Nickel-catalysed migratory hydroalkynylation and enantioselective hydroalkynylation of olefins with bromoalkynes

Xiaoli Jiang, Bo Han, Yuhang Xue, Mei Duan, Zhuofan Gui, You Wang & Shaolin Zhu

α-Chiral alkyne is a key structural element of many bioactive compounds, chemical probes, and functional materials, and is a valuable synthon in organic synthesis. Here we report a NiH-catalysed reductive migratory hydroalkynylation of olefins with bromoalkynes that delivers the corresponding benzylic alkynylation products in high yields with excellent regioselectivities. Catalytic enantioselective hydroalkynylation of styrenes has also been realized using a simple chiral PyrOx ligand. The obtained enantioenriched benzylic alkynes are versatile synthetic intermediates and can be readily transformed into synthetically useful chiral synthons.

1State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, China. †email: wangyou@nju.edu.cn; shaolinzhu@nju.edu.cn
As a key structural element, chiral alkynes motifs bearing an α stereocentre are often found in many bioactive compounds, chemical probes, and functional materials (Fig. 1a). In addition, they are also valuable synthons as the sp\(^3\)-hybridized carbons could undergo versatile transformations to deliver useful sp\(^2\)- or sp\(^3\)-hybridized carbons\(^1\). As a result, efficient strategies for catalytic, enantioselective C(sp\(^3\))–C(sp) coupling to generate such stereocentres have long been sought.

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**Fig. 1 Ni(I)H-catalyzed migratory hydroalkynylation and enantioselective hydroalkynylation.**

### a
Representative bioactive molecules bearing a chiral alkyne motif

- **AMG 837**
  - (a GPR40 agonist for type 2 diabetes)
- **Efavirenz**
  - (anti HIV)

### b
Common strategies for C(sp\(^3\))–C(sp) coupling

- **Cu-asymmetric Sonogashira**
  - Ni-asymmetric sp-sp\(^3\) coupling

### c
This work: chemo- & stereoselective NiH-catalyzed (migratory) hydroalkynylation of alkenes

#### i
NiH-catalyzed migratory hydroalkynylation

- Unrefined alkene + bromoalkyne
- Chemo- & stereo-selective
- Migratory hydroalkynylation

#### ii
Enantioselective NiH-catalyzed hydroalkynylation of vinylarenes

- Styrene + bromoalkyne
- Enantioenriched alkyne

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hydride coupling, here we report an appealing approach via metal-bonds. Liu has also used an alkene difunctionalization strategy to produce enantioenriched alkynylation product under copper catalyst. As a continued development of general alternatives for asymmetric C(sp^3)–C(sp^3) coupling, here we report an appealing approach via metal-hydride catalyzed asymmetric (remote) hydroalkynylation from readily available alkene starting materials.

Owing to its low-cost, facile oxidative addition, and availability of diverse oxidation states, nickel has emerged as a catalytic complementary to palladium over the past two decades, especially in cross-coupling reaction involving C(sp^3)–H bonds. Reductive migratory hydrometalation process that can discriminate between alkene and alkyne and (ii) an alkynylation process highly selective for one of the alkynickel species. A chiral alkyne bearing an α,β-substituted stereogenic C(sp^3)–H bond would be ultimately obtained from styrene through hydronickellation and subsequent enantioconvergent alkynylation. Here, we show the successful execution of this reaction.

**Results**

**Reaction design and optimization.** Our initial studies involved the migratory hydroalkynylation of 4-phenyl-1-butene (1a) using 1-bromo-2-(trisopropylsilyl)acetylene (2a) as an alkynylation reagent (Fig. 2). It was determined that NiI_2·xH_2O and the bathocuproine ligand (L) could generate the desired migratory alkylation product as a single regioisomer [rr (benzylic proton) > 99:1] in 82% yield (entry 1). Other nickel sources such as NiBr_2 led to lower yields and a moderate rr (entry 2). Ligand screening revealed that the previously used neocuproine (L2) resulted in significantly lower yield and rr (entry 3) while a similar ligand neocuproine (L2) led to a similar regioselectivity but a lower yield (entry 4). Other silanes such as trimethoxysilane and diethoxymethylsilane gave diminished yields (entries 5 and 6), and marginally lower yield was obtained when reducing the amount of PMHS to 2.5 equiv (entry 7). K_3PO_4·H_2O was shown to be an unsuitable base (entry 8). The addition of NaI as an additive improves both the yield and rr, presumably by promoting the regeneration of NiH species (entry 9). An evaluation of solvents

![Fig. 2 Variation of reaction parameters.](https://doi.org/10.1038/s41467-021-24094-9)"
revealed that THF was less effective than DME (entry 10), and conducting the reaction at 40 °C gave inferior results (entry 11).

