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 groups[3-10] 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 alkynes[25] 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[43-54] have been developed, but the majority focused on two-component systems involving coupling reactions of elaborated alkynes/alkenes as starting materials.[43,47-48,51-54] Three-component catalytic regimes[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,[44] and a second catalyst is sometimes required to promote C(sp)–C(sp^2) bond formation[44-45,49] which limit broad utility.

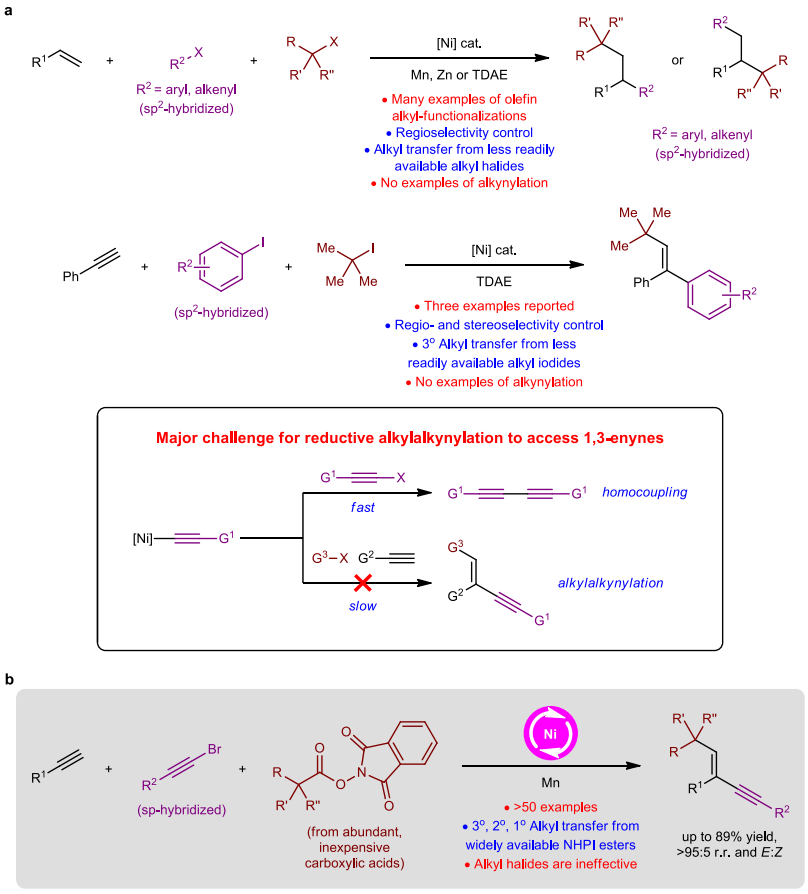


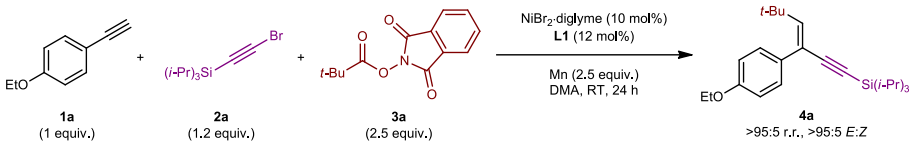
Fig. 1 | **The significance of developing site- and stereoselective reductive alkyne alkylalkynylation. a**, State-of-the-art advances in multicomponent reductive alkyl-functionalizations of unsaturated C–C bonds. Examples of reductive additions to alkynes with sp-hybridized electrophiles are yet to 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.

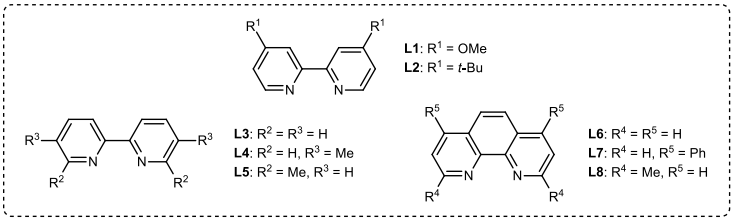
A growing class of three-component dicarbofunctionalization reactions pertain to the regioselective addition of carbogenic groups, derived from stable electrophilic organohalides (vs. the more sensitive organometallic reagents[55-56]), across C–C π bonds in the presence of a mild reducing agent.[57-62] 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.[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 alkylalkynylations in which alkyl halides fail to deliver, by minimizing rampant undesired pathways arising from homocoupling[63-64] and cross-coupling[14,16] of the alkynyl halide and NHPI ester reactants, as well as alkyne cyclotrimerization[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

