54} Three-component catalytic regimes\textsuperscript{44-46,49} starting from simpler, more readily accessible substrates offer a more practical approach to expeditiously assemble the desired products. However, these methods suffer from a number of shortcomings. Activated α-functionalized alkyl halides are frequently employed to generate a stabilized alkyl radical species for alkyne addition,\textsuperscript{44} and a second catalyst is sometimes required to promote C(sp)–C(sp\textsuperscript{2}) bond formation\textsuperscript{44-45,49} which limit broad utility.

Fig. 1 | The significance of developing site- and stereoselective reductive alkyne alkylalkynylation. a, State-of-the-art advances in multicomponent reductive alkyl-functionalizations of unsaturated C–C bonds. Examples of reductive additions to alkynes with sp-hybridized electrophiles are yet to be reported, presumably due to the difficulties of overcoming rapid homocoupling of the reactive alkynyl halide. b, Ni-catalyzed reductive alkylalkynylation of alkynes using NHPI esters and haloalkynes offers a convenient strategy to assemble stereodefined 1,3-enynes in one step by exploiting widely available redox-active esters as efficient alkyl group donors. R, functional group; X, halide; cat., catalyst; NHPI, N-hydroxyphthalimide; TDAE, tetrakis(dimethylamino)ethylene.
A growing class of three-component dicarbofunctionalization reactions pertain to the regioselective addition of carbogenic groups, derived from stable electrophilic organohalides (vs. the more sensitive organometallic reagents\textsuperscript{55-56}), across C–C π bonds in the presence of a mild reducing agent.\textsuperscript{57-62} To date, most reductive alkyl-functionalization processes involve alkyl-aryl or alkyl-alkenyl additions to olefins using iodo- or bromoalkanes as the alkyl group donor (Fig. 1a). In contrast, the corresponding transformations with alkynes are severely under-developed and restricted to alkyl-arylations using organoiodide reagents.\textsuperscript{57} One longstanding challenge that arises from three-component reductive alkynylation processes is the high propensity of the haloalkyne electrophile to undergo facile homocoupling in the presence of a Ni-based complex, inadvertently suppressing the desired alkylalkynylation pathway (Fig. 1a, inset; see Fig. 4 for further discussion). Notwithstanding these limitations, we reasoned that the union of an alkyne, an alkynyl halide and a redox-active NHPI ester can be achieved using a Ni-based catalyst under appropriate reductive conditions to give diverse 1,3-enynes with simultaneous control of site and stereoselectivity (Fig. 1b).

Our motivation to pursue this approach is twofold: (1) The greater variety of N-(acyloxy)phthalimides accessible from aliphatic carboxylic acids (vs. alkyl halides) means that diverse aliphatic units (tertiary, secondary, primary) can be incorporated; (2) The ability of NHPI esters to promote challenging alkylalkynylation in which alkyl halides fail to deliver, by minimizing rampant undesired pathways arising from homocoupling\textsuperscript{63-64} and cross-coupling\textsuperscript{14,16} of the alkynyl halide and NHPI ester reactants, as well as alkyne cyclotrimerization\textsuperscript{65} (see Fig. 4 for further discussion). Herein, we disclose the first reductive protocol that accomplishes selective alkyne alkylalkynylation using NHPI esters as efficient aliphatic group donors.

Results
Reaction optimization. Examination of conditions for the reaction of 1a (1 equiv.), 2a (1.2 equiv.) and 3a (2.5 equiv.) showed that the desired 1,3-enediyne product 4a could be obtained in 67% GC yield (>95% regio- and E selectivity) in the presence of 10 mol % of the Ni-based complex derived from NiBr₂·diglyme and L₁, Mn (2.5 equiv.) and DMA as solvent under ambient conditions (Table 1, entry 1). Switching the reducing agent to Zn or tetrakis(dimethylamino)ethylene (TDAE) led to poor yields of 4a with excessive by-product formation from 1a cyclotrimerization and 2a homocoupling (Table 1, entries 2 and 3). Other Ni-based complexes were less effective in promoting alkylalkynylation (Table 1, entry 4), while less electron-rich bipyridine and phenanthroline ligands L₂–L₈ afforded 4a in unsatisfactory yields (Table 1, entry 5). Changing DMA to other polar solvents also did not improve results (Table 1, entry 6).