**Substrate scope.** With these optimal reaction conditions, we examined the generality of the reaction. As shown in Fig. 3a, unactivated terminal alkenes bearing electron-donating (3c) or electron-withdrawing (3d–3g) substituents on the remote aryl ring are tolerated. A variety of functional groups are readily accommodated, including ethers (3c, 3h–3k, 3m), a trisubstituted ethynyl group (3d), and esters (3l). Importantly, tosylates (3j) and triflates (3k) commonly used for further cross-coupling, all remained intact. The reaction could also proceed with olefin substrate having longer chain length between the starting C–C bond and the remote aryl group, producing the benzylic alkynylation product exclusively although with a lower yield (3l). Remarkably, both silyl and sterically hindered alkyl substituted ethynyl bromides work well in this reaction (3m, 3n). Moreover, a variety of unactivated internal alkenes also proved to be competent coupling partners, regardless of the E/Z configuration or the position of the C=C bond (Fig. 3b, 3o–3w). As expected, styrenes themselves smoothly undergo hydroalkynylation to produce the benzylic alkynylation product exclusively (Fig. 3c, 3x–3z). Under these exceptionally mild reaction conditions, various substituents on the aryl ring (3z–3ze) as well as heteroaromatic styrenes (3f, 3g) were also suitable for this reaction.

In an effort to obtain enantioenriched benzylic alkynylation products, the asymmetric version of NiH-catalyzed hydroalkynylation of styrenes was explored and the results are in Fig. 4. It was found that a chiral PyrOX ligand (S)-L† under modified reaction conditions could produce the desired hydroalkynylation products in good yields and excellent ee. Substituents with a variety of substituents on the aromatic ring underwent asymmetric hydroalkynylation smoothly (5a–5q), including ethers (5d–5i), an easily reduced aldehyde (5j), a nitrite (5m, 5n), and esters (5o–5q). Substituents commonly used for further cross-coupling such as aryl chloride (5c), aryl bromide (5k), and boronic acid pinacol ester (5j) all were tolerated. A variety of functional groups are readily accommodated, including alkyl halides (5a–5i), alkenes (5m–5o), aldehydes (5p–5v), and boronic acid pinacol ester (5w). Substituents on the aromatic ring underwent asymmetric hydroalkynylation smoothly (5a–5q), including ethers (5d–5i), an easily reduced aldehyde (5j), a nitrite (5m, 5n), and esters (5o–5q). Substituents commonly used for further cross-coupling such as aryl chloride (5c), aryl bromide (5k), and boronic acid pinacol ester (5j) all were tolerated. A variety of functional groups are readily accommodated, including alkyl halides (5a–5i), alkenes (5m–5o), aldehydes (5p–5v), and boronic acid pinacol ester (5w).

**Fig. 3 NiH-catalyzed migratory hydroalkynylation of alkenes with bromoalkynes.** Yield under each product refers to the isolated yield of purified product (0.20 mmol scale, average of two runs), rr refers to regioisomeric ratio, representing the ratio of the major product to the sum of all other isomers as determined by GC analysis. *Diglyme was used as solvent. †10 mol% NiI2·H2O, 12 mol% L, and 20 mol% NaI were used. ‡DME (0.10 M) was used. TBS tert-butyldimethylsilyl, TBDDS tert-butyldiphenylsilylethyl, Tr trityl (triphenylmethyl).
The asymmetric migratory hydroalkynylation could also be realized. In a preliminary experiment with 3-aryl-1-propane (11) as substrate (Fig. 5a), chain-walking and subsequent asymmetric alkylation at benzylic position product ((S)-3i) was obtained with excellent ee (90% ee) as major isomer (90:10 rr). When the reaction was conducted on a 5 mmol scale, the functionalized chiral benzylic alkyne (5e) was obtained in high yield and with excellent enantioselectivity (Fig. 5b). To highlight the synthetic utility of the method, subsequent derivatizations were carried out (Fig. 5c). Desilylation of 5e yielded the enantioenriched terminal alkyne (6), which could further undergo a click reaction to form 7 or a hydration reaction to form 8. The semi-hydrogenation of alkyne (5a) by DIBAL-H (diisobutylaluminium hydride) could be highly stereoselective, giving the Z-alkene (9). In addition, oxidative cleavage of the triple bond in 5e could afford the corresponding chiral carboxylic acid (10).

