Ni-catalyzed regio- and stereo-defined intermolecular cross-electrophile dialkylation of alkynes without directing group

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The development of straightforward synthesis of regio- and stereodefined alkenes with multiple aliphatic substituents under mild conditions is an unmet challenge owing to competitive β-hydride elimination and selectivity issues. Herein, we report the nickel-catalyzed intermolecular cross-dialkylation of alkynes devoid of direct or activating groups to afford multiple aliphatic substituted alkenes in a syn-selective fashion at room temperature. The combination of two-electron oxidative cyclometallation and single-electron cross-electrophile coupling of nickel enables the syn-cross-dialkylation of alkynes at room temperature. This reductive protocol enables the sequential installation of two different alkyl substituents onto alkynes in a regio- and stereo-selective manner, circumventing the tedious preformation of sensitive organometallic reagents. The synthetic utility of this protocol is demonstrated by efficient synthesis of multi-substituted unfunctionalized alkenes and diverse transformations of the product.

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Multiple substituted alkenes are pivotal subunits which are commonly occurring in natural products, bioactive molecules, and material sciences, and serve as useful precursors for other functional groups and chiral centers. In addition, alkenes exhibit orthogonal reactivity with respect to polar functional groups, providing an opportunity for the late-stage derivatization of complex molecules. To this end, synthesis of olefins with stereo-selectivity control has become one of the major themes in the arena of synthetic chemistry and has evolved from Wittig reaction and elimination reactions to carbometallation-coupling reactions and olefin metathesis. Despite numerous progress in addressing this issue, stereodefined synthesis of trisubstituted alkenes remains a formidable synthetic challenge. On the other hand, Ni-catalyzed carbo-difunctionalization of alkynes represents an ideal route to access multiple substituted alkenes with molecular complexity via the spontaneous formation of two vicinal C–C bonds. Among which, alkylation of alkynes is more challenging due to the difficulties in forming Csp2–Csp3 bond. In general, three distinct strategies have been employed to address this issue. The first strategy is a Ni-catalyzed radical addition onto alkynes, followed by recombination and coupling with arylmetallic reagents, favoring anti-selectivity which is dominated by steric repulsion of vinyl radicals with nickel center. The use of terminal alkynes offers limited opportunity to afford trisubstituted alkenes. The second strategy is a carbometallation of alkynes to generate vinyl nickel species, which is followed by an electrophilic quench, favoring a syn-selectivity. This method suffers from regioselectivity issues, and could be only applied to electronically and sterically biased alkenes. In most cases, directing groups are required to improve regioselectivity. These two strategies require sensitive organometallic reagents, and can be applied to alkylarylation and diarylation of alkenes, dialkylation is inaccessible due to the difficulties in forming the second Csp2–Csp3 bond. The other is oxidative cyclization of Ni(0) complex with alkyl and a second π-component to form Ni(II) cyclic intermediates, followed by σ-bond metathesis or transmetalation with organometallic reagents to forge the second carbon-carbon bond. Among which, alkylation of alkynes is more challenging due to the difficulties in forming Csp2–Csp3 bond. In general, three distinct strategies have been employed to address this issue. The first strategy is a Ni-catalyzed radical addition onto alkynes, followed by recombination and coupling with arylmetallic reagents, favoring anti-selectivity which is dominated by steric repulsion of vinyl radicals with nickel center. The use of terminal alkynes offers limited opportunity to afford trisubstituted alkenes. The second strategy is a carbometallation of alkynes to generate vinyl nickel species, which is followed by an electrophilic quench, favoring a syn-selectivity. This method suffers from regioselectivity issues, and could be only applied to electronically and sterically biased alkenes. In most cases, directing groups are required to improve regioselectivity. These two strategies require sensitive organometallic reagents, and can be applied to alkylarylation and diarylation of alkenes, dialkylation is inaccessible due to the difficulties in forming the second Csp2–Csp3 bond. The other is oxidative cyclization of Ni(0) complex with alkyl and a second π-component to form Ni(II) cyclic intermediates, followed by σ-bond metathesis or transmetalation with organometallic reagents (Fig. 1b) to forge the second carbon-carbon bond. Montgomery, Jamison, Ikeda and Sato, as well as others extensively investigated the tandem oxidative cyclization of alkenes with C=C/C=N/C=O and coupling using different organometallic reagents (R–M, M = Zn, B, Mg, Zr, Sn) to give diverse substituted alkenes (Fig. 1b, top). In 2018, Montgomery reported a seminal reductive Ni-catalyzed intramolecular oxidative cyclization of internal alkynes with
Results

