Secondary Phosphine Oxide-Activated Nickel Catalysts for Site-Selective Alkene Isomerization and Remote Hydrophosphination

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Catalytic systems that are readily modifiable to achieve olefin migration or remote functionalization are highly sought-after in chemical synthesis. Here, we show that the combination of a commercially available nickel(II) pre-catalyst and a secondary phosphine oxide ligand enables site- and stereoselective alkene transposition for up to nine double-bond migrations within terminal and internal olefins under mild reductive conditions. Substrates bearing diverse functionalities including Brønsted acidic and reducible carbonyl groups are tolerated. Mechanistic and spectroscopic studies revealed the in situ generation of a catalytically active nickel-hydride species triggered by oxidative addition of the phosphine oxide. The reaction is amenable to regioconvergent isomerization as well as β-selective remote hydrophosphination when stoichiometric secondary phosphine oxide/base were employed.

The transposition of carbon-carbon double bonds[1,2] is arguably one of the most convenient approaches to convert an easily available olefin to another unsaturated molecule of interest, and has vast applications in various chemical industries[3,4]. Combining olefin isomerization with another functionalization reaction enables functional groups to be precisely incorporated at positions remote from the initial reaction site[1,5-8]. Such transformations offer new disconnection strategies in organic synthesis by allowing different substrates (e.g. regioisomeric alkene mixtures)[1,5-8] to be employed, and unlock new reactivity modes through formal (sp^3)C–H functionalization at typically less-activated sites[9]. Methodologies using catalyst systems derived from noble metals (e.g., Pd, Ir)[10-16] and base metals (e.g., Ni, Fe)[17-24] have been conceived for alkene isomerization over the years. Nonprecious nickel catalysis represents an attractive platform for reaction development. Until recently, however, strategies that involve nickel-based complexes typically employ harsh additives (e.g. strong acids[25-27] and hydrides[28-30]) or high reaction temperatures[31] to generate the active Ni–H species from Ni(0) precursors, consequently compromising functional group compatibility (Fig. 1a). A recent remarkable method[20] utilized a somewhat air-sensitive dimeric Ni(I) complex[32] to mediate efficient C=C bond migrations over

multiple positions, although isomerizations of internal olefins and regioisomeric mixtures are difficult[18].

Our recent work in catalytic olefin migrations[18] and tandem processes[9] led us to wonder if we can develop a new catalytic isomerization manifold using commercially available and inexpensive starting materials/reagents. Specifically, we sought to devise a versatile system that can be selectively tuned to generate either olefin isomerization or remote hydrofunctionalization[1,5-8,33,34] products. To this end, we questioned whether an appropriate mild hydride source in conjunction with a base metal complex can be identified to generate the requisite metal-hydride[1] species to promote chain-walking, and whether conditions can be readily modified to trigger further transformations following isomerization.

