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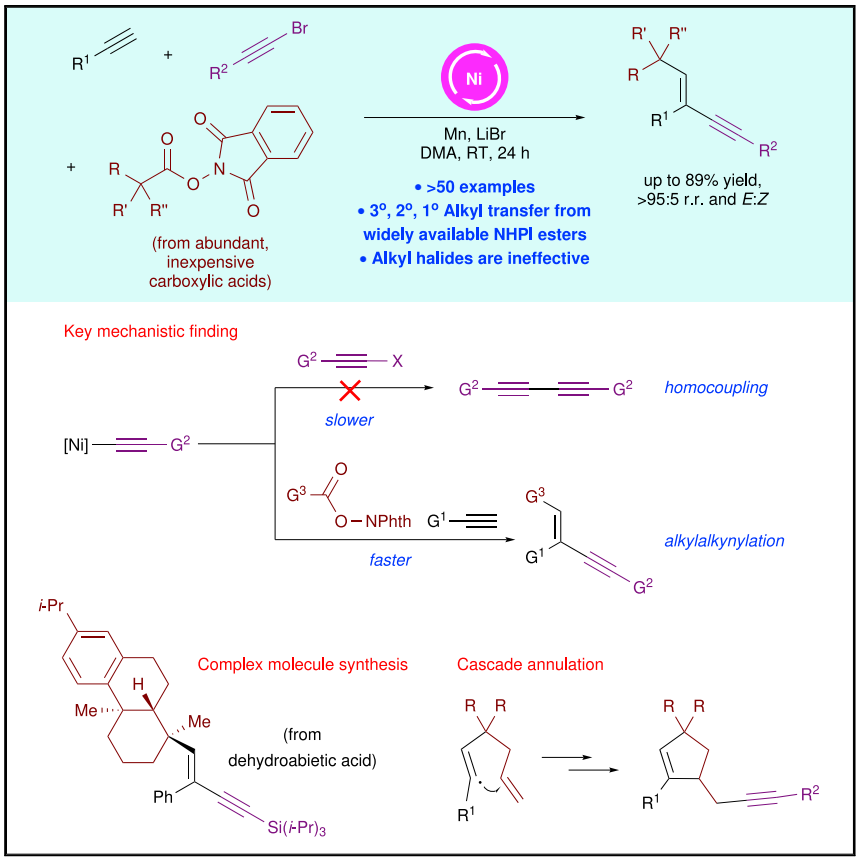
Nickel-catalyzed site- and stereoselective reductive alkylalkynylation of alkynes



Electrophilic redox-active esters and alkynyl halides can be synergistically employed in alkylalkynylation processes in the presence of a nonprecious Ni-based catalyst under mild reductive conditions. Diverse 1,3-enyne products can be obtained in excellent stereochemical purity, and further application to cascade annulation reactions can be implemented. Mechanistic evidence suggests that *N*-(acyloxy)phthalimides are uniquely capable of intercepting an *in situ*-generated alkynylnickel species to overcome haloalkyne homocoupling that would otherwise pose complications with an alkyl halide.

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HIGHLIGHTS

A Ni-catalyzed regime for reductive alkylalkynylation of alkynes is described

Readily accessible *N*-(acyloxy) phthalimides are used as alkyl group donors

Stereodefined 1,3-enynes bearing diverse functional groups can be generated

The method is amenable to cascade annulation transformations

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Nickel-catalyzed site- and stereoselective reductive alkylalkynylation of alkynes

Yi Jiang,[1] Jiaoting Pan,[1,2] Tao Yang,[1] Yu Zhao,[1,2,*] and Ming Joo Koh[1,3,*]

SUMMARY

The 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 an 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. This study underscores the crucial role of redox-active esters as superior alkyl group donors compared with haloalkanes in reductive alkyne dicarbofunctionalizations.

INTRODUCTION

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 with 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]

Various routes to architecturally analogous 1,3-enynes that contain a trisubstituted alkene moiety[43–54] have been developed, but a majority of them 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

The bigger picture

Despite key advances in multicomponent reductive dicarbofunctionalization, alkyl additions to alkynes remain limited, and examples involving sp-hybridized electrophiles have not been reported. An inherent challenge is the high propensity of the alkynyl halide to undergo undesired homocoupling side reactions, consequently suppressing product formation. As demonstrated here, a Ni-catalyzed method that selectively merges alkynes with readily available electrophilic *N*-(acyloxy) phthalimides and alkynyl bromides have been developed. This protocol enables access to valuable structurally sophisticated and stereodefined 1,3-enynes, which are amenable to further derivatization to other useful building blocks. The mechanistic insights derived from the synergistic combination of a redox-active ester and an organohalide are expected to provide practical solutions for addressing other longstanding problems in catalytic systems that employ multiple electrophiles.

addition,[44] and a second catalyst is sometimes required to promote C(sp)–C(sp^2) bond formation[44,45,49] that limits broad utility.

A growing class of three-component dicarbofunctionalization reactions pertain to the regioselective addition of carbogenic groups, derived from stable electrophilic organohalides and/or redox-active esters (versus the more sensitive organometallic reagents[55,56]), across C–C π bonds in the presence of a mild reducing agent.[57–63] 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 (Scheme 1A). In contrast, the corresponding transformations with alkynes are severely underdeveloped 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 (Scheme 1A, inset; see Scheme 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 (Scheme 1B).

Our motivation to pursue this approach is 2-fold: (1) The greater variety of *N*-(acyloxy)phthalimides accessible from aliphatic carboxylic acids (versus alkyl halides) means that diverse aliphatic units (tertiary, secondary, and 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[64,65] and cross-coupling[14,16] of the alkynyl halide and NHPI ester reactants, as well as alkyne cyclotrimerization[66] (Scheme 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 AND DISCUSSION

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 a 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[66] and **2a** homocoupling[64,65] (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,[64,65] various additives were experimented, as detailed in Table 1, entries 7–10. The addition of TMSCl (known to activate the Mn(0) surface[67]) to the reaction system was somewhat detrimental (Table 1, entry 7), whereas $ZnCl_2$ or $MgBr_2$ additives[68] 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). It merits mention that decreasing the loading

