

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

Xiaoli Jiang¹, Bo Han¹, Yuhang Xue¹, Mei Duan¹, Zhuofan Gui¹, You Wang ¹✉ & Shaolin Zhu ¹✉

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 carbons¹. As a result, efficient strategies for catalytic, enantioselective $C(sp^3)$ - $C(sp)$ coupling to generate such stereocentres have long been sought

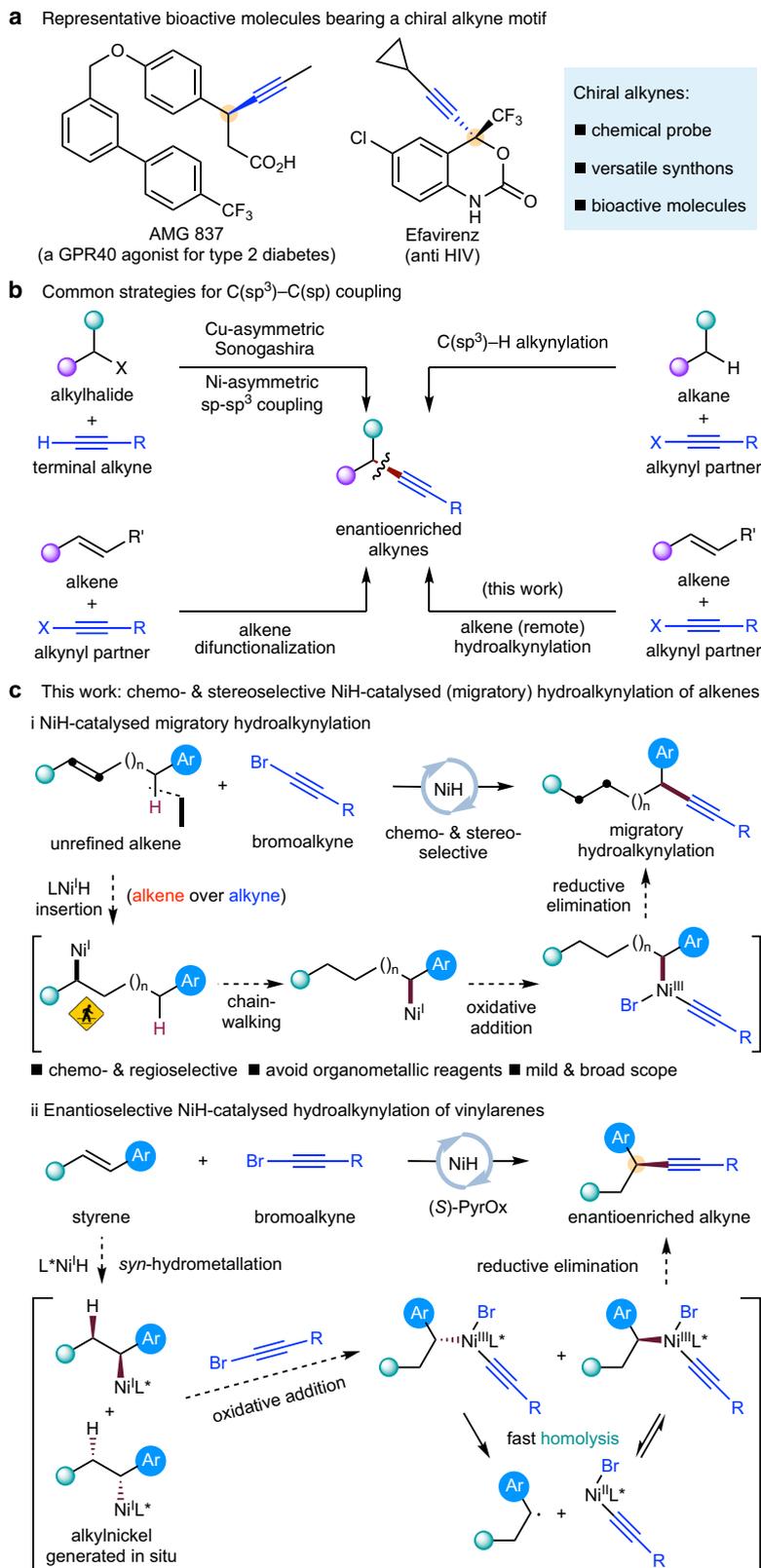


Fig. 1 Ni(I)H-catalysed migratory hydroalkynylation and enantioselective hydroalkynylation. **a** Representative bioactive molecules bearing a chiral alkyne motif. **b** Common strategies for $C(sp^3)$ - $C(sp)$ coupling. **c** Chemo- & stereoselective NiH-catalysed (migratory) hydroalkynylation of alkenes.

