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Nickel-Catalyzed Reductive 1,2-Dialkynylation of Alkenes Bearing an 8-Aminoquinoline Directing Group

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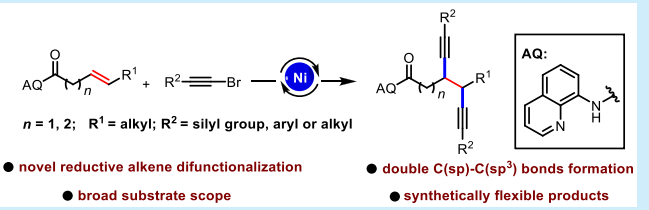
Supporting Information

ABSTRACT: An unprecedented nickel-catalyzed reductive 1,2-dialkynylation of alkenes bearing an 8-aminoquinoline directing group has been developed. This method proceeded through a migratory insertion/reductive-coupling process under mild conditions with a wide substrate scope and good functional group tolerance, providing direct access to the synthetically flexible 1,5-diynes. Moreover, the 1,2-dialkynylation products could be further converted to borate-ester- or azide-functionalized 1,5-dienes, ditriazole, β-diyne primary amide, and trisubstituted benzene.



Alkynes are fundamental structural motifs present in numerous natural products, pharmaceuticals, and functional materials.[1] Meanwhile, they also serve as highly versatile functional groups in synthetic transformation.[2] Therefore, tremendous contributions have been made for the incorporation of the alkynyl group into organic molecules.[3] Furthermore, the class of diyne compounds exhibits special reactivity patterns that are frequently employed as important synthons to construct diverse sophisticated and valuable structures including polysubstituted heterocyclic/aromatic rings, fused/spiro polycyclic compounds, and macromolecular polymers.[4,5] However, compared with their broad applications in organic chemistry, efficient synthetic methods to access diynes are relatively circumscribed.[6]

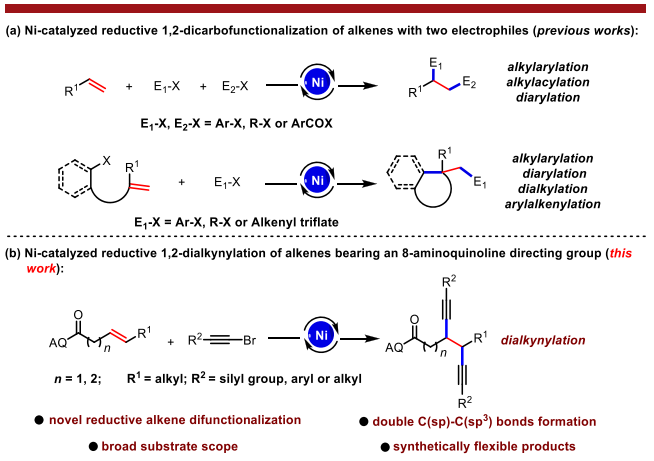
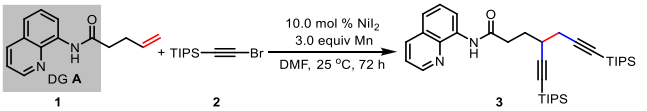


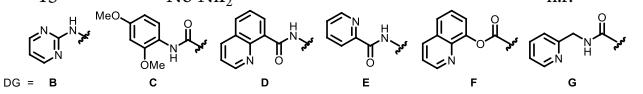
Figure 1. Nickel-catalyzed reductive dicarbofunctionalization of alkenes.

Over the past few decades, the transition-metal-catalyzed dicarbofunctionalization of alkenes has flourished in the organic community, as it represents a powerful tool to access functionalized and complex structures from simple alkenes with two C−C bonds forming in high efficiency.[7] Recently, the

Table 1. Effect of Reaction Parameters[a,b]



entry	deviation of standard conditions[a]	yield (%)[b]
1	none	93
2[c]	DG **B**−**F** instead of DG **A**	n.d.
3	DG **G** instead of DG **A**	17
4	$NiCl_2$(dme) instead of NiI_2	75
5	$NiBr_2$(dme) instead of NiI_2	84
6	$Ni(acac)_2$ instead of NiI_2	51
7	$Ni(OAc)_2 \cdot 4H_2O$ instead of NiI_2	73
8	THF instead of DMF	65
9	DME instead of DMF	40
10	DMA instead of DMF	84
11	MeCN instead of DMF	86
12	DMSO instead of DMF	33
13	Zn instead of Mn	60
14	Mg instead of Mn	48
15[d]	No NiI_2	n.r.