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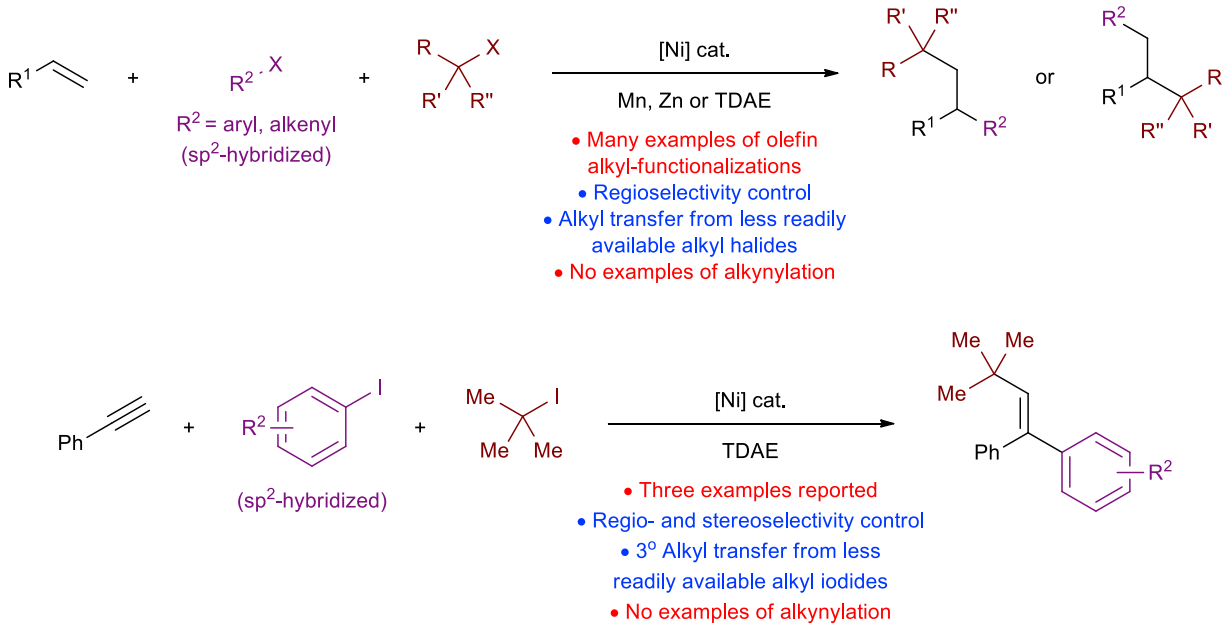
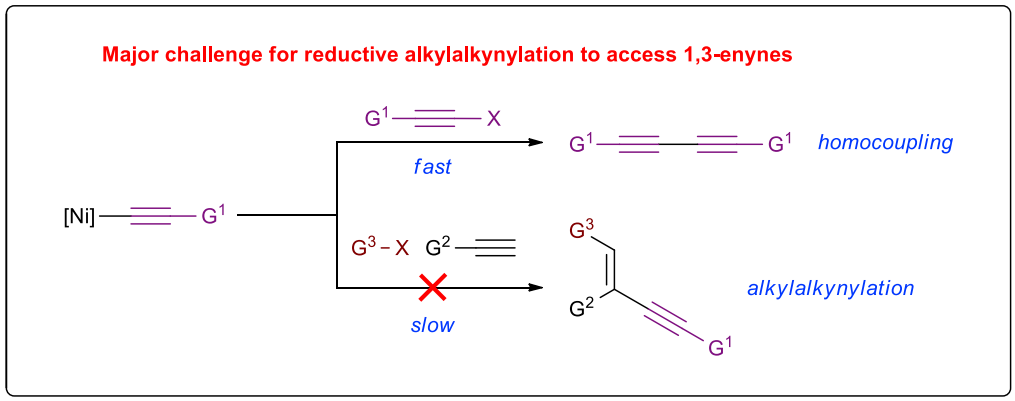
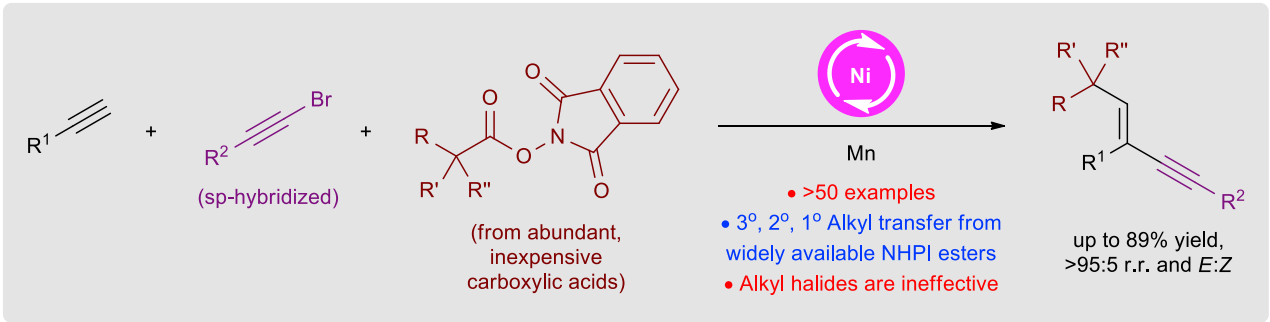
A State-of-the-art advances in multicomponent reductive alkyl-functionalizations of unsaturated C–C bonds



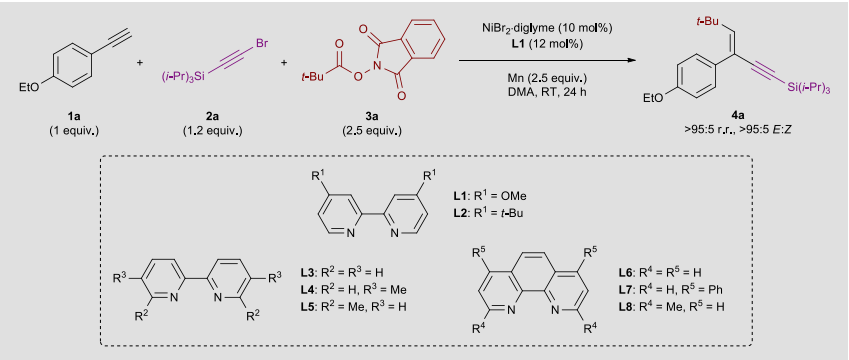


B This work: Ni-catalyzed reductive alkylalkynylation of alkynes using NHPI esters and haloalkynes



Scheme 1. The significance of developing site- and stereoselective reductive alkyne alkylalkynylation

Table 1. Evaluation of reaction conditions



Entry	Deviation from standard conditions	Conversion (%)[a]	Yield (%)[a]
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)

Abbreviations: 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.

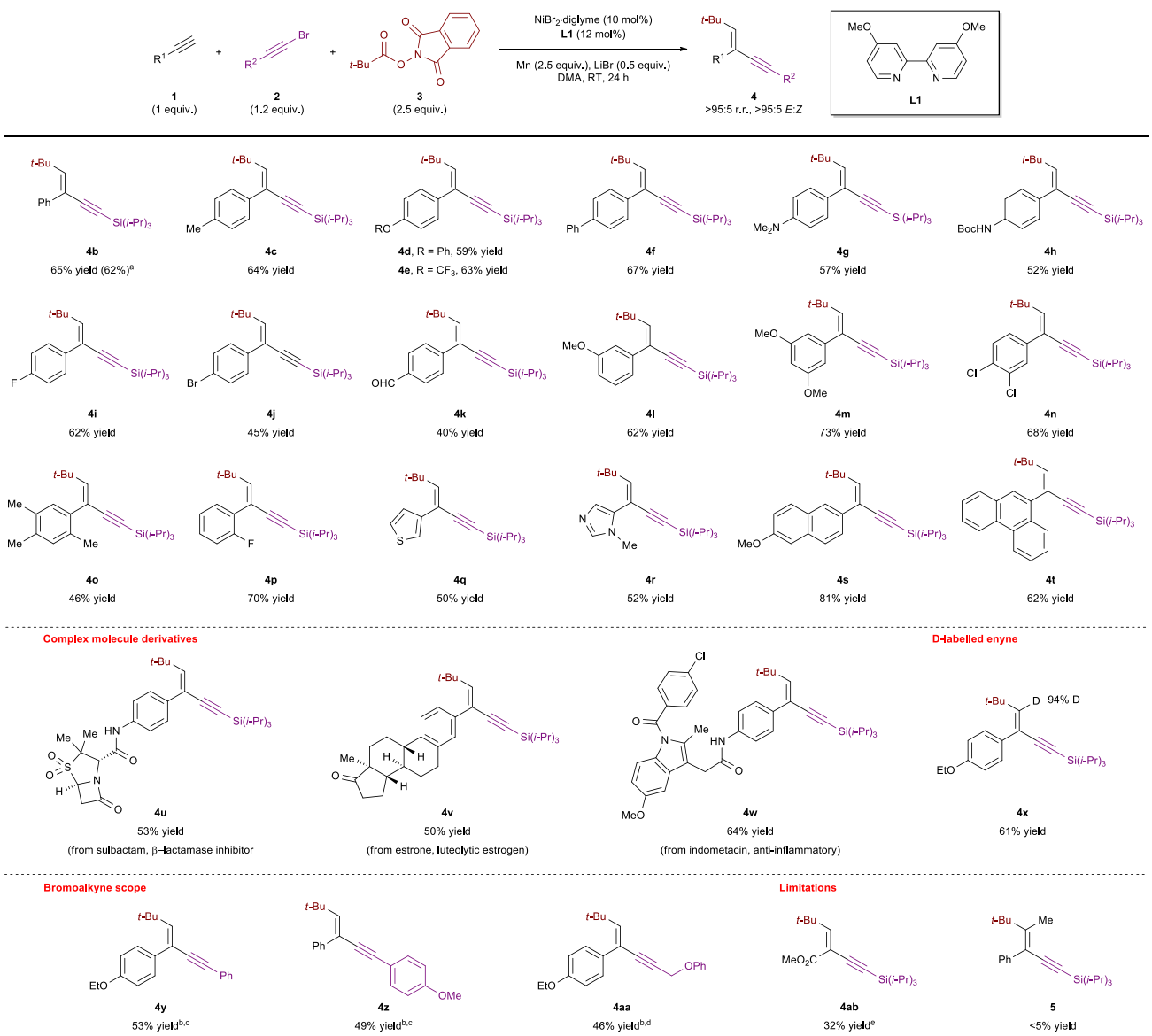
[a]Reactions were performed on a 0.1 mmol scale. Conversions (based on the consumption of **1a**) and yields were determined by GC analysis. Value in parentheses denotes isolated yield.