Reaction optimization. With these concerns in mind, we set out to examine the hypothesis using 1-hexyne (1a), 2-cyclohexen-1-one (2a) and 1-bromobutane (3a) as prototype substrates (Table 1). After extensive evaluation of a series of reaction parameters, we identified the use of NiBr₂·DME (10 mol%), 4-cyanopyridine (5 mol%, A₁), cerium chloride (0.8 equiv), potassium iodide (2.0 equiv), zinc (2.0 equiv), in the presence of water (1.5 equiv) in N,N-dimethylformamide (0.1 M) at room temperature as the optimal conditions, affording the desired three-component sequential dialkylation product 4a in 66% yield (Table 1, entry 1). The reaction demonstrated exclusive regio- and syn-selectivity, which is complementary to the regio- and stereo-selectivity of Ni-catalyzed radical addition pathway. Similar result was obtained when presynthesized precatalyst was used, giving the desired product 4a in 64% yield. The reaction showed lower efficiency in the absence of A₁, affording 4a in 37% yield (Table 1, entry 2). Increasing the loading of A₁ to 10 mol% and 20 mol% did not further improve the yield of 4a (Table 1, entries 3 and 4). Replacing A₁ with pentafluoropyridine (A₂) gave trialkylated alkene 4a in 34% yield (Table 1, entry 5). The use of other nickel catalyst precursors, such as NiBr₂, NiCl₂-DME, and Ni(COD)₂, led to inferior results (Table 1, entries 6–8). No desired product was detected in the absence of nickel catalyst or sacrificial reductant zinc (Table 1, entry 9). The presence of cerium chloride and potassium iodide are both crucial for the three-component reaction, trace amount of desired product was formed without either additive (Table 1, entry 10). The role of KI is likely to undergo halide exchange to generate alkyl iodide in situ slowly from alkyl bromide to maintain alkyl iodide in low concentration during the reaction course. Other Lewis acids proved to be unsuccessful in this reaction (Table 1, entry 11). Water plays a critical role as a mediator in this reaction, giving the optimal result with 1.5 equiv of water (Table 1, entries 12 and 13). Evaluation of solvent effect revealed that polar solvent is required for this reaction. The reaction delivered 4a in 23% and 43% yields, respectively, when the reaction was conducted in NMP or DMA (Table 1, entries 14 and 15).

Substrate scope. With the optimized conditions in hand, we turned to examine the scope of this transformation. To our delight, this reaction protocol is applicable to a wide variety of functionalized alkynes, alkyl bromides, and enones, furnishing various advanced tri- and tetrasubstituted alkenes with multiple functional groups. We have since expanded the substrate scope of this protocol to a variety of functionalized alkynes, alkyl bromides, and enones.
Fig. 2 Scope for the syn-cross-electrophile dialkylation of alkenes with respect to alkenes. Unless otherwise noted, isolated yield is shown on 0.2 mmol scale under standard conditions. See Table 1, entry 1 for detail.aIsolated yield on 10.0 mmol scale.bNiBr₂·DME (10 mol%), A₂ (20 mol%), Zn (2.5 equiv), KI (2.0 equiv), ZnBr₂ (10 mol%), 2-methyl-2-butanol (2.0 equiv), DMF (0.1 M), rt, overnight.cAlkyne was added in two portions. 1.0 equiv alkyne was added after 5 h.dAlkyne was added in two portions. 1.0 equiv alkyne was added after 3 h.eAlkyne (2.0 equiv), enone (0.2 mmol), alkyl bromide (3.5 equiv), NiBr₂·DME (10 mol%), Zn (5.0 equiv), CsI (5.0 equiv), ZnI₂ (30 mol%), 2-methyl-2-butanol (3.0 equiv), DMF (0.05 M) and 1.0 equiv alkyne was added after 3 h, rt, overnight.
aliphatic substituents in excellent levels of regio-, chemo-, and stereo-selectivity (Figs. 2 and 3). First, the scope of alkynes was investigated under the reaction conditions (Fig. 2). Aliphatic terminal alkynes with varied lengths of carbon chain gave corresponding trialkyl substituted alkenes in good yields (4a-4c).

| alkyl bromide | Scope for electrophiles |
|---------------|-------------------------|
| ![alkyl bromide](image1) | ![Scope for electrophiles](image2) |

Aliphatic alkynes tethered with chloride, ester, amides are tolerated in this method, furnishing corresponding functionalized alkenes in synthetic useful yields, rendering further elaboration opportunities for the products (4d-4h). The reaction could be applied to late-stage functionalization of natural products and