In order to enhance the catalytic efficiency and/or suppress the undesired formation of diyne by-products, various additives were experimented as detailed in Table 1, entries 7–10. Addition of TMSCl (known to activate the Mn(0) surface) to the reaction system was somewhat detrimental (Table 1, entry 7), whereas ZnCl₂ or MgBr₂ additives also reduced the yield of 4a (Table 1, entries 8 and 9). Considering the previously reported role of lithium salts in minimizing
diyne formation,\textsuperscript{14} we found that the use of LiBr (0.5 equiv.) indeed improved results, affording 4a in 76% yield (73% isolated; Table 1, entry 10).

\textbf{Substrate scope.} To examine the generality of the established conditions, we tested a range of electronically and sterically diverse aryl- and heteroaryl-substituted alkynes, and the desired products 4b–aa were isolated in 40–81% yield as single regio- and $E$ isomers (Fig. 2). Both electron-rich and electron-deficient arenes are tolerated, including those that contain a Lewis basic aniline (4g), Brønsted acidic NHBoc (4h) and electrophilic aldehyde (4k). Synthesis of 4j (<5% hydrodebrromination side products) that is functionalized with a bromoaryl substituent highlights the transformation’s remarkable chemoselectivity. As demonstrated by the preparation of 4b, the transformations may be performed on larger scale (3 mmol) without appreciable diminution in efficiency.

Products that bear heterocyclic units (4q and 4r), as well as those derived from complex bioactive compounds (4u–w) could be generated. By using a D-substituted alkyne, tetrasubstituted deuterium-labelled olefins such as 4x, which otherwise might be difficult to prepare by other means, could be secured through the present protocol. However, internal alkynes were resistant to alkylalkynylation (cf. 5; <5% conv. to product). Aliphatic alkynes were also found to be ineffective substrates under the standard conditions. Besides silyl-substituted bromoalkynes, aryl- and alkyl-functionalized alkynyl bromides also underwent efficient reaction to deliver the expected 1,3-enynes 4y–aa in 46–53% yield and 94–95% $E$ selectivity.
A wide assortment of aliphatic NHPI esters served as effective reagents for alkylalkynylation (Fig. 3). These include tertiary alkyl N-(acyloxy)phthalimides (affording 4ab–ar with quaternary carbon centers), secondary alkyl N-(acyloxy)phthalimides (affording 4au and 4av with tertiary carbon centers) as well as primary alkyl N-(acyloxy)phthalimides (4aw and 4ax). To facilitate secondary and primary alkyl additions, an additional 10 mol % of CuTC was added as co-catalyst to improve yields, possibly by stabilization of the corresponding alkyl radicals generated. The diversity of aliphatic groups which can be installed (such as oxetane 4af, pyrans 4ak and 4al,
piperidine 4an and acid-labile acetal 4am) compares favorably with previous methods that employed less readily available haloalkanes.\(^{57,60,69}\)

Fig. 3 | The scope of redox-active esters. Regioisomeric ratios (r.r.), diastereomeric ratios (d.r.) and E:Z ratios were determined by GC and \(^1\)H NMR analysis. Yields are for isolated and purified products. *The reactions were conducted with 1 (3 equiv.) and 2 (1 equiv.). \(^a\)The reactions were conducted with 1 (1 equiv.), 2 (1.5 equiv.) and \(\text{CF}_3\text{I}\) (1.7–2 equiv.). \(^b\)The reactions were conducted with 1 (3 equiv.), 2 (1 equiv.) and LiBr (1 equiv.) with \(L_4\) (12 mol %) as ligand and CuTC (10 mol %) as co-catalyst. \(^c\)The reactions were conducted with 1 (3 equiv.), 2 (1 equiv.) and LiBr (1 equiv.) with \(L_1\) (12 mol%) as ligand and CuTC (10 mol %) as co-catalyst. R, functional group; DMA, \(N,N\)-dimethylacetamide; RT, room temperature; TBS, tert-butyldimethylsilyl; Ts, \(p\)-toluenesulfonyl; TC, thiophene-2-carboxylate.