[a]Standard reaction conditions: NiI_2 (10.0 mol %), **1** (0.2 mmol), **2** (1.0 mmol), Mn (0.6 mmol), DMF (1.0 mL), 25 °C, 72 h, under argon. [b]Isolated yields. [c]n.d. = not detected. [d]n.r. = no reaction.

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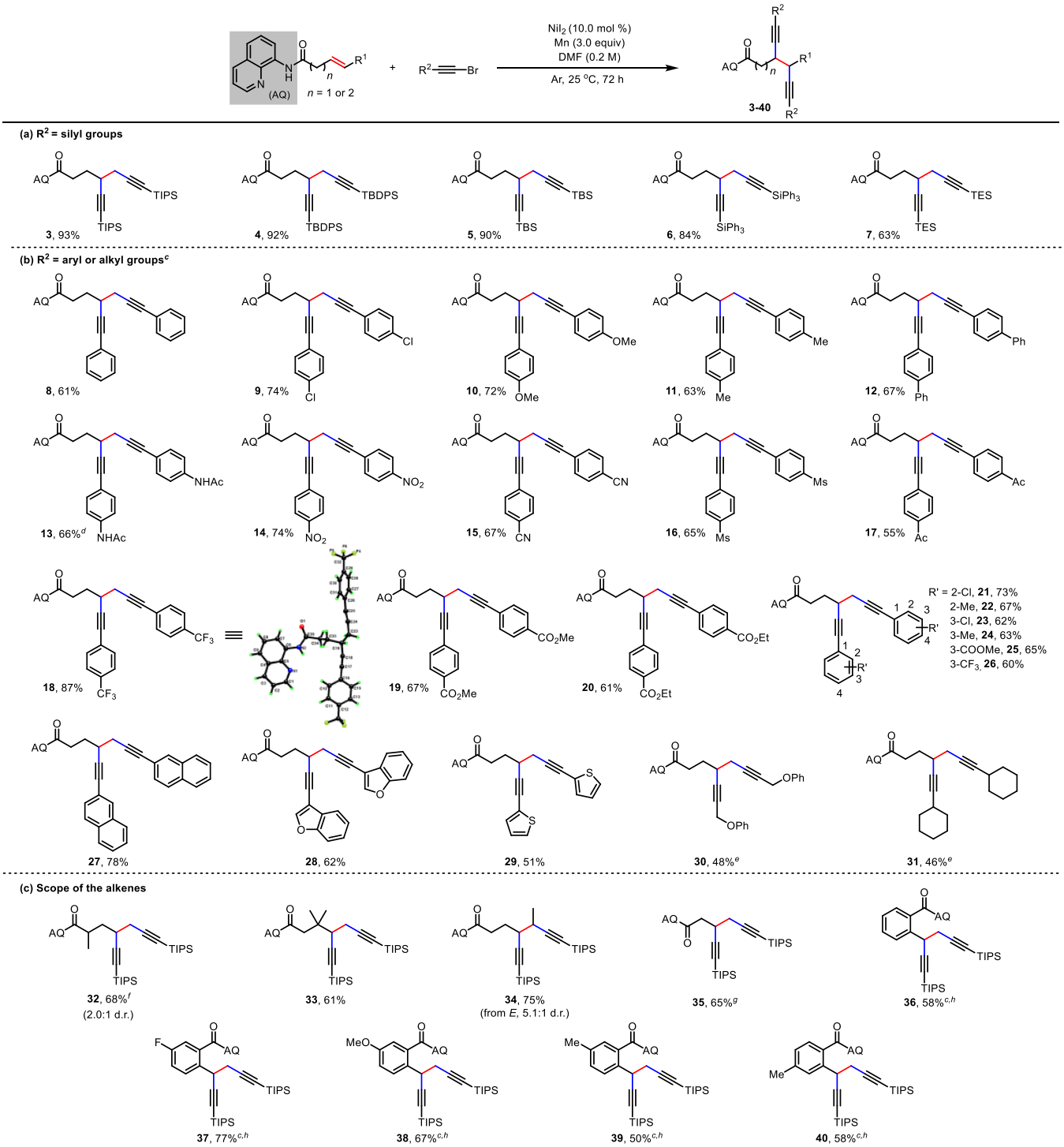
Scheme 1. Substrate Scope[a,b]