(Fig. 1b). For example, Liu^{2,3} reported an elegant work on Cu-catalyzed asymmetric Sonogashira $C(sp^3)$ – $C(sp)$ coupling^{4,5}. Shi⁶ and Liu⁷ have demonstrated that Pd- and Cu-catalyzed $C(sp^3)$ –H alkylation could be achieved in an enantioselective fashion. Liu⁸ has also used an alkene difunctionalization strategy to produce enantioenriched alkylation product under copper catalyst⁹. Suginome¹⁰ has reported a pioneering work on Ni-catalyzed asymmetric hydroalkynylation of 1,3-dienes based on their previous hydroalkynylation works^{11,12}. As a continued development of general alternatives for asymmetric $C(sp^3)$ – $C(sp)$ coupling, here we report an appealing approach via metal-hydride^{13–15} catalyzed asymmetric (remote) hydroalkynylation¹⁶ from readily available alkene starting materials.

Owing to its low-cost, facile oxidative addition, and availability of diverse oxidation states, nickel^{17,18} has emerged as a catalyst complementary to palladium over the past two decades, especially in cross-coupling reaction involving $C(sp^3)$ fragments. Reductive migratory hydrofunctionalization^{19–22} catalyzed by nickel hydride^{23–25} has recently been recognized as an alternative protocol for selective functionalization of remote $C(sp^3)$ –H bonds^{26–66}. Compared to conventional cross-coupling, this process (i) employs readily available, bench-stable alkenes or alkene precursors instead of specially generated organometallic reagents as starting materials and (ii) could also selectively functionalize a remote $C(sp^3)$ –H site in addition to the conventional *ipso*-position. Since its conception, significant progress has been made toward this synthetically useful process^{26–61}, which requires that the cross-coupling partner (e.g., aryl halide or alkyl halide) could selectively capture an alkylnickel species generated through iterative migratory insertion/ β -hydride elimination.

To explore this nickel-catalyzed migratory hydrofunctionalization further, we recently investigated if a bromoalkyne, an unsaturated

$C(sp)$ cross-coupling partner which is potentially reactive toward NiH, could be used to achieve remote hydroalkynylation (Fig. 1c, i). Successful implementation of this transformation will require (i) a hydrometalation process that can discriminate between alkene and alkyne and (ii) an alkylation process highly selective for one of the alkylnickel species. A chiral alkyne bearing an α -aryl-substituted stereogenic $C(sp^3)$ center^{2–5,7–10,67,68} would be ultimately obtained from styrene through hydronicellation and subsequent enantioconvergent^{52,53,55,56,69} alkylation (Fig. 1c, ii). 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-(triisopropylsilyl)acetylene (**2a**) as an alkylation reagent (Fig. 2). It was determined that $NiI_2 \cdot xH_2O$ and the bathocuproine ligand (**L**) could generate the desired migratory alkylation product as a single regioisomer [rr (benzylic product: all other isomers) > 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 ligand²⁹, 6,6'-dimethyl-2,2'-bipyridine (**L1**) 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). $K_3PO_4 \cdot H_2O$ 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