of **3a** to 1.5 equiv led to a diminution in product yield (58% versus 76% with 2.5 equiv **3a**, see Table S1 for details).

Scope of the method

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**–**4aa** were isolated in 40%–81% yield as single regio- and *E* isomers (Scheme 2). Both electron-rich and electron-deficient arenes were tolerated, including those that contained a NHBoc (**4h**), Lewis basic aniline (**4g**), and electrophilic aldehyde (**4k**). Synthesis of **4j** that is functionalized with a bromoaryl substituent highlights the transformation's remarkable chemoselectivity (<5% hydrodebromination side products). As demonstrated by the preparation of **4b**, the transformations may be performed on a 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**–**4w**), could be generated. By using a D-substituted alkyne, tetrasubstituted deuterium-labeled olefins such as **4x**, which otherwise might be difficult to prepare by other means, could be secured through the present protocol. However, erosion of stereoselectivity was observed in reactions with activated propiolates (**4ab**),[69] whereas internal alkynes were resistant to alkylalkynylation (cf. 5; <5% conversion [conv.] to product). Aliphatic alkynes were also found



Scheme 2. The scope of alkynes and alkynyl bromides in reductive alkylalkynylation

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.

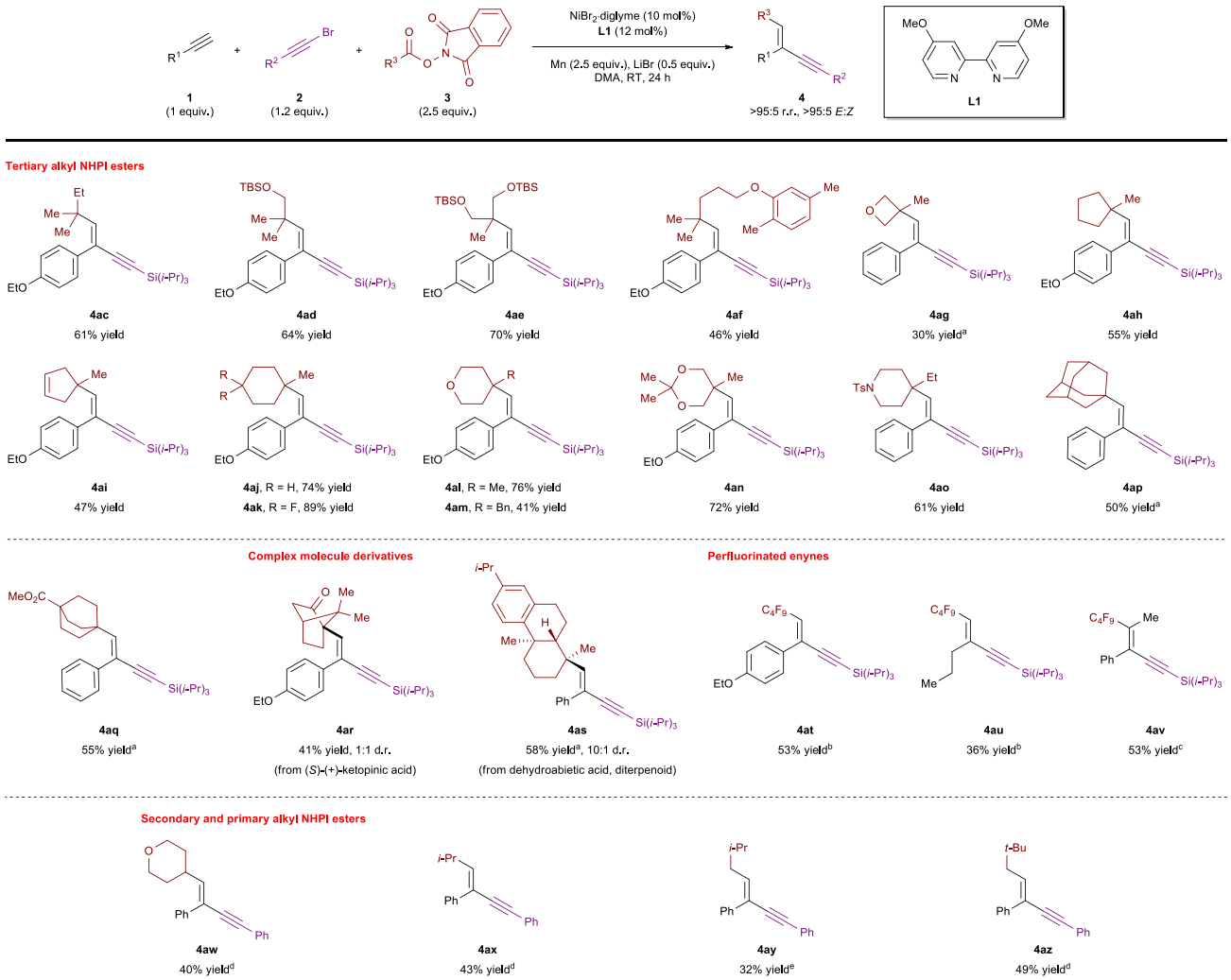
[c]The products were generated in 95:5 *E*:Z ratio.

[d]The product was generated in 94:6 *E*:Z ratio.

[e]The reaction was conducted with **1** (3 equiv) and **2** (1 equiv), and the product was generated in 63:37 *Z*:*E* ratio.

to be ineffective substrates under the standard conditions. Besides silyl-substituted bromoalkynes, aryl- and alkyl-functionalized alkynyl bromides also underwent an efficient reaction to deliver the expected 1,3-enynes **4y**–**4aa** in 46%–53% yield and 94%–95% *E* selectivity.