[a]Reaction conditions: NiI_2(10.0 mol %), alkene (0.2 mmol), alkyne (1.0 mmol) and Mn (3.0 equiv), DMF (1.0 mL) as solvent, 25 °C. [b]Isolated yields. [c]40 °C. [d]NiI_2 (20.0 mol %). [e]MeCN (1.0 mL) as solvent. [f]100 h. [g]THF (1.0 mL) as solvent. [h]Zn (3.0 equiv) as reductant.

nickel-catalyzed reductive approach has gained increasing concern, which directly uses two organohalide electrophiles as functionalization reagents, avoiding the additional steps in the preparation of sensitive organometallics or organic boronic acids. It shows unique merits in step economy and functional group tolerance. With this strategy, Nevado,[8a,d] Chu,[8b] and Diao[8c] have, respectively, described the nickel-catalyzed three-component reductive dicarbofunctionalization of alkenes to achieve alkene alkylarylation, alkylacylation, and diarylation (Figure 1a, top). The nickel-catalyzed reductive alkylarylation, dialkylation, diarylation, and arylalkenylation of tethered alkenes incorporated in organohalides have also been independently realized by Peng,[8e−h] Diao,[8i] Kong,[8j] Wang,[8k,l] and Shu[8m] (Figure 1a, bottom). Despite these elegant works, exploring the novel nickel-catalyzed reductive dicarbofunctionalization of alkenes to enrich the diversification of the introduced

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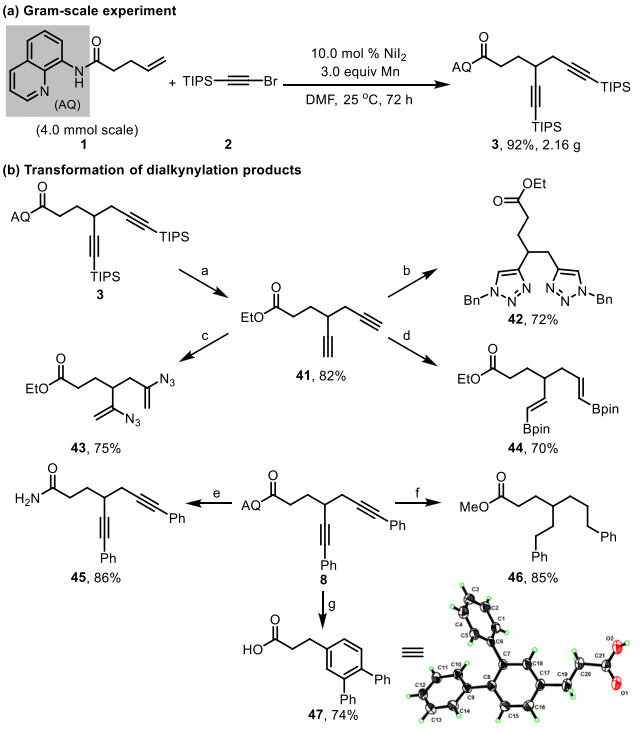
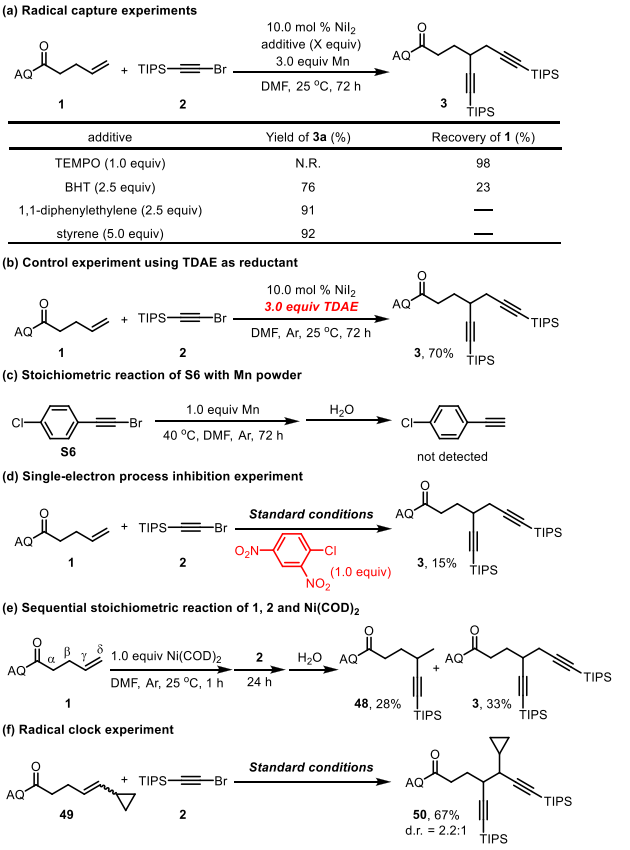
Scheme 2. Further Studies of the Reaction