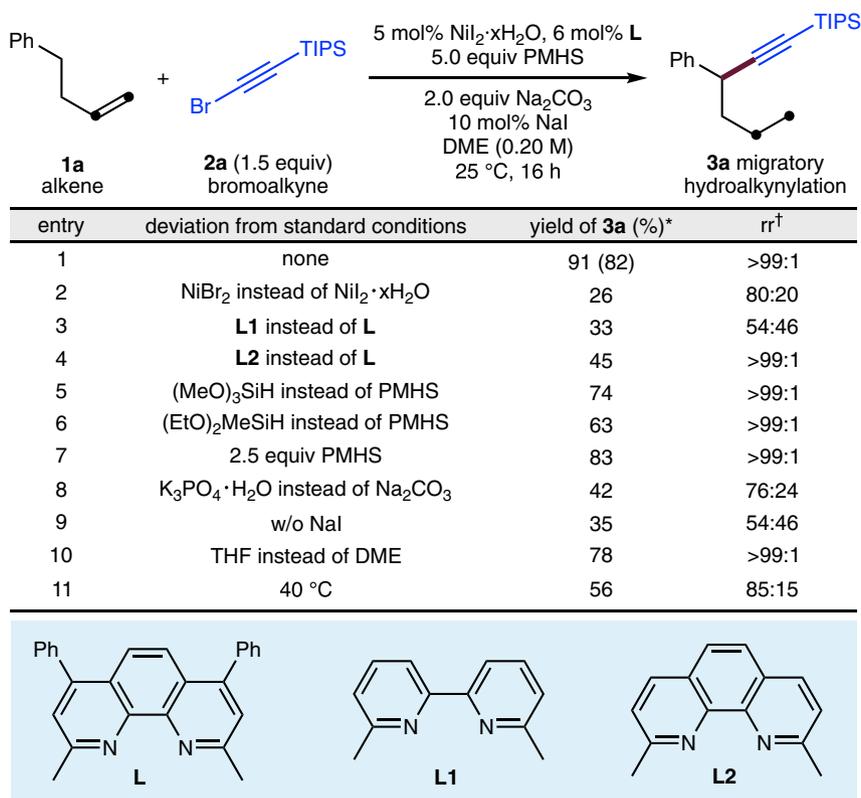


Fig. 2 Variation of reaction parameters. ^{*}Yields determined by GC using *n*-dodecane as the internal standard, the yield in parentheses is the isolated yield. [†]rr refers to regioisomeric ratio, representing the ratio of the major product to the sum of all other isomers as determined by GC analysis. PMHS polymethylhydrosiloxane, DME dimethoxyethane, TIPS triisopropylsilyl.

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 trifluoromethyl group (3d), and esters (3g, 3i). Importantly, tosylates (3j) and triflate (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 alkylation 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 alkylation product exclusively (Fig. 3c, 3x–3k'). Under these exceptionally mild reaction conditions, various substituents on the aryl ring (3z–3e') as well as heteroaromatic styrenes (3f', 3g') were also suitable for this reaction.

In an effort to obtain enantioenriched benzylic alkylation 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. Styrenes with a variety of substituents on the aromatic ring underwent asymmetric hydroalkynylation smoothly (5a–5q), including ethers (5d–5i), an easily reduced aldehyde (5l), a nitrile (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