Table 1 | Evaluation of reaction conditions for reductive alkylalkynylation





Entry	Deviation from standard conditions	Conversion (%)*	Yield (%)*
1	none	78	67
2	Zn instead of Mn	>95	16
3	TDAE instead of Mn	36	<5
4	$Ni(cod)_2$, $NiCl_2$·glyme or NiI_2 instead of $NiBr_2$·glyme	74–81	39–57
5	**L2**–**L8** instead of **L1**	31–82	<5–55
6	MeCN, DMF or DMSO instead of DMA	25–82	<5–41
7	TMSCl (0.5 equiv.) added	77	25
8	$ZnCl_2$ (0.5 equiv.) added	50	15
9	$MgBr_2$ (0.5 equiv.) added	68	36
10	LiBr (0.5 equiv.) added	85	76 (73)

Reactions were performed on 0.1 mmol scale. *Conversions (based on consumption of **1a**) and yields determined by GC analysis. Value in parentheses denotes isolated yield. DMA, *N*,*N*-dimethylacetamide; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; cod,1,5-cyclooctadiene; TDAE, tetrakis(dimethylamino)ethylene; TMSCl, trimethylsilyl chloride; RT, room temperature.

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-enyne 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 $NiBr_2$·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[65] and **2a** homocoupling[63-64] (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,[63-64] various additives were experimented as detailed in Table 1, entries 7–10. Addition of TMSCl (known to activate the Mn(0) surface[66]) to the reaction system was somewhat detrimental (Table 1, entry 7), whereas $ZnCl_2$ or $MgBr_2$ additives[67] also reduced the yield of **4a** (Table 1, entries 8 and 9). Considering the previously reported role of lithium salts in minimizing

diyne formation,[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).

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% hydrodebromination 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.