[a]Ni(tmhd)$_2$, EtOH, 120 °C, 48 h; then TBAF (1 M in THF), Et$_2$O, rt, 1 h. [b]BnN$_3$, CuSO$_4$·5H$_2$O, sodium L-ascorbate, DMF, rt, 48 h. [c]TMSN$_3$, Ag$_2$CO$_3$, H$_2$O, DMSO, 80 °C, 1 h. [d]HBpin, AgOAc, toluene, 120 °C, 48 h. [e]IBX, HFIP/H$_2$O, 60 °C, air atmosphere. [f]Ni(tmhd)$_2$, MeOH, 120 °C, 48 h; then Pd/C (10 wt %), B$_2$(OH)$_4$, H$_2$O, CH$_2$Cl$_2$, rt. [g]NaOH, EtOH, 130 °C, 24 h; then 1 M HCl.

Scheme 3. Mechanistic Studies



functionality is still highly desirable, which could ulteriorly enhance the applicability of this method. As our sustained focus on the field of alkene functionalization,[9] we herein describe a nickel-catalyzed reductive 1,2-dialkynylation of alkenes bearing an 8-aminoquinoline directing group to produce synthetically attractive 1,5-diyne compounds with double C(sp)−C(sp^3) bond formation for the first time (Figure 1b).

We initiated our study by identifying reliable conditions for this nickel-catalyzed reductive alkene dialkynylation reaction. After considerable screening of the reaction parameters (see the Supporting Information (SI) for details), the desired product **3** was obtained in 93% yield with 10.0 mol % NiI$_2$ as the catalyst, DG **A** as the directing group, and 3.0 equiv Mn as the reducing agent in DMF at 25 °C (Table 1, entry 1). The choice of DG **A** as the directing group was essential for the dialkynylation process. When alkenes bearing DG **B**−**G** were subjected to the optimized conditions, only DG **G** could promote the transformation in 17% yield (Table 1, entries 2 and 3). Other nickel catalysts performed this reaction with less efficiency (Table 1, entries 4−7). Conducting the reaction in THF, DME, DMA, MeCN, and DMSO led to 40−86% yield (Table 1, entries 8−12). When Zn or Mg was used as the reductant, product **3** was obtained in diminished yield (Table 1, entries 13 and 14). Without the nickel catalyst, no reaction occurred (Table 1, entry 15).

Having optimized the reaction conditions, we then focused on the substrate scope of this nickel-catalyzed reductive 1,2-dialkynylation of alkenes with respect to bromoalkynes (Scheme 1a,b). We were pleased to find that by converting the TIPS protecting group into other silyl groups, such as *t*-butyldiphenylsilyl (TBDPS), *t*-butyldimethylsilyl (TBS), triphenylsiyl, and triethylsilyl (TES), the corresponding products **4**−**7** could be isolated in 63−92% yield (Scheme 1a). To exhibit the robustness and generality of this reaction, we explored a wide range of aryl-substituted bromoalkynes (Scheme 1b). These transformations proceeded smoothly when halogen and electron-donating groups were installed on the phenyl unit (**9**−**13**). Good tolerance of functional groups including acylamino, nitro, cyano, methylsulfonyl, acetyl, and ester was observed in products **13**−**17**, **19**, and **20**. The alkynyl bearing *para*-trifluoromethyl in the phenyl moiety produced **18** in 87% yield, and its relative configuration was confirmed by X-ray crystal structure analysis (see the SI for details). The aryl-substituted bromoalkynes with ortho or meta substituents delivered the products **21**−**26** in 60−73% yield. Notably, substituents on the C−C triple bond could be other aryl groups such as naphthyl, benzofuryl, and thienyl, and these alkynylating reagents generated the corresponding products **27**−**29** in moderate to good yield. In addition, alkyl-substituted bromoalkynes could also be adaptable in this transformation, as illustrated by the formation of **30** and **31** (Scheme 1b).