To gain further insight into the mechanism of the hydrometallation process, isotope labeling experiments were conducted. As shown in Fig. 5d, the use of the deuterated trans-alkene (E-4h-D)
Methods

NiH-catalyzed migratory hydroalkynylation of alkynes. In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiI₂·H₂O (3.8 mg, 5.0 mol%), Na₂CO₃ (42.4 mg, 2.0 equiv), NaI (3.0 mg, 10.0 mol%) and anhydrous DME (1.0 mL). The mixture was stirred for 20 min at room temperature (stirred at 800 rpm) before the addition of (MeO)₅SiH (64 µL, 0.50 mmol, 2.5 equiv). Stirring was continued for an additional 5 min before the addition of olefin 1 (0.20 mmol, 1.0 equiv) and bromoalkyne 2 (0.30 mmol, 1.5 equiv). The tube was sealed with a teflon-lined screw cap, removed from the glove box and the reaction was stirred at 0°C for up to 12 h (the mixture was stirred at 800 rpm). After the reaction was complete, the reaction was quenched upon the addition of H₂O and the mixture was extracted with EtOAc. The organic layer was concentrated to give the crude product. n-Dodecane (20 µL) was added as an internal standard for GC analysis. The product was purified by flash column chromatography (petroleum ether/EtOAc) for each substrate. See Supplementary Information for more detailed experimental procedures and characterization data for all products.

Enantioselective NiH-catalyzed hydroalkynylation of styenes. In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiI₂·H₂O (3.8 mg, 5.0 mol%), Na₂CO₃ (42.4 mg, 2.0 equiv), K₃PO₄·H₂O (115.1 mg, 2.5 equiv), NaI (60.0 mg, 2.0 equiv) and anhydrous PhCF₃ (1.0 mL). The mixture was stirred for 20 min at room temperature (stirred at 800 rpm) before the addition of (MeO)₅SiH (64 µL, 0.50 mmol, 2.5 equiv). Stirring was continued for an additional 5 min before the addition of olefin 4 (0.20 mmol, 1.0 equiv) and bromoalkyne 2 (0.30 mmol, 1.5 equiv). The tube was sealed with a teflon-lined screw cap, removed from the glove box and the reaction was stirred at 0°C for up to 12 h (the mixture was stirred at 800 rpm). After the reaction was complete, the reaction was quenched upon the addition of H₂O and the mixture was extracted with EtOAc. The organic layer was concentrated to give the crude product. n-Dodecane (20 µL) was added as an internal standard for GC analysis. The product was purified by flash column chromatography (petroleum ether/ EtOAc) for each substrate. The enantiomeric excesses (% ee) were determined by HPLC analysis using chiral stationary phases. See Supplementary Information for more detailed experimental procedures and characterization data for all products.

Data availability

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its supplementary information files, or from the corresponding author upon reasonable request.

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Author contributions

X.J., Y.W., and S.Z. designed the project. X.J., B.H., Y.X., M.D., Z.G., Y.W., and S.Z. co-wrote the manuscript, analyzed the data, discussed the results, and commented on the manuscript. X.J., B.H., Y.X., M.D., and Z.G. performed the experiments. All authors contributed to discussions.

Competing interests

The authors declare the following competing interest(s): a patent for the synthesis of AMG 837 using this method has been filed.

Additional information

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Correspondence and requests for materials should be addressed to Y.W. or S.Z.

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