Nickel-catalysed selective migratory hydrothiolation of alkenes and alkynes with thiols

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Direct (utilize easily available and abundant precursors) and selective (both chemo- and regio-) aliphatic C–H functionalization is an attractive mean with which to streamline chemical synthesis. With many possible sites of reaction, traditional methods often need an adjacent polar directing group nearby to achieve high regio- and chemoselectivity and are often restricted to a single site of functionalization. Here we report a remote aliphatic C–H thiolation process with predictable and switchable regioselectivity through NiH-catalysed migratory hydrothiolation of two feedstock chemicals (alkenes/alkynes and thiols). This mild reaction avoids the preparation of electrophilic thiolation reagents and is highly selective to thiols over other nucleophilic groups, such as alcohols, acids, amines, and amides. Mechanistic studies show that the reaction occurs through the formation of an RS-Bpin intermediate, and THF as the solvent plays an important role in the regeneration of NiH species.
Organosulfur compounds, metabolites or macromolecules essential to life, are prevalent in pharmaceuticals, natural products, and materials (Fig. 1a)⁴⁻⁵. They compose ~20% of all Food and Drug Administration-approved drugs⁶⁻⁵. The development of protocols for the sustainable and efficient construction of C–S bonds is important in chemical synthesis. Commonly used methods for the construction of such bonds include Michael addition, S₈₂₂-type alkylation, and the powerful transition-metal-catalyzed C–S cross-coupling⁶⁻¹¹. One potential and more attractive strategy for their construction is through the selective C–H functionalization⁴⁻⁵, because this leads to the utilization of more widely available starting materials or more concise synthetic routes. However, to achieve excellent regio- and chemoselectivity, most of these processes need a polar directing group in the vicinity, and this limits their application in organic synthesis. As an alternative, the recently emerging metal-hydride-catalyzed⁴⁻⁵ C–H remote functionalization⁶⁻⁵³ can install a functional group at a distal position in a hydrocarbon chain under mild conditions. Starting from the ubiquitously available olefin-containing substrates, and using an extra hydride source, the NiH-catalyzed remote hydrofunctionalization⁵⁹⁻⁵³ with aryl/alkyl halides as electrophiles has been established as a powerful protocol for the construction of a diverse range of C–C bonds at a distal, inert sp³ C–H position (Fig. 1b)⁴⁻³⁻⁵. However, the electrophilic amination or thiolation reagents required to forge the more challenging carbon–heteroatom bond are generally not stable and often not commercially available, especially when bearing functional groups. Their preparation is nontrivial and time consuming, and often involves the use of the stoichiometric amounts of hazardous reagents.

To address these challenges, we enquired whether unmodified nucleophilic thiols that are widely available could be employed directly. Here we present the successful application of these ideas and describe an operationally trivial approach that allows the direct selective sp³ C–H thiolation with a naked thiol (Fig. 1c) at a distal benzylic position, the α-carbon of an ether, or a terminal position of the hydrocarbon chain of an alkene. A number of features of a transformation of this sort can be highlighted as follows: (a) high chemoselectivity of the thiol group in the presence of a series of potentially reactive functional groups such as amides, acids, alcohols, and amines; (b) excellent regioselectivity amongst multiple sites, including a benzylic position, a carbon α to the oxygen atom position, or a terminal position; (c) a regiodivergent process for the conversion, for example, of isomeric mixtures of olefins; and (d) feedstock thiols as thiolation reagents, such a process avoids the preparation of electrophilic thiolation reagents.