Structurally sophisticated alkyl additions could be implemented as exemplified by the products 4aq (from ketopinic acid) and 4ar (from dehydroabietic acid). To incorporate fluoroalkyl units, due to the difficulty of fluoroalkyl NHPI esters to generate the requisite fluorinated radical species,\(^{70}\) we turned to perfluoroalkyl iodide to deliver alkylalkynylation of both aryl- and alkyl-substituted alkynes. In the event, the F-containing 1,3-enynes 4as and 4at were successfully isolated in 53% and 36% yields, respectively.
Mechanistic studies. As shown in Fig. 4, studies were carried out to elucidate the mechanism of the reductive alkyne alkylalkynylation process.

Fig. 4 | Mechanistic investigations. a, Unsuccessful alkyalkynylation attempts using iodoalkane as alkyl group donor. b, Two-component control experiments. R, functional group; L, ligand; THF, tetrahydrofuran; Py, pyridine; TDAE, tetrakis(dimethylamino)ethylene; RT, room temperature.

Remarkably, control experiments showed that when NHPI ester 3a was replaced by the corresponding 2-iodo-2-methylpropane 6, there was <5% conv. to the 1,3-enyne product 4a. Instead, the alkyne 1a was fully consumed in cyclotrimerization to form arene side products,
and homocoupling of bromoalkyne 2a to give diyne 7 was detected (Fig. 4a). Repeating the reaction under previously established reductive dicarbofunctionalization conditions also did not yield 4a (<5% conv. of 1a, ~40% conv. of 2a to 7). These observations not only highlight the importance of the redox-active ester component as an effective alkyl donor in these multicomponent reactions, but also provide hints that the alkynyl bromide was probably much more reactive (vs. the alkyl iodide), inadvertently suppressing the desired alkylalkynylation pathway and causing homocoupling of the bromoalkyne to predominate.

Additional control experiments shed further light on the reaction (Fig. 4b). Under standard conditions, the reaction between bromoalkyne 2a and 6 led to full conversion of 2a to diyne 7 (<5% cross-coupling to 8 detected). When alkyne 1a was treated with 2a under the same conditions, >95% conv. to 7 was also detected and 1a underwent undesired cyclotrimerization. In contrast, replacing the iodoalkane 6 with NHPI ester 3a only afforded trace amounts of 7 (<5% cross-coupling to 8) and 3a was fully consumed (presumably by decomposition under the reductive conditions). These observations imply that the presence of 3a somehow inhibited 2a homocoupling by preferentially engaging with an in situ-generated organonickel species, albeit no productive reaction could occur if alkyne 1a was absent to trap the t-Bu radical formed (see Fig. 5). Notably, subjecting 1a to 3a under the established conditions selectively furnished Z alkene 9 in 14% GC yield, leading us to deduce that the C–C(t-Bu) bond and the adjacent C–Ni bond are generated in an anti configuration (presumably to minimize steric repulsions) within the alkenynickel intermediate I (see Fig. 5). In the absence of the alkynyl bromide, 9 might be formed by adventitious protodemetallation of I with residual moisture.

Based on our investigations and related studies, a tentative mechanism is proposed in Fig. 5. Starting from an in situ-generated Ni(0) species i (e.g. from reduction of the Ni(II) precatalyst, oxidative addition with bromoalkyne 2 followed by single-electron reduction in the presence of Mn gives rise to an alkynynickel(II) species iii. At this stage, a second molecule of 2 could potentially react with iii to give dialkynynickel(III) vii that subsequently reductively eliminates to afford the undesired diyne side product 7. However, if a NHPI ester 3 is present in the system, the reaction trajectory could be altered as 3 chemoselectively engages with iii, through a single-electron transfer (SET) decarboxylative pathway, to furnish alkynynickel(II) complex iv with concomitant ejection of CO2, phthalimide anion and an alkyl radical species. Facile capture of the alkyl radical by alkyne 1 generates an alkenyl radical that recombines with iv to form E-alkenynickel(III) complex v. The ensuing reductive elimination then generates Ni(I)
phthalimide vi and releases the desired 1,3-enzyme 4. Following another single-electron reduction by Mn, i is regenerated to turn over the catalytic cycle. On the other hand, a less reactive alkyl halide (vs. alkyl NHPI ester) is not capable of efficiently intercepting alkynynickel(I) complex iii, consequently allowing other side reactions such as homocoupling 2 to become competitive in the system.