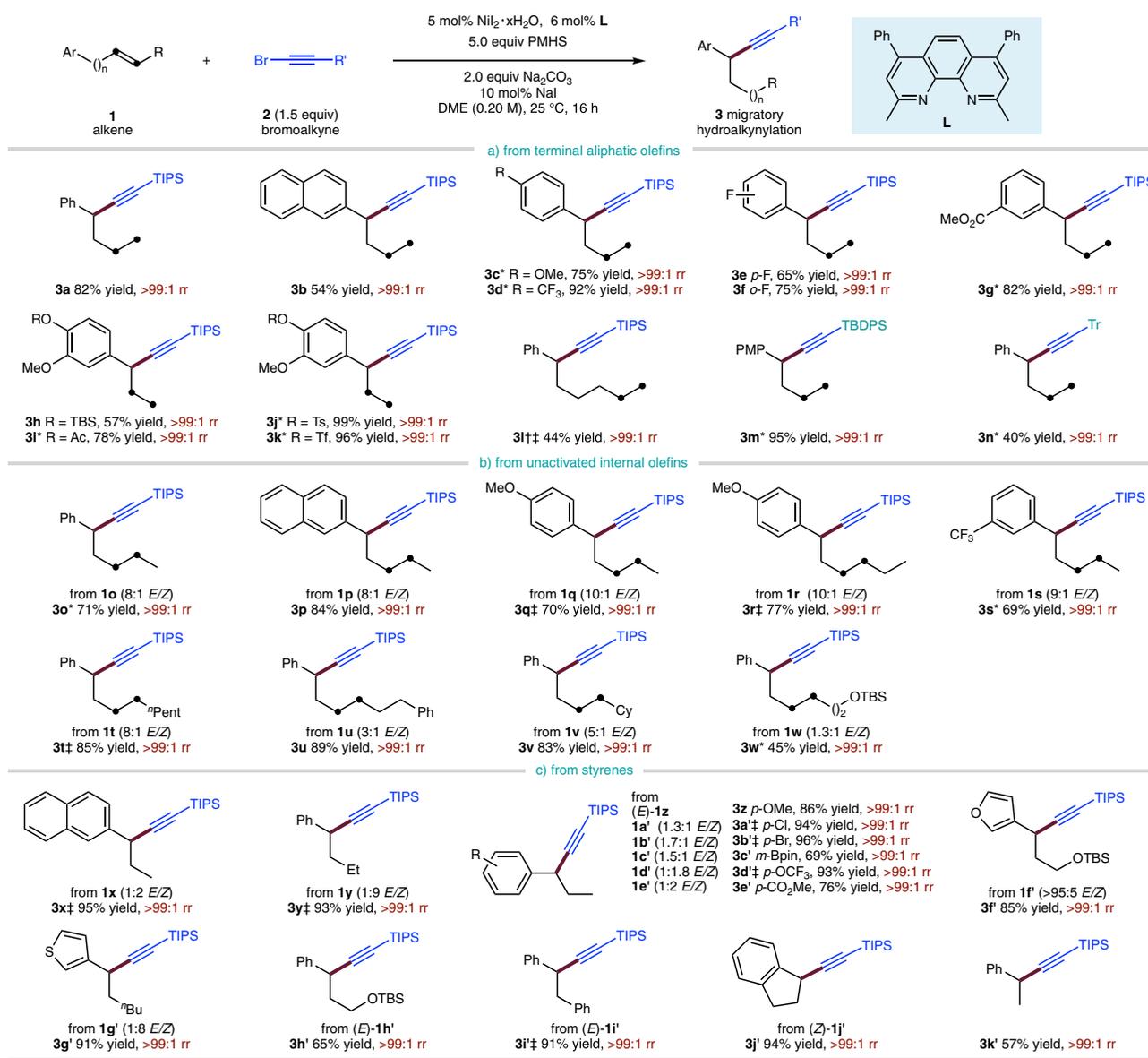


Fig. 3 NiH-catalyzed migratory hydroalkynylation of alkenes with bromoalkynes. Yield under each product refers to the isolated yield of purified product (0.20 mmol scale, average of two runs), rr refers to regioisomeric ratio, representing the ratio of the major product to the sum of all other isomers as determined by GC analysis. *Diglyme was used as solvent. †10 mol% NiI₂·xH₂O, 12 mol% L, and 20 mol% NaI were used. ‡DME (0.10 M) was used. TBS *tert*-butyldimethylsilyl, TBDPS *tert*-butyldiphenylsilyl; Tr trityl (triphenylmethyl).