**Results**

**Regiodivergent thiolation reaction design and optimization.** We began our investigation by examining the remote hydrothiolation of 4-phenyl-1-butene (1a) with benzyl mercaptan (2a). After careful evaluation of a variety of nickel sources, ligands, bases, hydride sources, and solvents (Fig. 2), we found that a reaction at 60 °C employing a combination of NiI₂ as a catalyst, bathocuproine (L₁, 2.9-dimethyl-4,7-diphenyl-1,10-phenanthroline) as a ligand, HBpin (pinacolborane) as the hydride source, Li₃PO₄ as the base, and mixed tetrahydrofuran/acetonitrile (THF/CH₃CN) as the solvent delivers the desired migratory benzylic thiolation product (3a) in 75% isolated yield as a single regioisomer [regioisomeric ratio (major product: all other isomers) >99:1] (Fig. 2, entry 1). Use of other nickel sources, such as NiCl₂ or NiBr₂, leads to diminished.

**Fig. 2** Optimization of regiodivergent remote hydrothiolation. *Yields were determined by gas chromatography (GC) analysis using n-tetradeacne as the internal standard. The yield within parentheses is the isolated yield and is an average of two runs (0.20 mmol scale). †r.r. refers to regioisomeric ratio, representing the ratio of the major product to the sum of all other isomers as determined by GC analysis. ‡The linear thioether (3A) is obtained as a single isomer; conditions B for terminal selectivity: NiI₂ (5 mol%), L₂ instead of L₁, (MeO)₂MeSiH (3.5 equiv.), DMSO (0.50 M), 50 °C, 48 h. Ph, phenyl; Bn, benzyl; †‡Pr, n-propyl; HBpin, pinacolborane; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide.
yields and selectivities (Fig. 2, entries 2 and 3). Ortho substituents in the bipyridine ligand are critical for the reaction, and use of a similar ligand (L2) leads to inferior yield and regioisomeric ratio (Fig. 2, entry 4). Changing the hydride source to silanes, such as dimethoxy(methyl)silane, results in none of the desired product (Fig. 2, entry 5). The addition of the base Li2PO4 improves the yield but is not essential (Fig. 2, entry 1 vs. entry 6). CsF, which we previously used in remote hydroarylation reactions45, leads to complete failure of the reaction (Fig. 2, entry 7). Notably, control experiments show that the cyclic ether solvent is necessary for the reaction to proceed (Fig. 2, entry 8 vs. entry 9). In addition, a slightly lower yield is obtained at lower temperature (Fig. 2, entry 8 vs. entry 10). Interestingly, after a thorough re-evaluation of the reaction parameters, we were able to change the thiolation site to the terminal position54–60 to generate a very good yield of the linear thioether as a single isomer (Fig. 2, entry 11).

**Substrate scope.** With the optimal conditions in hand, we sought to define the scope of the alkene component (Fig. 3). First, an array of terminal aliphatic alkenes with a variety of ortho, meta, and para substituents on the remote aryl ring (3c–3l) are found to perform well producing the desired benzylic thioether exclusively (Fig. 3a). Substrates containing both electron-rich (3c and 3g) and electron-deficient (3d–3f and 3h) arynes are suitable for this reaction. Structurally complex aromatic systems such as sugar-linked aryl ring (3j) and camphor-linked aryl ring (3k) are amenable to the migratory cross-coupling. Heteroaromatic substrates, such as those containing a pyridine-linked aryl ring (3l) or a thiophene (3m) in place of the aryl group, are also well tolerated. Unactivated internal olefins also readily undergo alkene isomerization-hydrothiolation smoothly (Fig. 3b). As expected, E/Z alkene mixtures (3n–3r and 3t) react well, and high selectivity for thiolation at the benzylic position is observed, regardless of the starting position of the C=C bond. For substrates with a tertiary carbon on a benzylic position, which previous reports43,46,48 have noted as challenging migration towards the benzylic position and subsequent thiolation to generate the S-containing tetrasubstituted carbon center is still preferred (3t). Styrenes themselves (3u–3v) are also well-tolerated under these conditions (Fig. 3c). Compounds with a variety of functional groups on the aryl ring of styrene are tolerated, including