Fig. 5 | Proposed catalytic mechanism for reductive alkylalkynylation. Unlike a haloalkane, NHPI ester 3 is capable of intercepting the putative alkynynickel intermediate iii to promote alkylalkynylation and suppress adventitious homocoupling of 2 to diyne 7. R, functional group; L, ligand; Phth, phthaloyl.

**Synthetic transformations.** Using redox-active esters 10 tethered to a terminal olefin, we postulated that a cascade pathway commencing from alkyl radical addition to the alkyne followed by an intramolecular 5-exo-trig cyclization with the C=C bond to give a second alkyl radical species III before reassociation with the Ni complex for subsequent alkynylation could occur (Fig. 6a). This would give rise to complex 1,5-enynes 11 bearing a trisubstituted cyclopentene nucleus and an alkyne appendage. Gratifyingly, the Ni-catalyzed cascade processes proceeded smoothly to generate the desired products 11a–e in up to 85% yield, further demonstrating the versatility of the alkylalkynylation regime by taking advantage of radical-based reactivity modes to construct complex molecules.
Fig. 6 | Application to cascade processes and further derivatization. **a**, Cascade radical addition/cyclization/alkynylation to furnish 1,5-enynes. **b**, Chemical transformations of stereodefined 1,3-enynes to synthetically valuable building blocks. R, functional group; DMA, N,N-dimethylacetamide; DCM, dichloromethane; THF, tetrahydrofuran; RT, room temperature; cat., catalyst; Bn, benzyl; Boc, tert-butoxycarbonyl; Tf, trifluoromethanesulfonyle; m-CPBA, *meta*-chloroperoxybenzoic acid.

Utility of the 1,3-enyne products is showcased through a series of synthetic manipulations involving both the olefin and alkyne motifs towards the preparation of diverse molecular structures (Fig. 6b). Using the desilylated derivative 12 from 4b, facile transformation of the terminal alkyne moiety to a spectrum of different products can be effected by partial hydrogenation to the 1,3-diene 13 in 52% yield, Au-catalyzed hydration to ketone 14 in 79% yield, and Cu-catalyzed azide-alkyne cycloaddition to 1,2,3-triazole 15 in 70% yield. In another
instance, chemoselective epoxidation of the trisubstituted olefin followed by Au-catalyzed cycloisomerization\(^7\) afforded the disubstituted furan derivative 16 in 51% overall yield. On the other hand, partial cis-selective hydrogenation of the internal alkyne in 4z generated sterically congested 1,3-diene 17 in 40% yield as a single Z isomer.

To conclude, we have demonstrated that a single Ni-based catalyst is capable of mediating regio- and stereoselective alkyl-alkynyl additions to alkynes to deliver valuable 1,3-enzyme products. Access to 1,5-enynes was achieved through a radical-based cascade transformation, and our investigations shed light on the superior performance of redox-active esters in overcoming undesired haloalkyne homocoupling by competitively intercepting a putative alkynylnickel intermediate. In situations where two electrophilic halides proved to be ineffective, the synergistic combination of a redox-active ester and an organohalide may provide viable solutions to address other longstanding challenges in dicarbofunctionalizations that employ multiple electrophiles.

**Data availability**

All data are available from the corresponding authors upon reasonable request.

**References**


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**Author contributions**
Y.J., J.P. and J.J.H.L. developed the catalytic method. M.J.K. and Y.Z. directed the investigations. M.J.K. wrote the manuscript with revisions provided by the other authors.

**Competing interests**

The authors declare no competing financial interests.