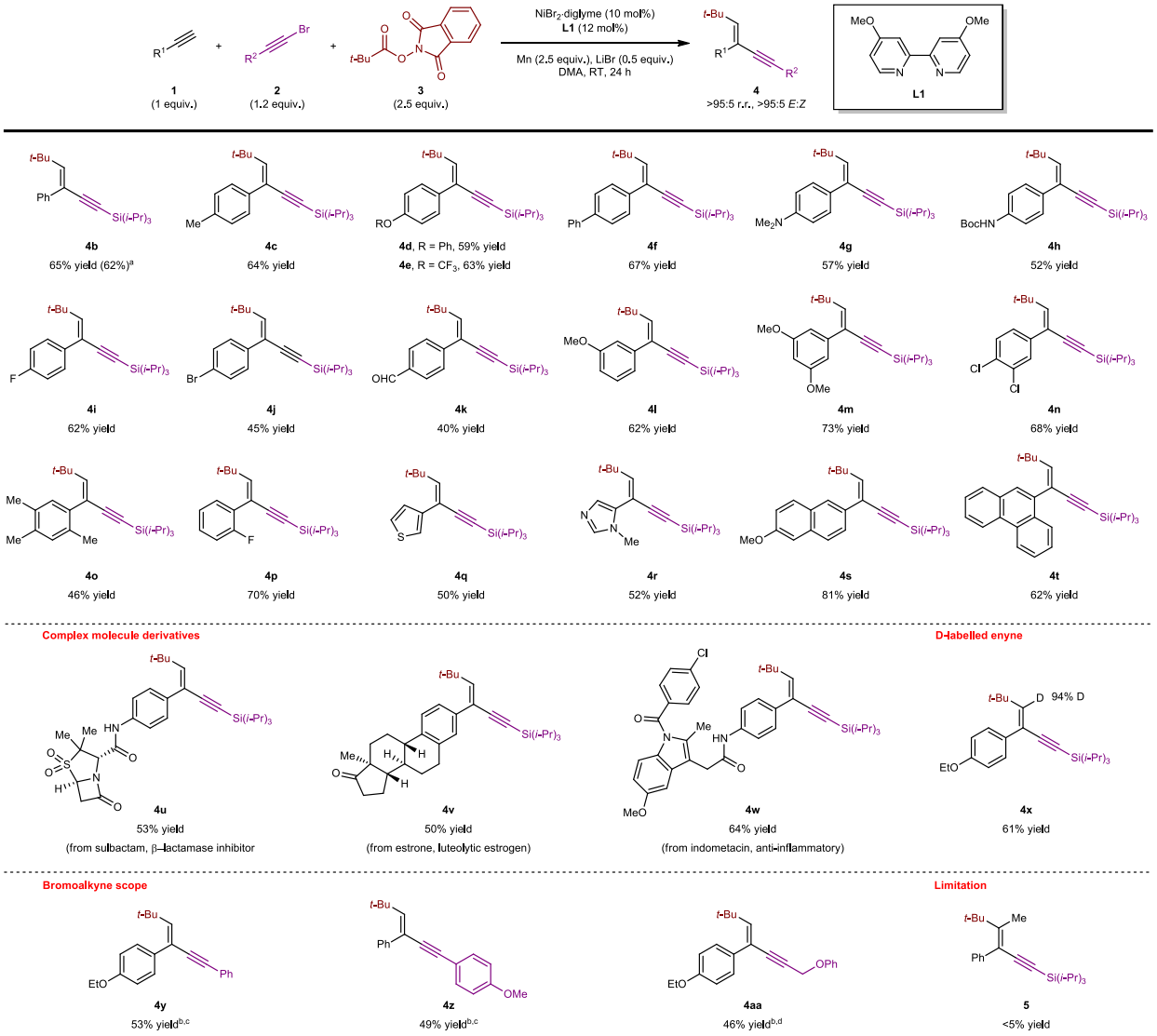


Fig. 2 | **The scope of alkynes and alkynyl bromides.** Regioisomeric ratios (r.r.) and *E*:*Z* ratios were determined by GC and ^{1}H NMR analysis. Yields are for isolated and purified products. [a]The reaction was conducted on 3 mmol scale. [b]The reactions were conducted with LiBr (1 equiv.) and DMSO as solvent. [c]The products were generated in 95:5 *E*:*Z* ratio. [d]The product was generated in 94:6 *E*:*Z* ratio. R, functional group; DMA, *N*,*N*-dimethylacetamide; RT, room temperature; Boc, *tert*-butoxycarbonyl.

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.[68] 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]