**Fig. 3 Scope for the syn-cross-electrophile dialkylation of alkynes with respect to alkyl electrophiles.** Unless otherwise noted, isolated yield is shown on 0.2 mmol scale under standard conditions. See Table 1, entry 1 for detail. aNiBr₂·DME (10 mol%), A2 (20 mol%), Zn (2.5 equiv), KI (2.0 equiv), ZnBr₂ (10 mol%), 2-methyl-2-butanol (2.0 equiv), DMF (0.1 M), rt, overnight. bThe reaction was conducted using 0.2 mmol of enone (1.0 equiv), alkyne (2.8 equiv), n-BuBr (3.5 equiv) in the presence of NiBr₂·DME (10 mol%), Zn (3.0 equiv), CsI (5.0 equiv), 2-methyl-2-butanol (2.0 equiv), and ZnI₂ (30 mol%) in DMF (0.05 M). cStandard conditions were used. dAlkyne was added in two portions. 1.0 equiv of alkyne was added after 5 h. eAlkyne was added in two portions. 1.0 equiv of alkyne was added after 3 h. fYield based on the recovery of enone.
drug molecules. Estrone and oxaprozin derived terminal alkynes could be transformed into the corresponding trialkylated products in 52% and 57% yields, respectively (4i and 4j). Notably, the reaction conditions could be applied to gram-scale synthesis (10.0 mmol scale) without erasing the efficiency of the reaction, affording 1.68 g of 4a in 67% yield. Second, terminal aromatic alkynes were tested. Electron-donating and electron-withdrawing substituted aryl alkynes are all good substrates for this transformation with A2 (20 mol%) and zinc bromide (10 mol%) as Lewis acid. In these cases, 2-methyl-2-butanol was used as proton source instead of water. Terminal aryl alkynes with para-, meta-, and ortho-substitution patterns could be converted to corresponding alkenes with two aliphatic substituents in moderate to good yields (5a-5k). It is noteworthy that alkynyl arylhalides are compatible in this reaction with halides intact (5f and 5g), leaving a chemical handle to build molecular complexity by cross-coupling reactions. The structure and stereochemistry of the product were determined unambiguously by X-ray diffraction analysis of 5c. Alkynyl indole could be converted to substituted vinyl indole in synthetic useful yield (5i). Third, internal alkynes were also examined, which could lead to synthetically challenging tetrasubstituted alkenes. Internal alkynes are challenging substrates for Ni-catalyzed carbo-difunctionalization of alkynes due to their steric hindrance. It is noteworthy that internal alkynes are compatible in this reaction. Diverse substituted 1-phenyl-2-alkylalkynes are good substrates under the reaction conditions, giving trialkaryl-substituted alkenes (6a-6e) in good yields with excellent regioselectivities. The regio- and stereochemistry was confirmed by X-ray diffraction analysis of 6b. Stereodefined alkenes with four aliphatic substituents could be obtained using this protocol in good yields with exclusive regio- and stereo-selectivity (6f-6i).

Next, we evaluated the scope of two electrophiles (Fig. 3). A wide variety of alkyl bromides proved amenable to this reaction, substantially expanding the synthetic potential of this protocol (Fig. 3, top). Alkyl bromides with different lengths of aliphatic chain as well as alkyl or aryl ethers, chlorides, could be combined with terminal and internal alkynes, affording tri- and tetrasubstituted alkenes in moderate to good yields (7a-7l). Notably, the reaction demonstrated excellent selectivity over alkynes and alkenes. Alkene or alkyne tethered alkyl bromides underwent cross-electrophile three-component reaction smoothly, delivering corresponding multiple substituted alkenes in 68% and 65% yields, respectively, leaving the double bond and triple bond

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**Fig. 4 Synthesis of unfunctionalized tri- and tetrasubstituted alkenes.** These results indicate that product of dialkylation of alkynes can be sufficiently transformed into unfunctionalized alkenes. Yields are for isolated and purified products. The detailed procedures have been presented in Supplementary Information (SI).