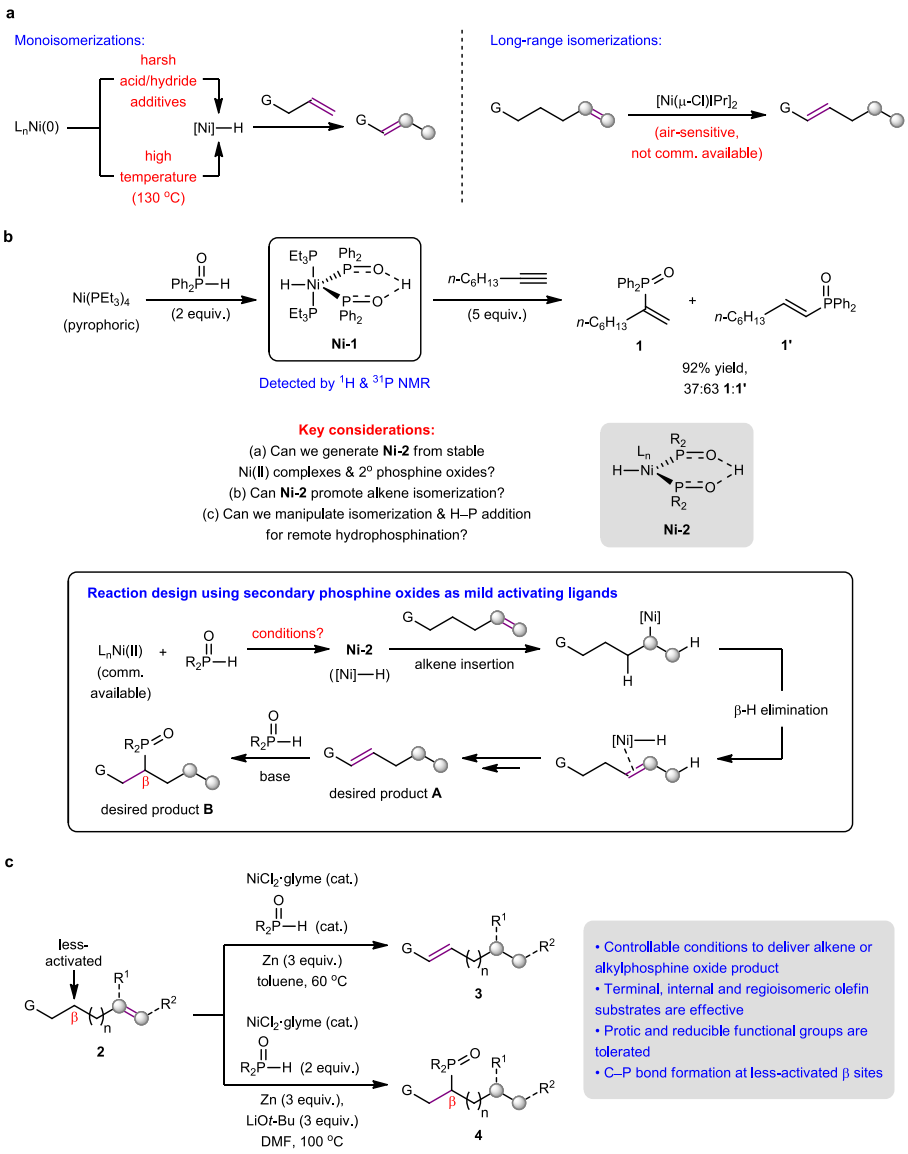


Fig. 1. The significance of designing an alkene isomerization/remote functionalization regime using nickel catalysis and secondary phosphine oxides as mild activating ligands. a, Representative Ni-catalyzed strategies for alkene isomerization and their associated limitations. **b**, Secondary phosphine oxides are previously reported to promote the formation of nickel-hydride species for alkyne hydrophosphination. However, it is unknown whether such a species can be generated from stable Ni(II) precursors and phosphine oxides under operationally mild conditions. If successful, the nickel-hydride species should be capable of mediating olefin chain-walking through sequential insertions/β-H eliminations. **c**, Development of a reductive Ni-catalyzed manifold that offers tunable access to valuable regiodefined alkene isomerization or remote hydrophosphination products.

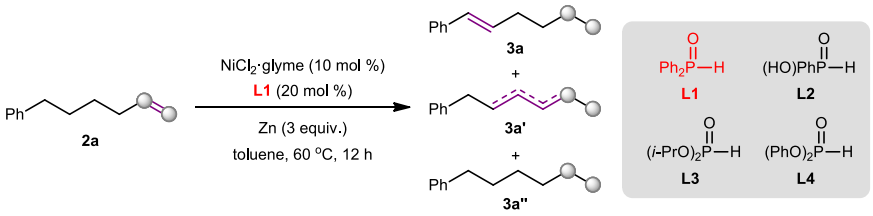
In light of these deliberations, we turned to pentavalent secondary phosphine oxides[35-39], which are known to tautomerize to trivalent phosphinous acids that serve as phosphane-type ligands when exposed to a transition metal-based complex[40-42]. Han and co-workers reported that a phosphine-nickel(0) complex could mediate regioselective H–P additions to alkynes using phosphine oxides as reagents[43]. Experimental evidence pointed to the intermediacy of a hydrogen bonding-stabilized five-coordinate nickel-hydride[43] complex **Ni-1** that drives hydronickelation followed by C(sp^2)–P bond-forming reductive elimination (Fig. 1b). Intrigued by these seminal observations, we envisioned that a catalytic combination of an organonickel(II) complex and a secondary phosphine oxide may be leveraged to furnish a putative nickel-hydride **Ni-2** analogous to **Ni-1**, in which the non-innocent[40] phosphine oxide plays a role as both a Lewis basic ligand and hydride donor. Although unprecedented, we surmised that such complexes should be capable of promoting olefin isomerization through consecutive Ni–H addition and β-H elimination[1,5-8] under appropriate parameters.