A wide assortment of aliphatic NHPI esters served as effective reagents for alkylalkynylation (Scheme 3). These include tertiary alkyl *N*-(acyloxy)phthalimides (affording **4ac**–**4as** with quaternary carbon centers), secondary alkyl *N*-(acyloxy)phthalimides



Scheme 3. The scope of redox-active esters in reductive alkylalkynylation

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 reaction was conducted with **1** (3 equiv), **2** (1 equiv) and C_4F_9I (2 equiv) with **L7** (12 mol %) as ligand.

[d]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.

[e]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.

(affording **4aw** and **4ax** with tertiary carbon centers), as well as primary alkyl *N*-(acyloxy)phthalimides (**4ay** and **4az**). To facilitate secondary and primary alkyl additions, an additional 10 mol % of CuTC was added as a co-catalyst to improve yields, possibly by stabilization of the corresponding alkyl radicals generated.[70] The diversity of aliphatic groups which can be installed (such as oxetane **4ag**, pyrans **4al** and **4am**, piperidine **4ao**, and acid-labile acetal **4an**) compares favorably with previous methods that employed less readily available haloalkanes.[57,60,71]

Structurally sophisticated alkyl additions could be implemented as exemplified by the products **4ar** (from ketopinic acid) and **4as** (from dehydroabietic acid). To incorporate fluoroalkyl units, due to the difficulty of fluoroalkyl NHPI esters to generate

the requisite fluorinated radical species,[72] we turned to perfluoroalkyl iodide to deliver alkylalkynylation of both aryl- and alkyl-substituted alkynes. In the event, the F-containing tri- and tetrasubstituted 1,3-enynes **4at–4av** were successfully isolated in 36%–53% yield.

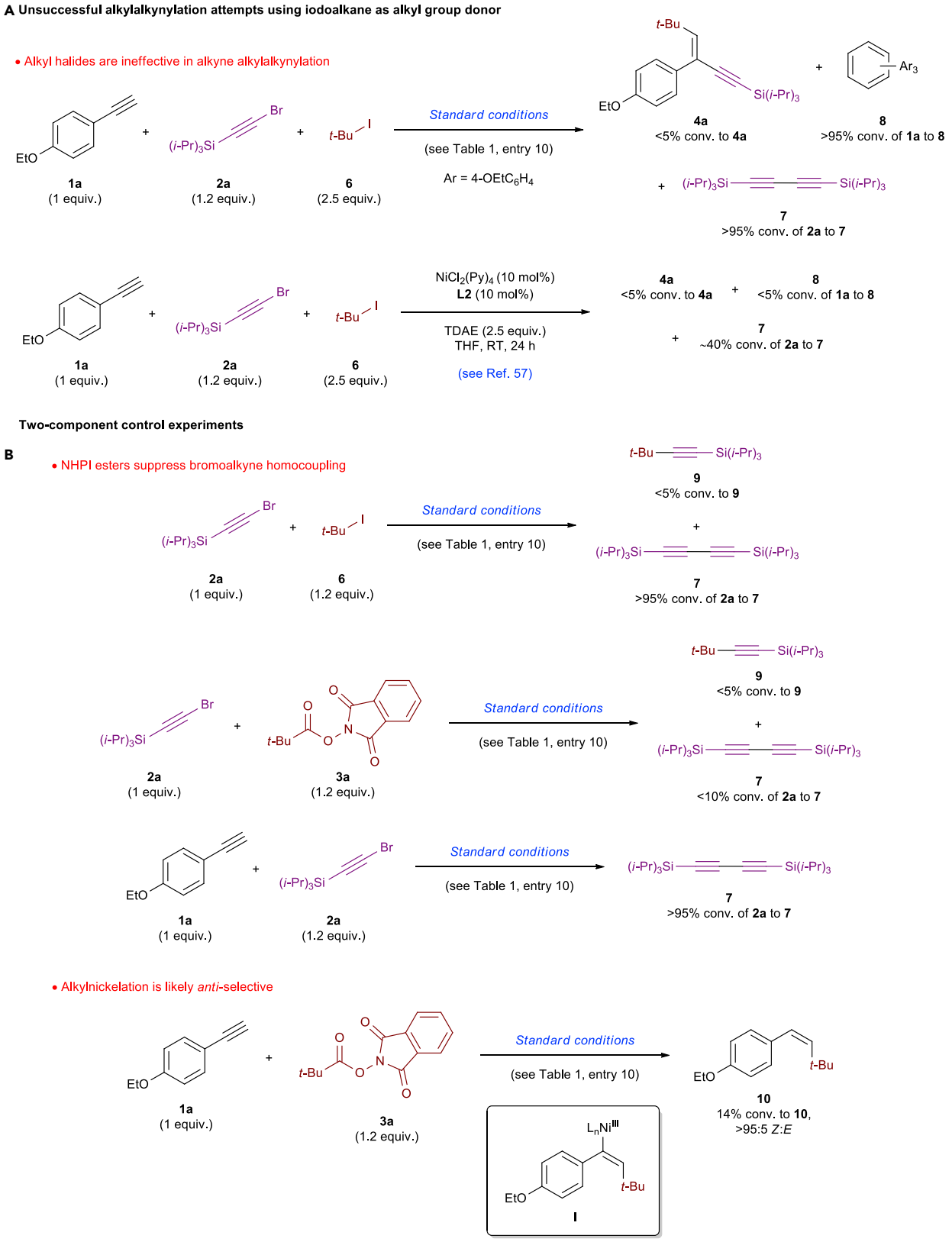
Mechanistic studies

As shown in Scheme 4, studies were carried out to elucidate the mechanism of the reductive alkyne alkylalkynylation process.

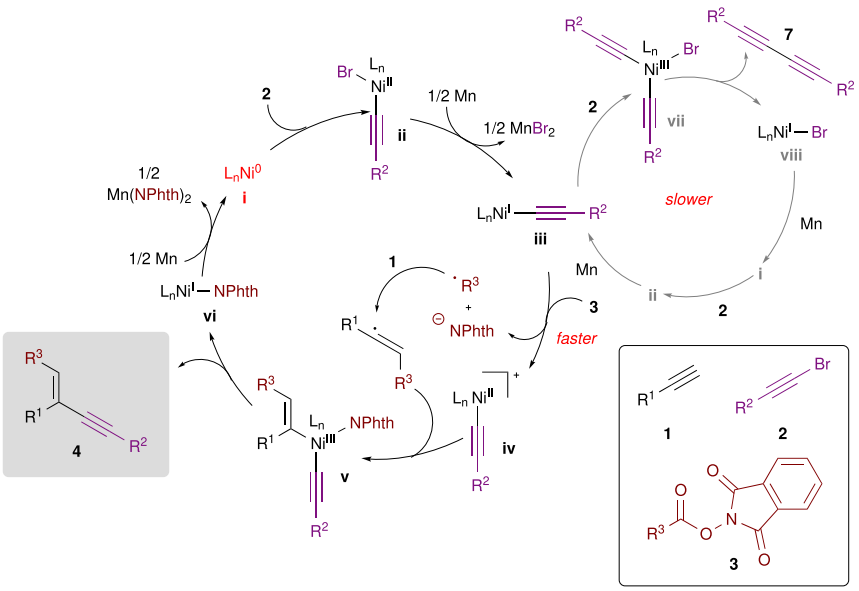
Remarkably, control experiments showed that when NHPI ester **3a** was replaced by the corresponding 2-iodo-2-methylpropane **6**, there was <5% conv. to the 1,3-enyne product **4a**. Instead, the alkyne **1a** was fully consumed in cyclotrimerization[66] to form mixtures of arene side product **8**, and homocoupling of bromoalkyne **2a** to give diyne **7** was detected (Scheme 4A). Repeating the reaction under previously established reductive dicarbofunctionalization conditions[57] also did not yield **4a** (~40% conv. of **2a** to **7**, <5% conv. of **1a** to **8**). 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 (versus 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 (Scheme 4B). Under standard conditions, the reaction between bromoalkyne **2a** and **6** led to full conversion of **2a** to diyne **7** (<5% cross-coupling to **9** 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 **9**), and **3a** was fully consumed (presumably by decomposition to isobutene/isobutane under the reductive conditions[73]). 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 (Scheme 5). Notably, subjecting **1a** to **3a** under the established conditions selectively furnished Z alkene **10** 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** (Scheme 5).[10,57] In the absence of the alkynyl bromide, **10** might be formed by adventitious protodemetallation of **I** with residual moisture.