Subsequently, the compatibility of alkene for this reaction was investigated (Scheme 1c). The alkenes bearing monosubstitution at the α-position and disubstitution at the β-position were well tolerated and afforded the products **32** and **33** in 68 and 61% yield, respectively. Moreover, three other types of alkenes, including internal alkene (**34**), β,γ-terminal alkene (**35**), and aryl-substituted alkenes (**36**−**40**) turned out to be successful substrates for this transformation.

To demonstrate the synthetic utility of this reaction, a gram-scale experiment (Scheme 2a) and further transformations of

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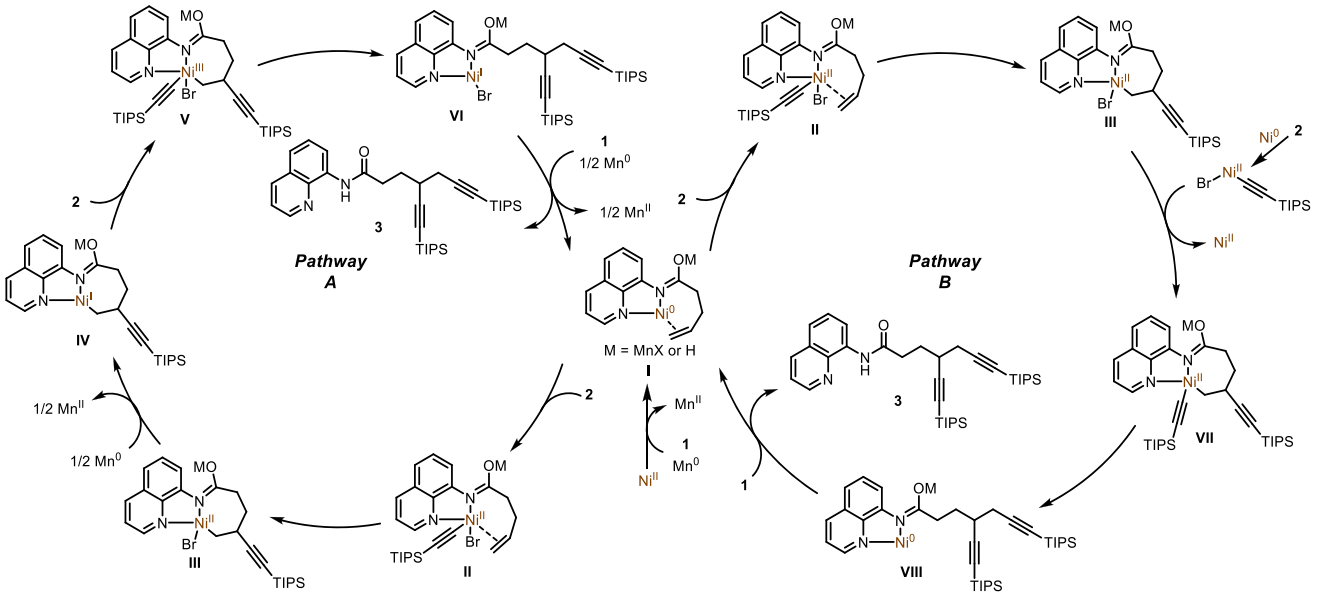
Scheme 4. Proposed Mechanism



the dialkynylation products (Scheme 2b) were carried out. When the reaction was tested on a 4.0 mmol scale, product **3** (2.16 g) could be obtained in 92% yield under the standard conditions. The terminal 1,5-diyne compound **41** was achieved in 82% yield through the sequential ethanolysis of aminoquinoline amide and the deprotection of TIPS of product **3**. Moreover, compound **41** could be further decorated via click cycloaddition to access ditriazole compound **42**, which has a potential application in the synthesis of metal−organic frameworks and metal complexes.[10] The silver-catalyzed hydroazidation and hydroboration of compound **41** could afford the azide- or borate-ester-functionalized 1,5-diene compounds **43** and **44** with good efficiency. Furthermore, the quinoline group could be easily removed, producing β-diyne primary amide compound **45** in 86% yield by 2-iodoxybenzoic acid (IBX) oxidation. A palladium-catalyzed hydrogenation reaction efficiently converted product **8** to the corresponding alkane **46**. When we treated product **8** with NaOH in EtOH at 130 °C, a Bergman-cyclization-type product **47** was obtained in 74% yield, which has been confirmed by X-ray analysis (see the SI for details).