Moreover, when stoichiometric phosphine oxide is used in the presence of a base[44-47], remote hydrophosphination may be potentially implemented. However, manipulating alkene isomerization to precede hydrophosphination can be challenging, and a slow chain-walking process will inevitably result in premature phosphinyl additions and hence undesirable regioisomeric product mixtures[45,48]. If successfully obtained, the α-branched alkylphosphine oxides not only function as stable precursors of the oxidation-labile phosphines[49-51], but are also useful as Lewis bases[52-54] and ligands in organometallic chemistry[35-42]. To the best of our knowledge, there is no precedence of remote alkene hydrophosphination in which the phosphinyl unit is installed at less-reactive sites vicinal (β) to a pendant entity[9]. This will open up unexplored avenues towards the preparation of novel organophosphorus compounds for diverse applications such as drug synthesis[55,56] and ligand design[57,58]. Herein, we report our findings in Ni-mediated olefin migration and remote hydrophosphination under reductive conditions (Fig. 1c).

Results

Reaction optimization. We commended our studies by examining conditions (see Supplementary Information (SI) Section 2 for details) for the complete isomerization of terminal olefin **2a** to **3a** (Table 1). After extensive experimentation, best results could be achieved using commercially available $NiCl_2$·glyme (10 mol %) and diphenylphosphine oxide **L1** (20 mol %) with excess Zn as reducing agent and toluene as solvent, furnishing **3a** in 79% GC yield (78% isolated yield) exclusively as the *E* isomer at 60 °C (entry 1). Substituting the ligand on the Ni(II) chloride complex had a non-negligible impact on isomerization efficiency, with more electron-donating phosphines giving greater amounts of undesired alkene regioisomers **3a'** and hydrogenated **3a''** (entry 2). Other Ni(II) salts were significantly less effective in promoting olefin migration (entries 3–4). With reference to Fig. 1b, we speculated that a ligated Ni(0) species was generated in situ by reduction of a Ni(II) complex[59,60] prior to activation by **L1**. However, isomerization was inefficient with $Ni(cod)_2$ as pre-catalyst, and adding catalytic (or stoichiometric) quantities of DME as a coordinating ligand did not improve results substantially (entry 5).

Table 1. Evaluation of reaction conditions for alkene isomerization



Entry	Deviation from standard conditions	Conversion (%)	Yield (**3a**:**3a'**+**3a''**) (%)
1	none	96	79:17
2	$NiCl_2(PCy_3)_2$ (10 mol %)	92	66:26
3	$NiCl_2$ (10 mol %)	28	3:25
4	$Ni(OTf)_2$ or $Ni(acac)_2$ (10 mol %)	32–39	6:26–13:26
5	$Ni(cod)_2$ (10 mol %), with or without DME (30 mol %)	34–66	6:28–11:55
6	**L2**, **L3** or **L4** as ligand	2–53	<2–17:36
7	Zn (1–2 equiv.) as reductant	65–93	40:25–73:20
8	Mn (3 equiv.) as reductant	33	12:21
9	DME, DMF or DMA as solvent	96–98	76:20–77:21
10	THF as solvent	68	31:37
11	40°C	63	33:30

Reactions were carried out on 0.1 mmol scale. Conversions and yields were determined by GC analysis with n-decane as an internal standard. **3a** was obtained in >98:2 *E*:*Z* ratio in all cases.