**Fig. 5 Synthetic applications of 4a.** Reaction conditions: a Reductive amination. (1) PhNH₂, MgSO₄, AcOH, DCM (0.2 M), rt, 2 h; (2) NaBH₃CN, MeOH, rt, 10 h. b Reduction. NaBH₄, MeOH, rt, 2 h. c Wittig Olefination. n-BuLi, Ph₃PCH₂Br, THF, −30 °C to rt, overnight. d Epoxidation. m-CPBA, NaHCO₃, DCM, 0 °C, 2 h. e Desaturation. Pd(TFA)₂, 1 atm O₂, DMSO, 85 °C, 14 h. f Aromatization. Pd(TFA)₂, PTSA, N,N-dimethylpyridin-2-amine, 1 atm O₂, DMSO, 80 °C, 24 h.
intact (7m and 7n). Moreover, functional groups, such as ester and amide, which are sensitive to organometallic reagents, could be tolerated under the reaction conditions (7o-7r).

Secondary alkyl halides, such as 4-iodotetrahydro-2H-pyran, could be converted to corresponding alkenes 7s in 52% yield. Unfortunately, tertiary alkyl halides could not form the desired product. Additionally, various cyclic and acyclic enones could be involved in this cross-electrophilic dialkylation process (Fig. 3, bottom). Cycloheptenone could be coupled with alkyne and n-butylbromide to give 8a in 61% yield. A couple of acyclic enones were also good substrates in this three-component reaction, furnishing corresponding multialkylated alkenes with regio- and stereocontrol in 53%-61% yields (8b-8e). Cyclohexenones with diverse bulky substitutions were also tolerated in the reaction, delivering the desired products (8f and 8g) in 52% and 66% yields, respectively. Acyclic enones with more sterically hindered substituents and acrylamides could be involved in the reaction, albeit in lower efficiency (8h and 8i). The major competing side reactions include the alkylalkynylation (8h′) and hydroalkylation of alkynes (8i′) (Supplementary Figs. 11-18).

Derivatization. Unfunctionalized alkenes with multiple substitutions are important yet difficult to access13. The resulting alkenes could be transformed into unfunctionalized alkenes by removing the carbonyl group in good yields (9a-9f), providing a useful method to tri- and tetrasubstituted all-carbon alkenes without any functional group (Fig. 4). Notably, this protocol...

Fig. 6 Mechanistic investigations and control experiments. a Reaction in the presence of deuterated water. b Treat the product 6a under reaction conditions with deuterated water. c The reaction of deuterated phenylacetylene. d Radical clock reaction using cyclopropylmethylbromide. e Radical clock reaction using 17. f Radical trap with TEMPO.
The acyclic product \( \text{4a} \) was obtained in 76% yield by Wittig reaction. The formation of \( \text{4b} \) was achieved in 57% yield, \( \text{4c} \) in 72% yield, and \( \text{4d} \) in 58% yield using \( \text{tBuLi} \) and \( \text{AlCl}_{3} \) in 58% and 90% yields, respectively. When solid \( \text{NiBr}_{2} \cdot \text{DME} \) (10 mol%) was used instead of liquid, \( \text{NiCl}_{2} \) (0.8 equiv), I\( _{2} \) (2.0 equiv), solid alkene (2.0 equiv, if solid), and alkyl bromide (2.0 equiv, if solid) were added into an oven-dried glove box. 4-Cyanopyridine (5 mol%), \( \text{CeCl}_{3} \) (0.8 equiv), DMF (0.1 M) in DMF was added, and rapid stirring was commenced. Then \( \text{H}_{2} \text{O} \) (1.5 equiv), solid alkene (2.0 equiv, if liquid), enone (0.2 mmol), and alkyl bromide (2.0 equiv, if liquid) were added and washed with brine (50 mL). The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was dried over magnesium sulfate, filtered, evaporated and purified by silica gel chromatography with hexanes/ethyl acetate as eluent to give the corresponding product in pure form.

**Mechanistic consideration.** To shed light on the detail of this sequential three-component reaction, we set up a series of experiments to probe the reaction mechanism (Fig. 6). First, 1-phenyl-1-propyne was exposed to the reaction conditions in the presence of \( \text{D}_{2} \text{O} \) (4 equiv) in lieu of \( \text{H}_{2} \text{O} \). \( \text{6a-d} \) was obtained in 72% yield with 96% deuteriation of single proton at \( \alpha \)-position to carbonyl as a mixture of diastereomers. While no deuterium incorporation was observed when \( \text{6a} \) was subjected to the reaction conditions in the presence of deuterated water. When deuterated phenylacetylene was subjected to the reaction conditions, \( \text{5a-d} \) was obtained in 42% yield. No deuterium scrambling from terminal position of phenylacetylene to \( \alpha \)-position to carbonyl was observed. These results indicate one \( \alpha \)-proton of ketone is from water during the reaction course and non-exchangable with surroundings. Next, radical clock experiments were carried out. When (bromomethyl)cyclopropane was used in the reaction, skipped diene \( \text{16} \) was obtained in 58% yield by ring-opening/cross-coupling reaction process without the formation of \( \text{16}^{'s} \). Moreover, homoallylic bromide \( \text{17} \) could be transformed into \( \text{18} \) via radical cyclization/cross-coupling process in 16% yield along with the formation of byproducts \( \text{19} \) and \( \text{20}^{'s} \). The acrylic product \( \text{18}^{'s} \) was not detected. In addition, the use of TEMPO completely shut down the desired reaction. The formation of \( \text{21} \) and \( \text{22} \) were detected by mass. No n-butyl zinc species was detected during the reaction course (Supplementary Figs. 5–9). The combined results suggest the involvement of alkyl radical species in this reaction.