To provide insight into the mechanism of this nickel-catalyzed reductive dialkynylation, a series of control experiments were designed and performed. Adding 1.0 equiv of TEMPO to the standard reaction system, the reaction was completely shut down with 98% recovery of substrate **1** (Scheme 3a). Considering that TEMPO could serve to poison the Ni catalyst, the inhibition of this reaction cannot necessarily be taken as proper evidence in favor of the radical process.[11] In contrast, the reaction could go smoothly in the presence of other radical scavengers (Scheme 3a). These results (Scheme 3a) indicated that a radical process might not be involved. With the employment of tetrakis(dimethylamino)ethylene (TDAE) as an organic reductant instead of Mn, product **3** could be obtained in 70% yield (Scheme 3b). In addition, when bromoalkyne **S6** was subjected to react with equivalent Mn (Scheme 3c), 92% of **S6** was recovered, and the hydrodebrominated terminal alkyne was not detected. Taking these results (Scheme 3b,c) into consideration, the formation of alkynylmanganese intermediate could be ruled out. Moreover, the addition of 1-chloro-2,4-dinitrobenzene, a single electron transfer (SET) inhibitor,[12] led to an obvious retardation of the transformation under the standard conditions (Scheme 3d). This result revealed a plausible catalytic cycle involving the SET processes, capable of reducing the oxidized Ni intermediates with Mn. Then, the sequential stoichiometric reaction of substrates **1** and **2** with equivalent $Ni(COD)_2$ was performed (Scheme 3e). After quenching the reaction with water, reductive Heck byproduct **48** and product **3** were isolated in 28 and 33% yield with 32% recovery of **1** (Scheme 3e). Compound **48** might be produced from the migratory insertion of alkynyl−Ni^{II} species into the γ-position of **1** and the subsequent protonation process (Scheme 3e). Besides, even in the absence of reductants, this stoichiometric reaction could also furnish the dialkynylation product **3** in an appreciable yield. This result demonstrated the existence of another plausible catalytic cycle that required Mn in the initial step of reducing Ni^{II} to Ni^0 into the catalytic chain rather than the subsequent intermediate reduction. In the radical clock experiment (Scheme 3f), only the 1,2-dialkynylation product **50** was obtained, whereas the ring-opening product was not observed. This result could exclude the existence of the C-center radical generated by homolytic Ni−alkyl bond cleavage after the migratory insertion process.

On the basis of the aforementioned experimental results and previous literature,[3j,u,8,13,14] two possible catalytic cycles involved in this transformation are depicted in Scheme 4 using alkene **1** and bromoalkyne **2** as the examples. Initially, a Ni^0 species **I** is generated under the reductive conditions, which undergoes oxidative addition with bromoalkyne to afford the Ni^{II} species **II**. After migratory insertion, an alkyl−Ni^{II} complex **III** is formed, which could generate the byproduct **48** if protonation occurs (Scheme 3e). In plausible pathway A, the alkyl−Ni^{I} complex **IV**, which is generated from the reduction of intermediate **III**, would go through a second oxidative addition of bromoalkyne **2** to achieve the Ni^{III} complex **V**. The reductive elimination of the intermediate **V** furnishes the Ni^{I} species **VI**, which undergoes a subsequent reduction and ligand exchange to offer product **3** and regenerate the Ni^0 species **I** to the next catalytic cycle. In plausible pathway B, the intermediate **III** would continue the transmetalation with an alkynyl−Ni^{II} species

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to form Ni^{II} complex **VII**. After the reductive elimination and ligand-exchange process, product **3** is formed.

In conclusion, we have developed a nickel-catalyzed reductive 1,2-dialkynylation of alkenes using 8-aminoquinoline as the directing group under mild conditions with sequential formation of two C(sp)−C(sp^3) bonds. This reaction provided an efficient method to access diverse synthetically flexible 1,5-diynes. The more detailed mechanistic investigations of this reaction as well as the further expansion of the nickel-catalyzed reductive difunctionalization of alkene with novel electrophiles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03147.

Experiment procedures, detailed reaction optimization, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 1936009 and 1940841 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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