![Fig. 3 Substrate scope of alkene component. Under each product are given yield in percent, and regioisomeric ratio (r.r.). Yield refers to isolated yield of purified product (0.20 mmol scale, average of two experiments). r.r. represents the ratio of the major product to the sum of all other isomers as determined by gas chromatography (GC) analysis, ratios reported as >95:5 were determined by crude proton nuclear magnetic resonance (1H NMR) analysis.](https://doi.org/10.1038/s41467-019-09783-w)
an aryl fluoride (3u), a boronic acid pinacol ester (3v), an aryl nitrile (3w), and an ester (3c'). The reaction can also be extended to α-methyl styrenes to provide exclusively the benzylic thioethers (3b' and 3c') with a fully substituted carbon center.

It is important to highlight that alkynes, another type of easily prepared starting material, could undergo reductive remote hydrothiolation to deliver the same migratory thiolation products (3d' and 3e'), Fig. 3d). Mechanistically, the vinylnickel intermediate formed upon hydrometallation of the alkyne is selectively captured by a proton source (thiol) forming an alkene. Isotope labeling experiments indicated that the source of protons in this reaction is mainly from the thiol (see Supplementary Fig. 10 for details), while the alkylnickel intermediate formed upon hydrometallation of this alkene selectively engages with the NiH-catalyzed chainwalking-thiolation reaction. Finally, the current details), while the alkylnickel intermediate formed upon hydrometallation of the alkyne is selectively isomers.

Further investigation of the reaction demonstrated the broad scope of thiol partner (Fig. 4). In general, both aliphatic (4b–4m) and aromatic (4n–4c') thioles are excellent reaction partners and give the corresponding benzylic thioethers with good to excellent yields and regioselectivities. An array of primary and secondary aliphatic thioles all prove to be competent substrates, delivering the desired benzylic thiolation products in good to excellent yields (4b–4l). For the steric hindered tertiary thiol, a disulflde (Remote C–H thiolation) isomerization proceeds with fast dissociation and reassociation of the NiH species. Furthermore, the corresponding isotope labeling experiments were carried out with deuterothiol and deuteropinacolborane, respectively (Fig. 5b). No deuterium incorporation in the desired product is noted when deuterothiol is used, indicating that the thiol is not involved in chainwalking process. As expected, deuterium scrambling and deuterium incorporation is observed at all positions along the aliphatic chain, with the exception of the benzylic position. Mass spectrometric analysis revealed that a mixture of undeuterated, monodeuterated, and polydeuterated products is obtained. This is consistent with the hypothesis that chainwalking occurs with

**Discussion**

To gain some insights into the chainwalking process of olefin isomerization, olefin 1a was subjected to the standard reaction conditions in the absence of any thiol. A significant amount of other olefin isomers arising from the olefin isomerization is observed within 1 h, which indicates that occurrence of olefin isomerization does not depend on the presence of the thiol and also suggests that olefin isomerization is unrelated to C–S coupling (Fig. 5a, above). Additionally, consistent with our previously reported results, a mixture of olefins is observed when the reaction is run to partial conversion (Fig. 5a, below), indicating that olefin isomerization proceeds with fast dissociation and reassociation of the NiH species. Furthermore, the corresponding isotope labeling experiments were carried out with deuterothiol and deuteropinacolborane, respectively (Fig. 5b). No deuterium incorporation in the desired product is noted when deuterothiol is used, indicating that the thiol is not involved in chainwalking process. As expected, deuterium scrambling and deuterium incorporation is observed at all positions along the aliphatic chain, with the exception of the benzylic position. Mass spectrometric analysis revealed that a mixture of undeuterated, monodeuterated, and polydeuterated products is obtained. This is consistent with the hypothesis that chainwalking occurs with
dissociation and reassociation of free NiH/NiD from the NiH/NiD-alkene complex. Finally, no migratory reaction takes place when the linear sulfide (3A) is resubjected to the standard conditions, suggesting that chainwalking precedes the C–S coupling (Fig. 5c, above). Following the detection of trace amounts of a remote hydroboration product (6), this migrated hydroboration intermediate was resubjected to the standard conditions. However, no desired thiolation product was observed, suggesting that the C–S coupling step does not proceed through the remote hydroboration intermediate (Fig. 5c, below).