**Proposed reaction mechanism.** Based on the experimental results and literature, a proposed mechanism of this reaction is depicted in Fig. 7. First, \( \text{Ni (0)} \) species generated from \( \text{Ni (II)} \) by reduction initiated metallocyclic intermediate \( \text{A} \) via cross-oxidative cyclometaliation between alkene and enone. C-bound intermediate \( \text{B} \) could equilibrate with O-bound intermediate \( \text{C} \). In the presence of Lewis acid (\( \text{CeCl}_{3} \) or \( \text{ZnBr}_{2} \)), intermediate \( \text{C} \) was formed via transmetalation, which could further undergo protonation to give vinylnickel intermediate \( \text{D} \) with proton source. The presence of Lewis acid might facilitate the generation of \( \text{C} \) by forming M-O bond (\( \text{M=Ce} \) or \( \text{Zn} \)). \( \text{D} \) could be reduced by zinc to give \( \text{Ni (I)} \) intermediate \( \text{E} \), which could undergo oxidative addition to alkyl bromide to form \( \text{Ni (III)} \) intermediate \( \text{F} \) via single stepwise electron transfer and radical recombination with \( \text{F} \). Intermediate \( \text{G} \) underwent reductive elimination to form the final product along with \( \text{Ni (I)} \) intermediate, which could be further reduced by \( \text{Zn} \) to complete the catalytic cycle.

**Discussion**

In summary, we have demonstrated a Ni-catalyzed fully intermolecular regio- and stereo-selective cross-dialkylation of alkynes in the presence of alkyl halides and \( \alpha \)-unsaturated compounds, affording stereodefined tri- and tetrasubstituted alkenes with multiple alkyl substitutions58–62. Notably, the reaction enables syn-selective dialkylation of alkynes with exclusive regioselectivity in the absence of any direction group, providing an alternative to access multi-substituted unfunctionalized alkenes from readily-accessible reagents. The use of reductive conditions allows for the reaction to proceed at room temperature, circumventing the use of air- and moisture-sensitive organometallic reagents.

**Methods**

**General procedure for the fully intermolecular dialkylation of alkynes.** The reaction was operated in a nitrogen-filled glove box. 4-Cyanopyridine (5 mol%), \( \text{CeCl}_{3} \) (0.8 equiv), \( \text{K}_{2}(\text{CO}_{3}) \) (2.0 equiv), \( \text{NiBr}_{2} \cdot \text{DME} \) (10 mol%), alkene (2.0 equiv, if solid), and alkyl bromide (2.0 equiv, if solid) were added into an oven-dried vial containing a magnetic stirring bar. If the alkene or alkyl bromide is a solid, it was added along with other solid reagents. Anhydrous \( \text{DMF} \) (0.1 M) was added, and rapid stirring was commenced. Then \( \text{H}_{2} \text{O} \) (1.5 equiv), alkene (2.0 equiv, if liquid), enone (0.2 mmol), and alkyl bromide (2.0 equiv, if liquid) were added sequentially via syringe. The vial was sealed with parafilm and stirred vigorously for 48 h. The reaction was filtered with ethyl acetate (30 mL) and washed with brine (50 mL). The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was dried over magnesium sulfate, filtered, evaporated, and purified by silica gel chromatography with hexanes/ethyl acetate as eluent to give the corresponding product in pure form.

**Data availability**

The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers of CCDC 1983359 and CCDC 1983360. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
Y.Z.Z. discovered and developed the reaction. W.S. conceived and designed the project. Y.Z.Z. and N.X. performed the experiments and collected the data. W.S. wrote the manuscript with contributions from all authors.

Competing interests
The authors declare no competing interests.

Additional information

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