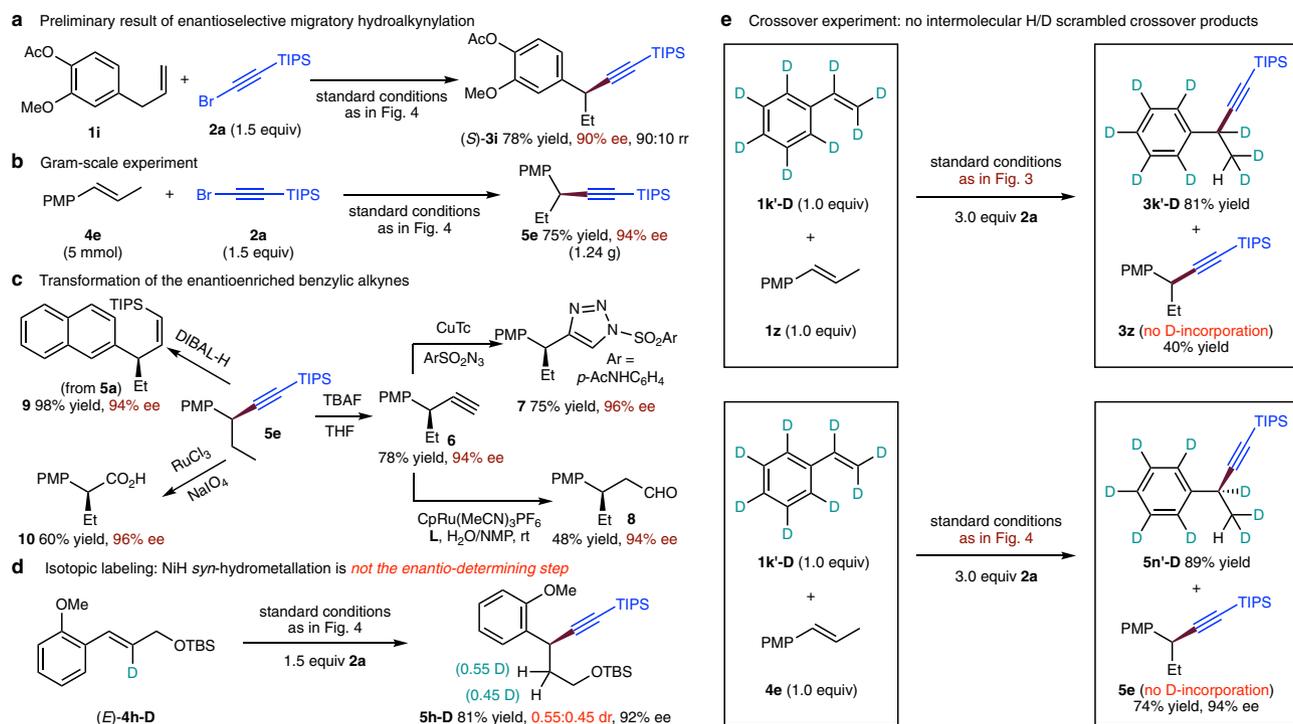


Fig. 5 Enantioselective migratory hydroalkynylation, gram-scale, derivatization, and isotopic labeling experiments. **a** Preliminary result of enantioselective migratory hydroalkynylation. **b** Gram-scale experiment. **c** Transformation of the enantioenriched benzylic alkynes. **d** Isotopic labeling experiment. **e** Crossover experiment.

led to the formation of both diastereomers in approximately equal amounts (0.55:0.45 dr), which indicated that the *syn*-hydrometallation is not the enantio-determining step because if it was, a diastereomerically pure 5h-D should be formed. This observation is consistent with our initial mechanistic proposal that the benzylic stereocentre is formed through rapid homolysis of the alkyl-Ni(III) bond and subsequently enantioconvergent process, reforming only one Ni(III) enantiomer from Ni(II) and benzylic radical (see Fig. 1c, ii). Furthermore, no intermolecular H/D scrambled crossover products were obtained in both migratory and asymmetric hydroalkynylation conditions, revealing that hydrometallation of NiH/NiD species to styrene is irreversible (Fig. 5e).

In conclusion, we report a NiH-catalyzed strategy to form functionalized benzylic alkylation products, which are versatile synthetic intermediates. Both migratory hydroalkynylation and asymmetric hydroalkynylation can be realized. These two mild, efficient, and straightforward processes tolerate a wide range of functional groups on both the alkene and bromoalkyne components. A broad substrate scope as well as synthetic utility of this protocol have been demonstrated. An investigation of the mechanism and the development of a migratory enantioselective version of this transformation are currently in progress.

Methods

NiH-catalyzed migratory hydroalkynylation of alkenes. In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiI₂·xH₂O (3.8 mg, 5.0 mol%), L (4.3 mg, 6.0 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 PMHS (60 μL, 1.0 mmol, 5.0 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 25 °C for up to 16 h (the mixture was stirred at 1000 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 styrenes. In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiI₂·xH₂O (3.8 mg, 5.0 mol%), (*S*)-L* (3.3 mg, 6.0 mol%), 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)₃SiH (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.

Received: 12 March 2021; Accepted: 24 May 2021;
Published online: 18 June 2021

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Acknowledgements

Research reported in this publication was supported by NSFC (21822105, 21772087), NSF of Jiangsu Province (BK20190281, BK20201245), Six Kinds of Talents Project of Jiangsu Province (JNHB-003), programs for high-level entrepreneurial and innovative

talents introduction of Jiangsu Province (group program), and Fundamental Research Funds for the Central Universities (020514380263).

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

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41467-021-24094-9>.

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

Peer review information *Nature Communications* thanks the anonymous reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

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