To shed light on the thiolation process, a variety of experiments were carried out. When 0.5 equiv. of a symmetrical disulfide is used instead of 1.0 equiv. of the corresponding thiol, the desired remote hydrothiolation product is obtained in a comparable yield (Fig. 6a), indicating that the disulfide might be the potential reactive intermediate of the thiol. Monitoring the remote hydrothiolation reaction of a disulfide by $^{19}$F NMR (fluorine-19 nuclear magnetic resonance), however, indicates that the disulfide ($\delta = -114.9$ ppm) is first transformed into an RS-Bpin intermediate ($\delta = -116.8$ ppm) (Fig. 6b). Significantly, analogous experiments on the corresponding thiol substrate ($\delta = -118.9$ ppm) also reveal the generation of this RS-Bpin intermediate ($\delta = -116.8$ ppm) with no trace of disulfide detected (Fig. 6c). Meanwhile, the generation of H$_2$ in this standard reaction is also observed by gas chromatography (GC) analysis. Overall, these results reinforce the notion that the disulfide is not involved as the active intermediates from the thiol, and suggests that the in situ generated RS-Bpin might be the actual thiolation reagent.

Encouraged by these results, we wondered whether the pre-generated RS-Bpin reagent could be employed directly instead of a thiol. Indeed, as shown in Fig. 7, changing the thiolation reagent from a thiol to RS-Bpin 2A’, generated in situ from the thiol and HBpin, a competent yield of 3a is obtained. In this case, only a stoichiometric amount of the alkene is required and the desired thiolation product could still be obtained in comparable yield (cf. Fig. 7, entries 3–6). For instance, 3a is obtained in 84% yield when

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**Fig. 5** Mechanistic studies of chainwalking. **a** Alkene isomerization. **b** Isotopic labeling. **c** Potential migratory process

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**Fig. 6** Potential reactive intermediate of thiol. **a** Potential intermediates: disulfide. **b** Disulfide reaction progress monitored by in situ $^{19}$F NMR. **c** Standard reaction progress monitored by in situ $^{19}$F NMR
1:1 stoichiometry of alkene and RS-Bpin is used and the yields are even better (88 and 93%, respectively) when a slightly excess of alkene or RS-Bpin is used (1.2 equiv.). This finding, together with the results disclosed in Fig. 6, suggests that the reactive intermediate of thiol is the RS-Bpin complex.

Control experiments reveal that the solvent THF plays an important role. Only 5% yield of desired product is observed in the absence of this solvent. As shown in Fig. 8a, a different reactivity is observed when the solvent THF is replaced by a variety of other ethers in the standard reaction conditions. The nature of the ether backbone plays a crucial role, we found that only cyclic ethers with a β-hydride can produce the desired product in a reasonable yield. In contrast, acyclic ethers or cyclic ethers lacking a β-hydride do not have such a profound effect on reactivity. We postulated that the ether might participate in the catalytic cycle. To verify this hypothesis, additional studies about the amount and consumption of ethers were carried out. As shown in Fig. 8b, both the yields and regioselectivities improved when the amount of THF is increased. The consumption of ether could also be observed during the reaction process (Fig. 8c). Only trace amounts of product (~1% yield) are produced during the first 6 h and the regioselectivity is poor in the first 12 h of the reaction. Subsequently, the yield of desired product increases significantly, but the yield of other regioisomers (linear isomer) fails to increase after the first 12 h (Fig. 8c, entry 3 vs. entry 1). The origin of this apparent induction period as well as initial low regioselectivity is still under investigation. Finally, as shown in Fig. 4d, when deuterated THF-d₈ is used in both standard and modified standard reactions, a small amount of deuterium scrambling and deuterium incorporation at all positions except the benzylic position along the aliphatic chain of the desired product is observed by ²H NMR and mass spectrometric analysis. This indicates that a small amount of NiD is involved in the chainwalking process and the small amount of NiD should come from the deuterated THF-d₈.