Other commercially available secondary phosphine oxides **L2**–**L4** were incompetent in promoting olefin transposition (entry 6), while reducing the Zn loading or changing the reductant had deleterious effects (entries 7–8). The alkene transposition could be conducted in polar solvents such as DME, DMF and DMA with similar chain-walking efficiency (entry 9), but THF was

visibly less effective (entry 10). Reaction temperature was crucial since poorer conversion to an unsatisfactory mixture was detected at 40 °C (entry 11).

Site- and stereoselective alkene isomerization. We proceeded to evaluate a range of functionalized terminal and internal alkene substrates under the established olefin migration conditions (Fig. 2). Monoisomerizations could be accomplished with monosubstituted olefins to deliver a diverse assortment of di- and trisubstituted products in 70–96% yield and >98:2 *E*:*Z* ratios. These include styrenyl products bearing electron-deficient (**3b**–**3c**) and electron-rich (**3d**–**3g**) arenes as well as those containing reactive functionalities such as a reducible ketone (**3b**), nitrile (**3c**) and Brønsted acidic phenol (**3d**). Boryl and silyl units were also amenable migration terminus, enabling access to synthetically valuable 1,2-disubstituted alkenylboronates[61] (**3h**) and alkenylsilanes[62] (**3i**–**3j**). Starting from monosubstituted or exocyclic 1,1-disubstituted substrates, transformations leading to sterically demanding trisubstituted cyclic (**3k**–**3l**) or acyclic (**3m**) C=C bonds proceeded without a diminution in reaction efficiency.

Longer-distance migrations could be similarly induced, furnishing the fully isomerized internal alkenes **3n**–**3z** in 54–90% yield and >98% *E* selectivity. The reaction could be performed on gram scale with comparable efficiency (**3n**), highlighting the robustness of the catalytic regime. Synthesis of *N*-alkenyl indole **3t** shows that isomerization may be terminated by a nitrogen group. Notably, *E*-**3z** was isolated cleanly in 54% yield from a chain-walking process featuring nine double-bond shifts, comparing favorably with past reports[18,20]. 1,2-Disubstituted internal olefins also underwent migration to give the desired products (**3aa**–**3ab**), which is complementary in scope to a previous Ni-catalyzed report[20]. However, tri- and tetrasubstituted C=C bonds were unreactive. The opportunity then arises to test the limits of our protocol in regioconvergent isomerization where a complex mixture of four regioisomeric substrates **2a**, **5**–**7** (each containing *E* and *Z* isomers) was subjected to the standard conditions. In the event, *E*-**3x** was secured in 81% yield as the sole product, providing an attractive streamlined approach to convert mixtures of low-cost olefin feedstock to value-added isomerically pure products.