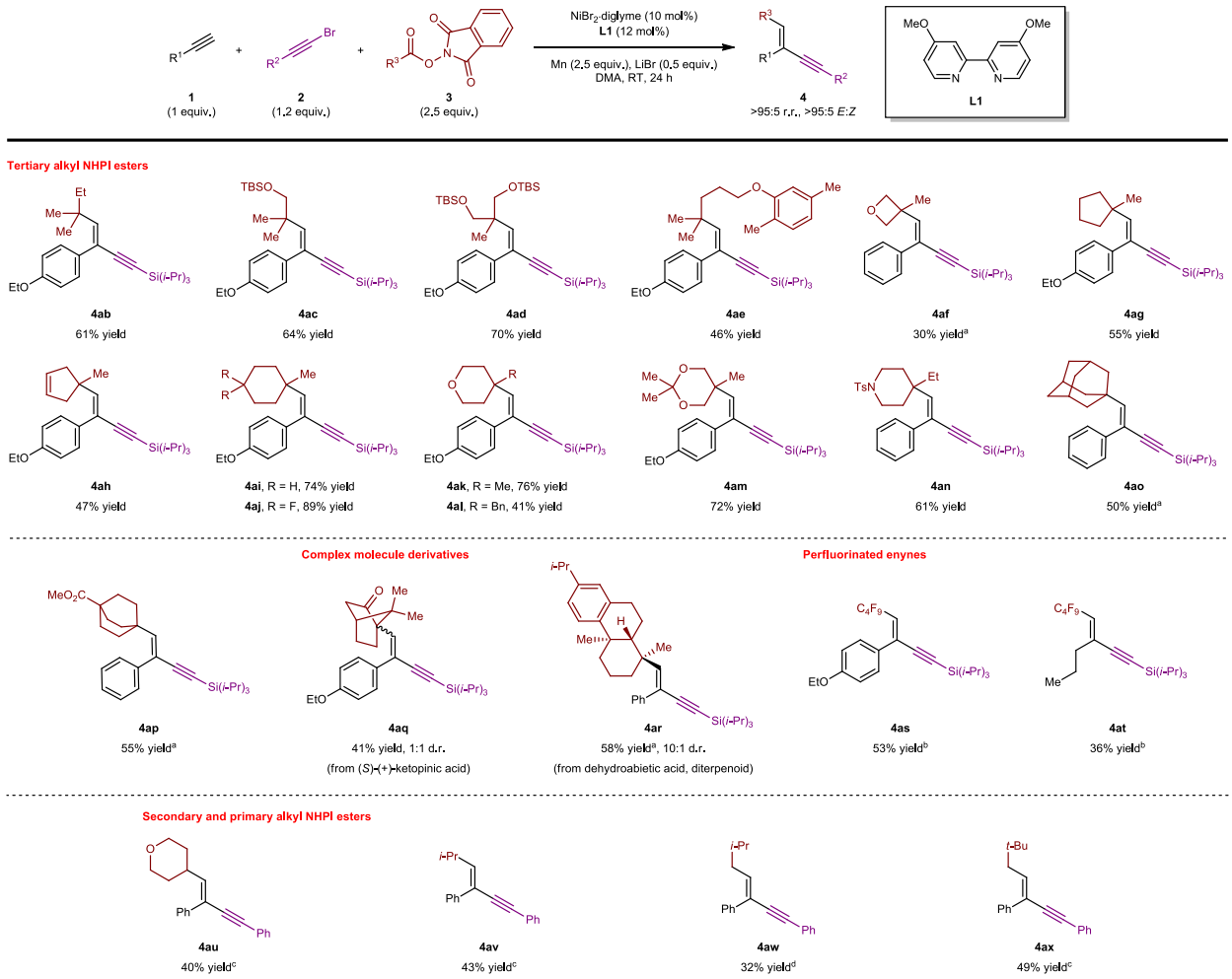


Fig. 3 | **The scope of redox-active esters.** Regioisomeric ratios (r.r.), diastereomeric ratios (d.r.) and *E*:*Z* ratios were determined by GC and ^{1}H NMR analysis. Yields are for isolated and purified products. [a]The reactions were conducted with **1** (3 equiv.) and **2** (1 equiv.). [b]The reactions were conducted with **1** (1 equiv.), **2** (1.5 equiv.) and C_4F_9I (1.7–2 equiv.). [c]The reactions were conducted with **1** (3 equiv.), **2** (1 equiv.) and LiBr (1 equiv.) with **L4** (12 mol %) as ligand and CuTC (10 mol %) as co-catalyst. [d]The reactions were conducted with **1** (3 equiv.), **2** (1 equiv.) and LiBr (1 equiv.) with **L1** (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.