Based on our investigations and related studies,[14,60,65] a tentative mechanism is proposed in Scheme 5. Starting from an *in situ*-generated Ni(0) species **i** (e.g., from the reduction of the Ni(II) pre-catalyst[14,65]), oxidative addition with bromoalkyne **2** followed by a single-electron reduction in the presence 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**. Alternatively, **1** could be activated by associating with the Ni center in **iii** or **iv** prior to alkyl radical addition to give **v**. The ensuing reductive elimination then generates Ni(I) phthalimide **vi** and releases the desired 1,3-enyne **4**. Following another single-



Scheme 4. Mechanistic investigations



Scheme 5. Proposed catalytic mechanism for reductive alkylalkynylation

electron reduction by Mn, **i** is regenerated to turn over the catalytic cycle. On the other hand, a less reactive alkyl halide (versus alkyl NHPI ester) is not capable of efficiently intercepting alkynylnickel(I) complex **iii**, consequently allowing other side reactions such as homocoupling of **2** to become competitive in the system.

Synthetic transformations

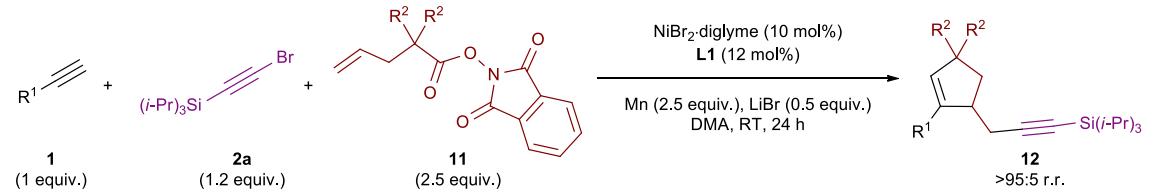
Using redox-active esters **11** tethered to a terminal olefin, we postulated that a cascade pathway[74] commencing from alkyl radical addition to the alkyne followed by an intramolecular 5-*exo*-*trig* cyclization with the C=C bond to give a second alkyl radical species **III** before reassociation with the Ni complex for subsequent alkynylation could occur (Scheme 6A). This would give rise to complex 1,5-enynes **12** bearing a trisubstituted cyclopentene nucleus and an alkyne appendage. Gratifyingly, the Ni-catalyzed cascade annulation processes proceeded smoothly to generate the desired products **12a–12e** 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.

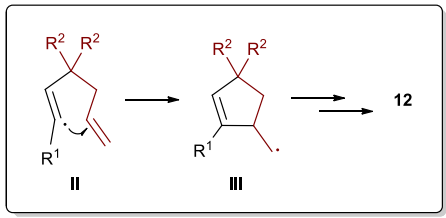
The utility of the 1,3-enyne products is showcased through a series of synthetic manipulations involving both the olefin and alkyne motifs toward the preparation of diverse molecular structures (Scheme 6B). Using the desilylated derivative **13** from **4b**,[75] facile transformations of the terminal alkyne moiety to a spectrum of different products can be affected by partial hydrogenation to the 1,3-diene **14** in 52% yield,[76] Au-catalyzed hydration to ketone **15** in 79% yield,[77] and Cu-catalyzed azide-alkyne cycloaddition to 1,2,3-triazole **16** in 70% yield.[78] In another instance, chemoselective epoxidation of the trisubstituted olefin followed by Au-catalyzed cycloisomerization[79] afforded the disubstituted furan derivative **17** in 51% overall yield. On the other hand, partial *cis*-selective hydrogenation of the internal alkyne in **4z** generated sterically congested 1,3-diene **18** in 40% yield as a single *Z* isomer.

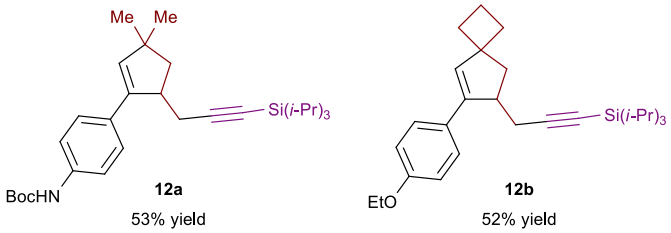
Conclusion

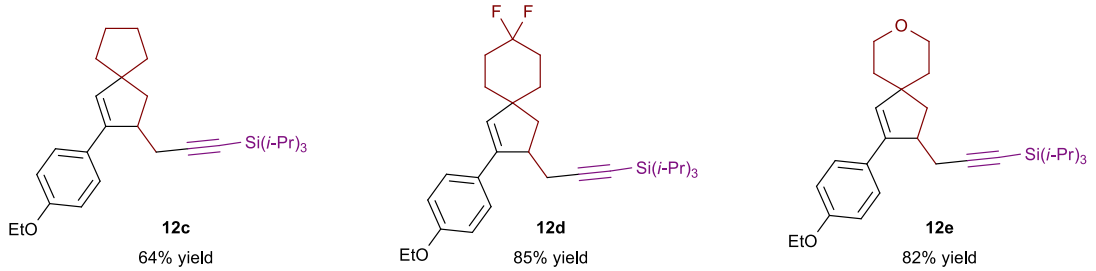
To conclude, we have demonstrated that a single Ni-based catalyst is capable of mediating regio- and stereoselective alkyl-alkynyl additions to alkynes to deliver valuable 1,3-enyne products. Access to 1,5-enynes was achieved through a radical-based

A Cascade radical addition/cyclization/alkynylation to furnish 1,5-enynes

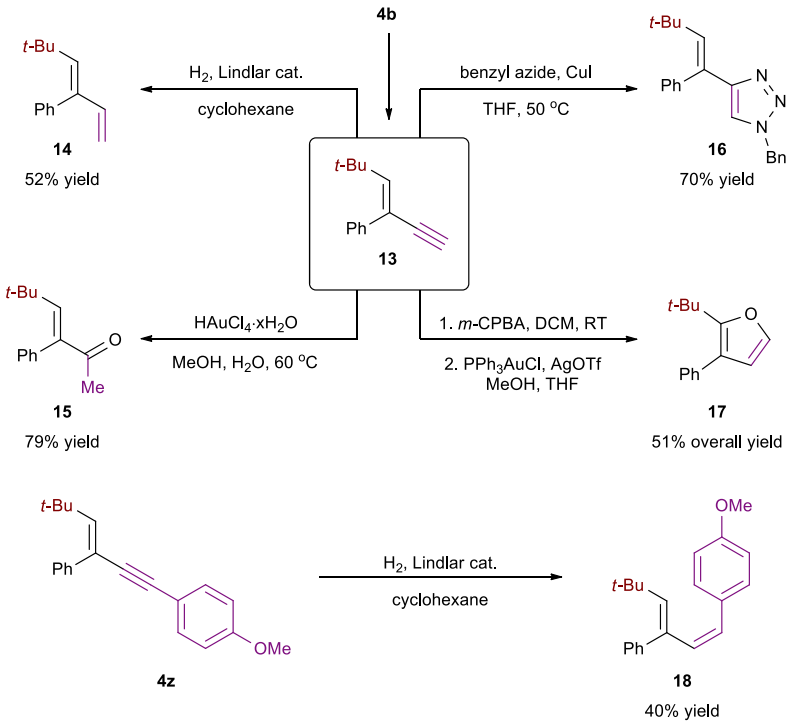








B Chemical transformations to synthetically valuable building blocks



Scheme 6. Application to cascade annulation processes and further derivatization
Regioisomeric ratios (r.r.) were determined by GC and ^{1}H NMR analysis. Yields are for isolated and purified products.