To probe further the role of THF, Boron-11 NMR (¹¹B NMR) experiments were carried out to trace the standard reaction. As shown in Fig. 8e, the generation of RS-Bpin intermediate (δ = 33.6 ppm) is confirmed again by ¹¹B NMR spectroscopic analysis. We could also observe two new boron signals accompanied with the consumption of THF, which matches the signals of BpinO–Bpin (δ = 21.2 ppm) and ROBpin (δ = 22.5 ppm).

Although an in-depth mechanistic discussion must await further investigation, a description of the proposed pathway, based on the above mechanistic studies, is shown in Fig. 9. The active nickel(I) hydride species (I) ⁶¹–⁶⁶, which is initially formed from a Ni(II) precursor, a ligand, and an hydride source, inserts into the alkene (1a), and initiates the relatively fast and reversible chainwalking process through iterative β-hydride elimination/migration reinsertion processes. A series of isomeric alkynickel(I) species (II, IV, …) is then accessed through this chainwalking process. Controlled by the choice of ligand, selective reaction of the benzylic alkynickel(I) intermediate (IV) with the thiolation reagent, the RS-Bpin (2A’) generated in situ from thiol and pinacolborane, probably through an oxidative addition and sequential facile reductive elimination ⁶⁷–⁶⁸ process then delivers the benzylic thiolation product (3a) along with LNi(I)Bpin (V). The active LNi(I)Bpin (V) species is then captured by THF to
Terminal alkenes can be effectively hydrothiolated under a modified reaction conditions. A series of terminal alkenes can be effectively hydrothiolated at a modified reaction conditions (8a–8d).

In summary, we have developed a NiH-catalyzed remote hydrothiolation reaction of alkenes using thiols directly as thiolating reagents. This transformation utilizes readily accessible alkenes/alkynes and thiols as starting materials and earth-abundant nickel salts as catalysts. The mild process allows the direct installation of a thioether group at a benzylic, terminal position with excellent regio- and chemoselectivity, as well as high functional group tolerance. Moreover, mechanistic studies reveal that the activated thiolation reagent is the RS–Bpin intermediate, and the ether solvent plays an important role in the regeneration of NiH species. Finally, the practical value of this transformation is highlighted by the regioconvergent conversion of unrefined isomeric mixtures of alkenes. The application of this protocol in cysteine bioconjugation as well as an asymmetric version of the current transformation is currently in progress and will be reported in due course.

**Methods**

**General procedure for NiH-catalyzed remote hydrothiolation.** To an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar was added NiI2 (3.2 mg, 5.0 mol%) and bathocuproine (L1, 2.9-dimethyl-4,7-diphenyl-1,10-phenanthroline) (4.0 mg, 6.0 mol%). The vial was introduced into a nitrogen-filled glove box and stirred at 60 °C for 24 h (the mixture was stirred at 750 rpm). After the reaction was complete, the reaction mixture was immediately filtered through a short pad of silica gel (using EtOAc in hexanes) to give the crude product. n-Tetradecane (20 μL) was added as an internal standard for GC analysis. 1H NMR analysis of the crude material. The product was purified by chromatography on silica gel for each substrate. The yields reported are the average of at least two experiments, unless otherwise indicated. 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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**Fig. 10** Regioconvergent and expanded site-selectivity experiments. **a** Regioconvergent conversion of isomeric mixtures of olefins. **b** Switch to terminal selectivity: anti-Markovnikov hydrothiolation
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Author contributions

Y.Z. and S.Z. designed the project. Y.Z., X.X., and S.Z. co-wrote the manuscript, analyzed the data, discussed the results, and commented on the manuscript. Y.Z. and X.X. performed the experiments. All authors contributed to discussions.