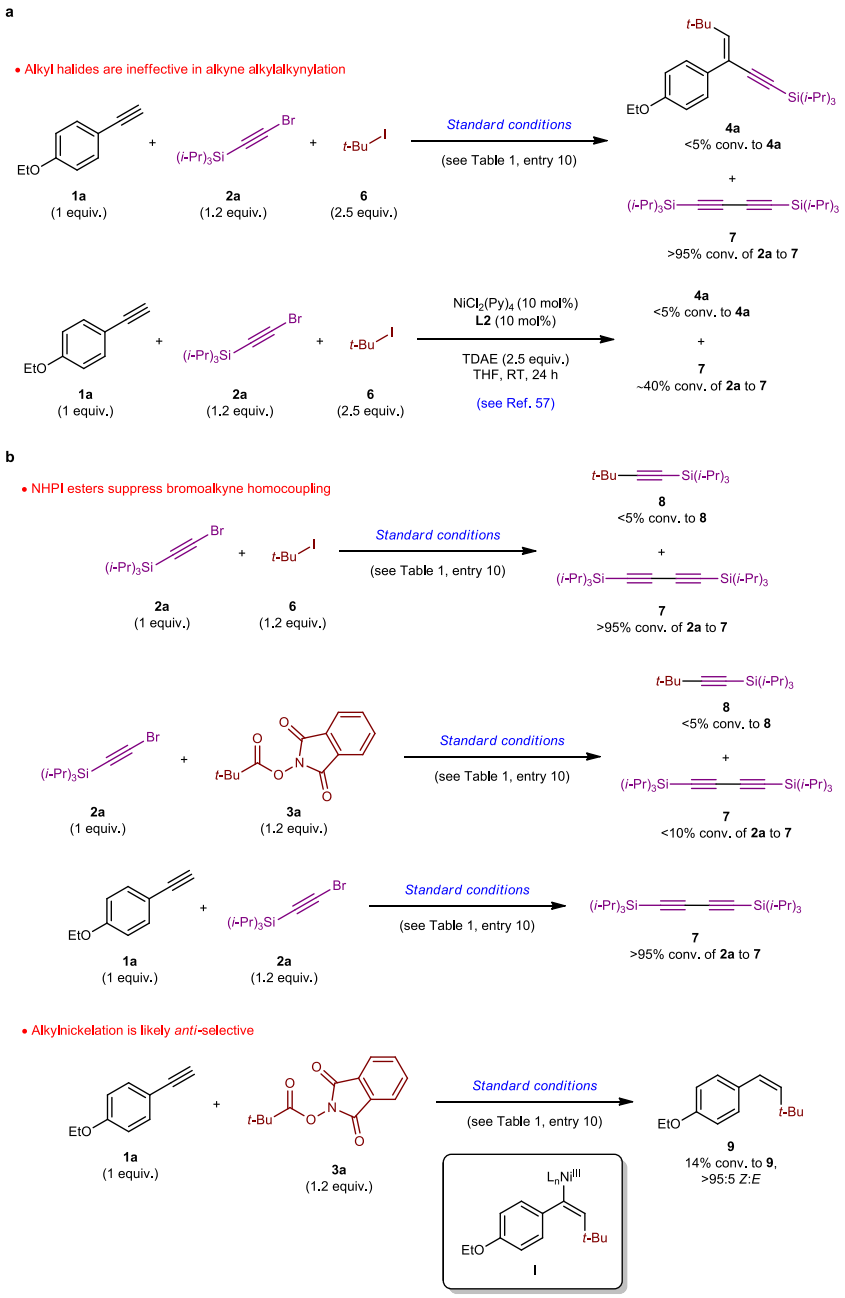


Fig. 4 | **Mechanistic investigations. a**, Unsuccessful alkylalkynylation attempts using iodoalkane as alkyl group donor. **b**, Two-component control experiments. R, functional group; L, ligand; THF, tetrahydrofuran; Py, pyridine; TDAE, tetrakis(dimethylamino)ethylene; RT, room temperature.

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[65] 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[57] 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[71]). 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 alkenylnickel 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,[14,60,64] 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) pre-catalyst[14,64], oxidative addition with bromoalkyne **2** followed by single-electron reduction in the presene of Mn gives rise to an alkynylnickel(I) species **iii**. At this stage, a second molecule of **2** could potentially react with **iii** to give dialkynylnickel(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,[14] to furnish alkynylnickel(II) complex **iv** with concomitant ejection of CO_2, 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*-alkenylnickel(III) complex **v**. The ensuing reductive elimination then generates Ni(I)

phthalimide **vi** and releases the desired 1,3-enyne **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 alkynylnickel(I) complex **iii**, consequently allowing other side reactions such as homocoupling **2** to become competitive in the system.

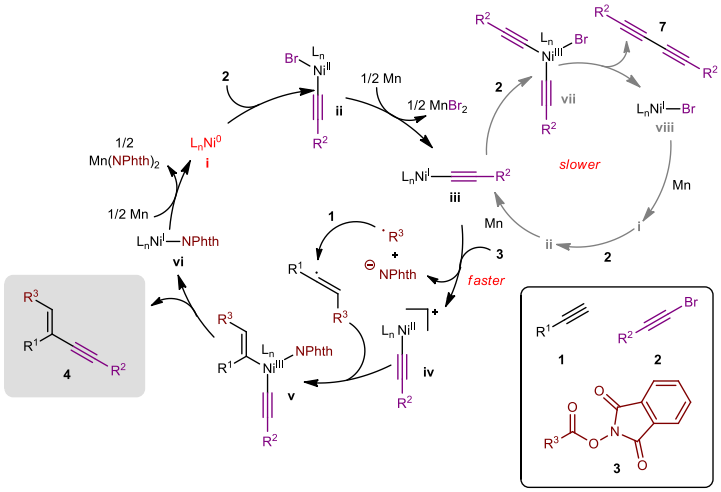


Fig. 5 | **Proposed catalytic mechanism for reductive alkylalkynylation.** Unlike a haloalkane, NHPI ester **3** is capable of intercepting the putative alkynylnickel intermediate **iii** to promote alkylalkynylation and suppress adventitious homocoupling of **2** to diyne **7**. R, functional group;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

Synthetic transformations. Using redox-active esters **10** tethered to a terminal olefin, we postulated that a cascade pathway[72] 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.