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[63] may provide viable solutions to address other longstanding challenges in dicarbofunctionalizations that employ multiple electrophiles.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Ming Joo Koh (chmkmj@nus.edu.sg).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

This study did not generate any datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2020.12.024.

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AUTHOR CONTRIBUTIONS

Y.J., J.P., and T.Y. 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.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Straathof, A.J. (2014). Transformation of biomass into commodity chemicals using enzymes or cells. Chem. Rev. *114*, 1871–1908.

2. Patra, T., and Maiti, D. (2017). Decarboxylation as the key step in C–C bond-forming reactions. Chemistry *23*, 7382–7401.

3. Xuan, J., Zhang, Z.G., and Xiao, W.J. (2015). Visible-light-induced decarboxylative functionalization of carboxylic acids and their derivatives. Angew. Chem. Int. Ed. Engl. *54*, 15632–15641.

4. Kautzky, J.A., Wang, T., Evans, R.W., and MacMillan, D.W.C. (2018). Decarboxylative trifluoromethylation of aliphatic carboxylic acids. J. Am. Chem. Soc. *140*, 6522–6526.

5. Till, N.A., Smith, R.T., and MacMillan, D.W.C. (2018). Decarboxylative hydroalkylation of alkynes. J. Am. Chem. Soc. *140*, 5701–5705.

6. Rahman, M., Mukherjee, A., Kovalev, I.S., Kopchuk, D.S., Zyryanov, G.V., Tsurkan, M.V., Majee, A., Ranu, B.C., Charushin, V.N., Chupakhin, O.N., and Santra, S. (2019). Recent advances on diverse decarboxylative reactions

of amino acids. Adv. Synth. Catal. *361*, 2161–2214.

7. McMurray, L., McGuire, T.M., and Howells, R.L. (2020). Recent advances in photocatalytic decarboxylative coupling reactions in medicinal chemistry. Synthesis *52*, 1719–1737.

8. Mega, R.S., Duong, V.K., Noble, A., and Aggarwal, V.K. (2020). Decarboxylative conjunctive cross-coupling of vinyl boronic esters using metallaphotoredox catalysis. Angew. Chem. Int. Ed. Engl. *59*, 4375–4379.

9. Wang, H., Liu, C.F., Song, Z., Yuan, M., Ho, Y.A., Gutierrez, O., and Koh, M.J. (2020). Engaging α-fluorocarboxylic acids directly in decarboxylative C–C bond formation. ACS Catal *10*, 4451–4459.

10. Yue, H., Zhu, C., Kancherla, R., Liu, F., and Rueping, M. (2020). Regioselective hydroalkylation and Arylalkylation of alkynes by photoredox/nickel dual catalysis: application and mechanism. Angew. Chem. Int. Ed. Engl. *59*, 5738–5746.

11. Cornella, J., Edwards, J.T., Qin, T., Kawamura, S., Wang, J., Pan, C.M., Gianatassio, R., Schmidt, M., Eastgate, M.D., and Baran, P.S. (2016). Practical Ni-catalyzed aryl-alkyl cross-coupling of secondary redox-active esters. J. Am. Chem. Soc. *138*, 2174–2177.

12. Qin, T., Cornella, J., Li, C., Malins, L.R., Edwards, J.T., Kawamura, S., Maxwell, B.D., Eastgate, M.D., and Baran, P.S. (2016). A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. Science *352*, 801–805.

13. Edwards, J.T., Merchant, R.R., McClymont, K.S., Knouse, K.W., Qin, T., Malins, L.R., Vokits, B., Shaw, S.A., Bao, D.-H., Wei, F.-L., et al. (2017). Decarboxylative alkenylation. Nature *545*, 213–218.

14. Huang, L., Olivares, A.M., and Weix, D.J. (2017). Reductive decarboxylative alkynylation of *N*-Hydroxyphthalimide esters with bromoalkynes. Angew. Chem. Int. Ed. Engl. *56*, 11901–11905.

15. Sandfort, F., O'Neill, M.J., Cornella, J., Wimmer, L., and Baran, P.S. (2017). Alkyl-(hetero)aryl bond formation via decarboxylative cross-coupling: a systematic analysis. Angew. Chem. Int. Ed. Engl. *56*, 3319–3323.

16. Smith, J.M., Qin, T., Merchant, R.R., Edwards, J.T., Malins, L.R., Liu, Z., Che, G., Shen, Z., Shaw, S.A., Eastgate, M.D., and Baran, P.S. (2017). Decarboxylative alkynylation. Angew. Chem. Int. Ed. Engl. *56*, 11906–11910.

17. Murarka, S. (2018). *N*-(acyloxy)phthalimides as redox-active esters in cross-coupling reactions. Adv. Synth. Catal. *360*, 1735–1753.

18. Ni, S., Garrido-Castro, A.F., Merchant, R.R., de Gruyter, J.N., Schmitt, D.C., Mousseau, J.J., Gallego, G.M., Yang, S., Collins, M.R., Qiao, J.X., et al. (2018). A general amino acid synthesis enabled by innate radical cross-coupling. Angew. Chem. Int. Ed. Engl. *57*, 14560–14565.

19. Chen, T.G., Zhang, H., Mykhailiuk, P.K., Merchant, R.R., Smith, C.A., Qin, T., and Baran, P.S. (2019). Quaternary centers by nickel-catalyzed cross-coupling of tertiary carboxylic acids and (hetero)aryl zinc reagents. Angew. Chem. Int. Ed. Engl. *58*, 2454–2458.

20. Ishii, T., Kakeno, Y., Nagao, K., and Ohmiya, H. (2019). *N*-heterocyclic carbene-catalyzed decarboxylative alkylation of aldehydes. J. Am. Chem. Soc. *141*, 3854–3858.

21. Ni, S., Padial, N.M., Kingston, C., Vantourout, J.C., Schmitt, D.C., Edwards, J.T., Kruszyk, M.M., Merchant, R.R., Mykhailiuk, P.K., Sanchez, B.B., et al. (2019). A radical approach to anionic chemistry: synthesis of ketones, alcohols, and amines. J. Am. Chem. Soc. *141*, 6726–6739.

22. Wang, J., Cary, B.P., Beyer, P.D., Gellman, S.H., and Weix, D.J. (2019). Ketones from nickel-catalyzed decarboxylative, non-symmetric cross-electrophile coupling of carboxylic acid esters. Angew. Chem. Int. Ed. Engl. *58*, 12081–12085.

23. Kakeno, Y., Kusakabe, M., Nagao, K., and Ohmiya, H. (2020). Direct synthesis of dialkyl ketones from aliphatic aldehydes through radical *N*-heterocyclic carbene catalysis. ACS Catal *10*, 8524–8529.

24. Johnston, C.P., Smith, R.T., Allmendinger, S., and MacMillan, D.W. (2016). Metallaphotoredox-catalysed sp^3-sp^3 cross-coupling of carboxylic acids with alkyl halides. Nature *536*, 322–325.

25. Dai, G.L., Lai, S.Z., Luo, Z., and Tang, Z.Y. (2019). Selective syntheses of *Z*-alkenes via photocatalyzed decarboxylative coupling of *N*-Hydroxyphthalimide esters with terminal arylalkynes. Org. Lett. *21*, 2269–2272.

26. Chu, L., Ohta, C., Zuo, Z., and MacMillan, D.W. (2014). Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of (+/−)-pregabalin. J. Am. Chem. Soc. *136*, 10886–10889.

27. Jian, W., Ge, L., Jiao, Y., Qian, B., and Bao, H. (2017). Iron-catalyzed decarboxylative alkyl etherification of Vinylarenes with aliphatic acids as the alkyl source. Angew. Chem. Int. Ed. Engl. *56*, 3650–3654.

28. Qin, T., Malins, L.R., Edwards, J.T., Merchant, R.R., Novak, A.J., Zhong, J.Z., Mills, R.B., Yan, M., Yuan, C., Eastgate, M.D., and Baran, P.S. (2017). Nickel-catalyzed Barton decarboxylation and Giese reactions: a practical take on classic transforms. Angew. Chem. Int. Ed. Engl. *56*, 260–265.

29. Tlahuext-Aca, A., Garza-Sanchez, R.A., and Glorius, F. (2017). Multicomponent oxyalkylation of styrenes enabled by hydrogen-bond-assisted photoinduced electron transfer. Angew. Chem. Int. Ed. Engl. *56*, 3708–3711.

30. Bloom, S., Liu, C., Kölmel, D.K., Qiao, J.X., Zhang, Y., Poss, M.A., Ewing, W.R., and MacMillan, D.W.C. (2018). Decarboxylative alkylation for site-selective bioconjugation of native proteins via oxidation potentials. Nat. Chem. *10*, 205–211.

31. Tlahuext-Aca, A., Garza-Sanchez, R.A., Schäfer, M., and Glorius, F. (2018). Visible-light-mediated synthesis of ketones by the oxidative alkylation of styrenes. Org. Lett. *20*, 1546–1549.

32. Wang, G.Z., Shang, R., and Fu, Y. (2018). Irradiation-induced palladium-catalyzed decarboxylative heck reaction of aliphatic *N*-(acyloxy)phthalimides at room temperature. Org. Lett. *20*, 888–891.

33. Wang, J., Lundberg, H., Asai, S., Martín-Acosta, P., Chen, J.S., Brown, S., Farrell, W., Dushin, R.G., O'Donnell, C.J., Ratnayake, A.S., et al. (2018). Kinetically guided radical-based synthesis of C(sp^3)-C(sp3) linkages on DNA. Proc. Natl. Acad. Sci. USA *115*, E6404–E6410.

34. Guo, J.Y., Zhang, Z.Y., Guan, T., Mao, L.W., Ban, Q., Zhao, K., and Loh, T.P. (2019). Photoredox-catalyzed stereoselective alkylation of enamides with *N*-hydroxyphthalimide esters via decarboxylative cross-coupling reactions. Chem. Sci. *10*, 8792–8798.

35. Ishii, T., Ota, K., Nagao, K., and Ohmiya, H. (2019). *N*-heterocyclic carbene-catalyzed radical relay enabling vicinal alkylacylation of alkenes. J. Am. Chem. Soc. *141*, 14073–14077.

36. Dang, H.T., Haug, G.C., Nguyen, V.T., Vuong, N.T.H., Nguyen, V.D., Arman, H.D., and Larionov, O.V. (2020). Acridine photocatalysis: insights into the mechanism and development of a dual-catalytic direct decarboxylative conjugate addition. ACS Catal *10*, 11448–11457.

37. Huang, H.-M., Koy, M., Serrano, E., Pflüger, P.M., Schwarz, J.L., and Glorius, F. (2020). Catalytic radical generation of π-allylpalladium complexes. Nat. Catal. *3*, 393–400.

38. Zein, N., Sinha, A.M., McGahren, W.J., and Ellestad, G.A. (1988). Calicheamicin gamma 1I: an antitumor antibiotic that cleaves double-stranded DNA site specifically. Science *240*, 1198–1201.

39. Nussbaumer, P., Leitner, I., Mraz, K., and Stütz, A. (1995). Synthesis and structure-activity relationships of side-chain-substituted analogs of the allylamine antimycotic terbinafine lacking the central amino function. J. Med. Chem. *38*, 1831–1836.

40. Myers, A.G., Hammond, M., Wu, Y., Xiang, J.N., Harrington, P.M., and Kuo, E.Y. (1996). Enantioselective synthesis of neocarzinostatin chromophore aglycon. J. Am. Chem. Soc. *118*, 10006–10007.

41. Hussain, H., Green, I.R., Krohn, K., and Ahmed, I. (2013). Advances in the total synthesis of biologically important callipeltosides: a review. Nat. Prod. Rep. *30*, 640–693.

42. Ma, X., Banwell, M.G., and Willis, A.C. (2013). Chemoenzymatic total synthesis of the phytotoxic geranylcyclohexentriol (-)-phomentrioloxin. J. Nat. Prod. *76*, 1514–1518.

43. Cornelissen, L., Lefrancq, M., and Riant, O. (2014). Copper-catalyzed cross-coupling of vinylsiloxanes with bromoalkynes: synthesis of enynes. Org. Lett. *16*, 3024–3027.

44. Che, C., Zheng, H., and Zhu, G. (2015). Copper-catalyzed trans-carbohalogenation of terminal alkynes with functionalized tertiary alkyl halides. Org. Lett. *17*, 1617–1620.

45. Cheung, C.W., and Hu, X. (2015). Stereoselective synthesis of trisubstituted alkenes through sequential iron-catalyzed reductive *anti*-carbozincation of terminal alkynes and base-metal-catalyzed negishi cross-coupling. Chemistry *21*, 18439–18444.

46. Lee, J.T.D., and Zhao, Y. (2016). Access to acyclic *Z*-enediynes by alkyne trimerization: cooperative bimetallic catalysis using air as the oxidant. Angew. Chem. Int. Ed. Engl. *55*, 13872–13876.

47. Rivada-Wheelaghan, O., Chakraborty, S., Shimon, L.J.W., Ben-David, Y., and Milstein, D. (2016). *Z*-selective (cross-)dimerization of terminal alkynes catalyzed by an iron complex. Angew. Chem. Int. Ed. Engl. *55*, 6942–6945.

48. Trost, B.M., and Masters, J.T. (2016). Transition metal-catalyzed couplings of alkynes to 1,3-enynes: modern methods and synthetic applications. Chem. Soc. Rev. *45*, 2212–2238.

49. Wang, N.N., Huang, L.R., Hao, W.J., Zhang, T.S., Li, G., Tu, S.J., and Jiang, B. (2016). Synergistic rhodium/copper catalysis: synthesis of 1,3-enynes and *N*-aryl enaminones. Org. Lett. *18*, 1298–1301.

50. Zhou, Y., Zhang, Y., and Wang, J. (2016). Recent advances in transition-metal-catalyzed synthesis of conjugated enynes. Org. Biomol. Chem. *14*, 6638–6650.