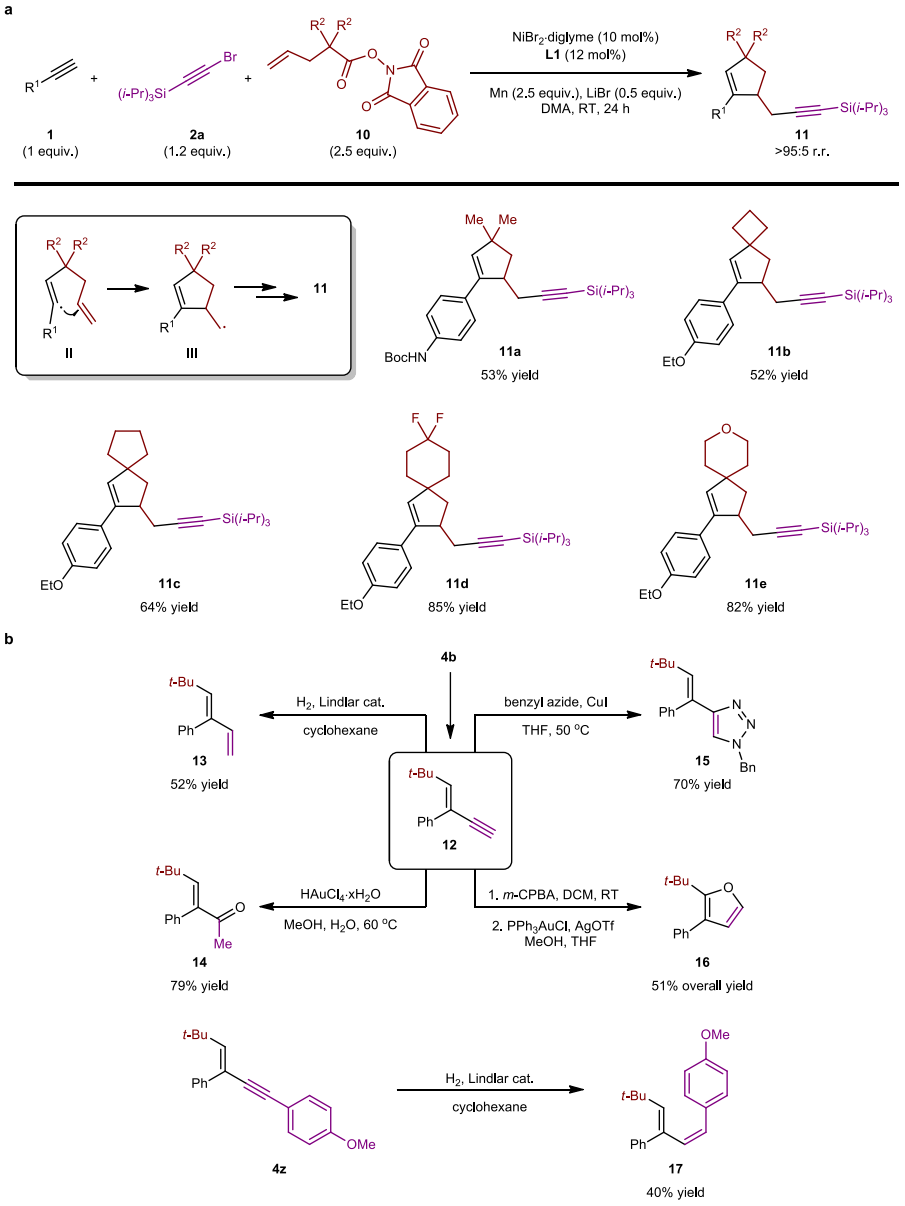


Fig. 6 | **Application to cascade processes and further derivatization. a,** Cascade radical addition/cyclization/alkynylation to furnish 1,5-enynes. **b,** Chemical transformations of stereodefined 1,3-enynes to synthetically valuable building blocks. R, functional group; DMA, *N*,*N*-dimethylacetamide; DCM, dichloromethane; THF, tetrahydrofuran; RT, room temperature; cat., catalyst; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Tf, trifluoromethanesulfonyl; *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**,[73] 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,[74] Au-catalyzed hydration to ketone **14** in 79% yield,[75] and Cu-catalyzed azide-alkyne cycloaddition to 1,2,3-triazole **15** in 70% yield.[76] In another

instance, chemoselective epoxidation of the trisubstituted olefin followed by Au-catalyzed cycloisomerization[77] 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-enyne 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.

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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.