51. Gorgas, N., Alves, L.G., Stöger, B., Martins, A.M., Veiros, L.F., and Kirchner, K. (2017). Stable, yet highly reactive nonclassical iron(II) polyhydride pincer complexes: *Z*-selective dimerization and hydroboration of terminal alkynes. J. Am. Chem. Soc. *139*, 8130–8133.

52. Yan, Z., Yuan, X.A., Zhao, Y., Zhu, C., and Xie, J. (2018). Selective hydroarylation of 1,3-diynes using a dimeric manganese catalyst: modular synthesis of *Z*-enynes. Angew. Chem. Int. Ed. Engl. *57*, 12906–12910.

53. Ye, C., Qian, B., Li, Y., Su, M., Li, D., and Bao, H. (2018). Iron-catalyzed dehydrative alkylation of propargyl alcohol with alkyl peroxides to form substituted 1,3-enynes. Org. Lett. *20*, 3202–3205.

54. Cembellín, S., Dalton, T., Pinkert, T., Schäfers, F., and Glorius, F. (2020). Highly selective synthesis of 1,3-enynes, pyrroles, and furans by manganese(I) catalyzed C–H activation. ACS Catal *10*, 197–202.

55. Dhungana, R.K., Kc, S., Basnet, P., and Giri, R. (2018). Transition metal-catalyzed dicarbofunctionalization of unactivated olefins. Chem. Rec. *18*, 1314–1340.

56. Derosa, J., Apolinar, O., Kang, T., Tran, V.T., and Engle, K.M. (2020). Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes. Chem. Sci. *11*, 4287–4296.

57. García-Domínguez, A., Li, Z., and Nevado, C. (2017). Nickel-catalyzed reductive dicarbofunctionalization of alkenes. J. Am. Chem. Soc. *139*, 6835–6838.

58. Shu, W., García-Domínguez, A., Quirós, M.T., Mondal, R., Cárdenas, D.J., and Nevado, C. (2019). Ni-catalyzed reductive dicarbofunctionalization of nonactivated alkenes: scope and mechanistic insights. J. Am. Chem. Soc. *141*, 13812–13821.

59. Zhao, X., Tu, H.Y., Guo, L., Zhu, S., Qing, F.L., and Chu, L. (2018). Intermolecular selective carboacylation of alkenes via nickel-catalyzed reductive radical relay. Nat. Commun. *9*, 3488.

60. Yang, T., Chen, X., Rao, W., and Koh, M.J. (2020). Broadly applicable directed catalytic reductive difunctionalization of alkenyl carbonyl compounds. Chem *6*, 738–751.

61. Wei, X., Shu, W., García-Domínguez, A., Merino, E., and Nevado, C. (2020). Asymmetric Ni-catalyzed radical relayed reductive coupling. J. Am. Chem. Soc. *142*, 13515–13522.

62. Tu, H.Y., Wang, F., Huo, L., Li, Y., Zhu, S., Zhao, X., Li, H., Qing, F.L., and Chu, L. (2020). Enantioselective three-component fluoroalkylarylation of unactivated olefins through nickel-catalyzed cross-electrophile coupling. J. Am. Chem. Soc. *142*, 9604–9611.

[63]. Yang, T., Jiang, Y., Luo, Y., Lim, J.J.H., Lan, Y., and Koh, M.J. (2020). Chemoselective union of olefins, organohalides, and redox-active esters enables regioselective alkene dialkylation. J. Am. Chem. Soc. *142*, 21410–21419.

64. Chen, Z., Jiang, H., Wang, A., and Yang, S. (2010). Transition-metal-free homocoupling of 1-haloalkynes: a facile synthesis of symmetrical 1,3-diynes. J. Org. Chem. *75*, 6700–6703.

65. Ping, Y., Wang, K., Pan, Q., Ding, Z., Zhou, Z., Guo, Y., and Kong, W. (2019). Ni-catalyzed Regio- and enantioselective domino reductive cyclization: one-pot synthesis of 2,3-fused cyclopentannulated indolines. ACS Catal *9*, 7335–7342.

66. Orsino, A.F., Gutiérrez Del Campo, M., Lutz, M., and Moret, M.E. (2019). Enhanced catalytic activity of nickel complexes of an adaptive diphosphine-benzophenone ligand in alkyne cyclotrimerization. ACS Catal *9*, 2458–2481.

67. Poremba, K.E., Dibrell, S.E., and Reisman, S.E. (2020). Nickel-catalyzed enantioselective reductive cross-coupling reactions. ACS Catal *10*, 8237–8246.

68. Montgomery, J. (2004). Nickel-catalyzed reductive cyclizations and couplings. Angew. Chem. Int. Ed. Engl. *43*, 3890–3908.

69. Chen, L., Yang, J., Li, L., Weng, Z., and Kang, Q. (2014). Cobalt-catalyzed direct C–C Bond formation between tetrahydrofuran and alkynes. Tetrahedron Lett *55*, 6096–6100.

70. Cheung, C.W., Zhurkin, F.E., and Hu, X. (2015). *Z*-selective olefin synthesis via iron-catalyzed reductive coupling of alkyl halides with terminal arylalkynes. J. Am. Chem. Soc. *137*, 4932–4935.

71. Zhu, C., Yue, H., Chu, L., and Rueping, M. (2020). Recent advances in photoredox and nickel dual-catalyzed cascade reactions: pushing the boundaries of complexity. Chem. Sci. *11*, 4051–4064.

72. Allen, L.J., Cabrera, P.J., Lee, M., and Sanford, M.S. (2014). *N*-Acyloxyphthalimides as nitrogen radical precursors in the visible light photocatalyzed room temperature C-H amination of arenes and heteroarenes. J. Am. Chem. Soc. *136*, 5607–5610.

73. Huihui, K.M., Caputo, J.A., Melchor, Z., Olivares, A.M., Spiewak, A.M., Johnson, K.A., DiBenedetto, T.A., Kim, S., Ackerman, L.K., and Weix, D.J. (2016). Decarboxylative cross-electrophile coupling of *N*-hydroxyphthalimide esters with aryl iodides. J. Am. Chem. Soc. *138*, 5016–5019.

74. Gao, Y., Zhang, P., Ji, Z., Tang, G., and Zhao, Y. (2017). Copper-catalyzed cascade radical addition–cyclization halogen atom transfer between alkynes and unsaturated α-halogenocarbonyls. ACS Catal *7*, 186–190.

75. Tsukada, N., Ninomiya, S., Aoyama, Y., and Inoue, Y. (2007). Palladium-catalyzed selective cross-addition of triisopropylsilylacetylene to internal and terminal unactivated alkynes. Org. Lett. *9*, 2919–2921.

76. Lindlar, H., and Dubuis, R. (1966). Palladium catalyst for partial reduction of acetylenes. Org. Synth. *46*, 89–92.

77. Capreti, N.M., and Jurberg, I.D. (2015). Michael addition of soft carbon nucleophiles to alkylidene isoxazol-5-ones: a divergent entry to beta-branched carbonyl compounds. Org. Lett. *17*, 2490–2493.

78. Kálai, T., Hubbell, W.L., and Hideg, K. (2009). Click reactions with nitroxides. Synthesis *2009*, 1336–1340.

79. Alonso, P., Pardo, P., Fontaneda, R., Fañanás, F.J., and Rodríguez, F. (2017). Synthesis and applications of cyclohexenyl halides obtained by a cationic carbocyclisation reaction. Chemistry *23*, 13158–13163.