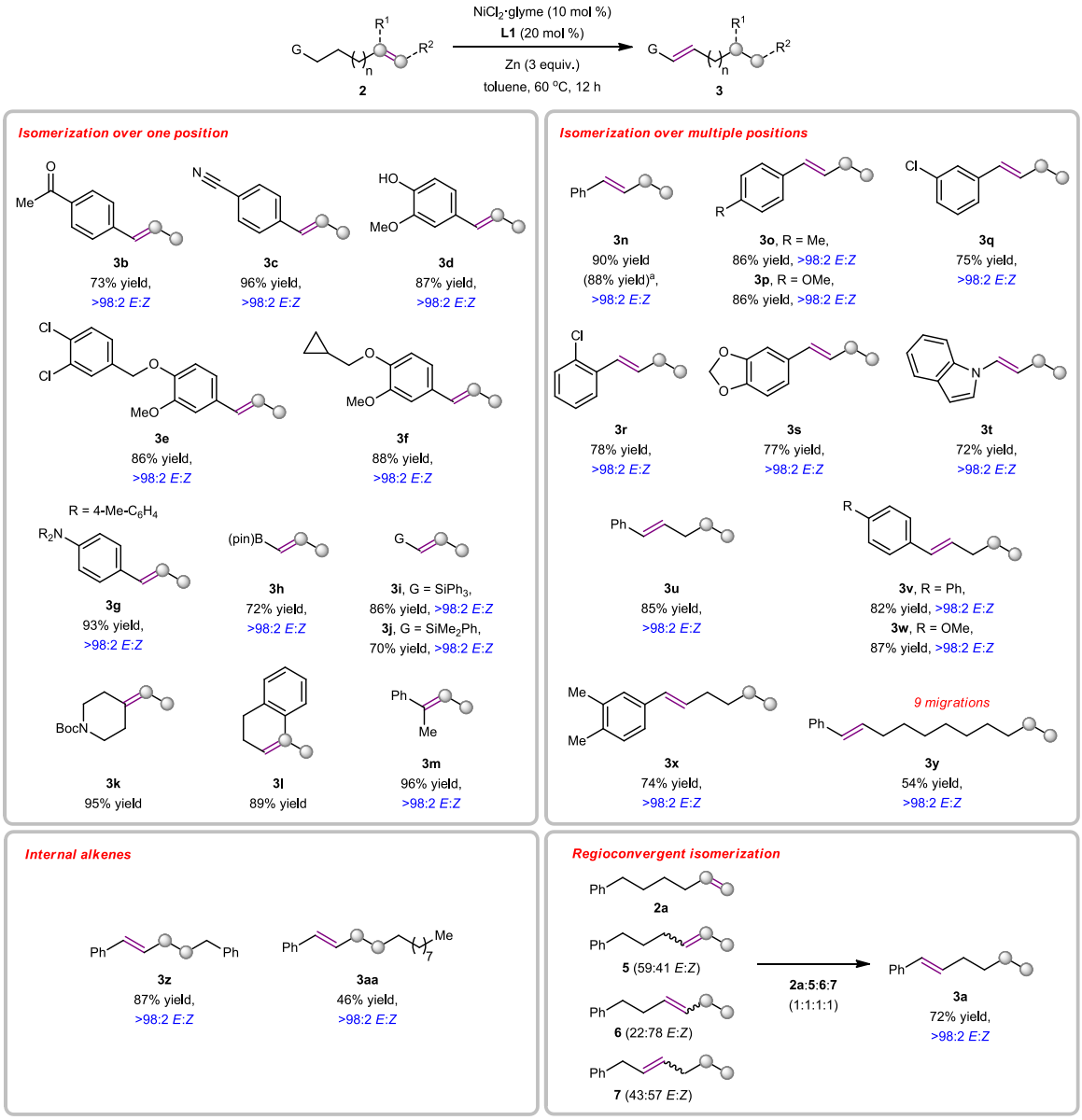


Fig. 2. The scope of Ni-catalyzed alkene isomerization. Reactions were carried out on 0.2 mmol scale. *E*:*Z* ratios were determined by ^{1}H NMR analysis of the isolated and purified products. Yields are for isolated and purified products. [a]The reaction was conducted on 10 mmol scale.

β-Selective remote hydrophosphination. We then investigated the feasibility of implementing remote alkene hydrophosphination (Fig. 3). Control experiments indicated that addition of stoichiometric **L1** did not promote hydrophosphination in the absence of base (only chain-walking observed, which suggests that alkene isomerization precedes hydrophosphination). Although base-mediated 1,2-hydrophosphination of activated alkenes[45-47] has been documented, it remains to be determined if our Ni-mediated chain-walking system is compatible with exogenous bases, and whether the two processes of olefin migration and H–P addition can

be controlled to selectively incorporate phosphinyl groups. After surveying various parameters, the reaction of **2a** afforded alkylphosphine oxide **4a** bearing a β-phosphionyl unit in 71% isolated yield as a single regioisomer, using the $NiCl_2$·glyme/**L1**/Zn system in DMF in the presence of excess LiO*t*-Bu (optimal base) at 100 °C. Decreasing the base loading proved detrimental to efficiency (primarily olefin isomerization detected with 15% yield of **4a** using 1 equiv. of base), and less polar solvents (e.g. toluene) were ineffective (see SI Table S3 for details).

Regardless of the chain length, reliable P-installation at the β-position (>98% regioselectivity across the board) was obtained for a wide array of alkenes containing arenes (**4b**–**4f**, **4h**–**4k**, **4n**), heteroarenes (**4g**) and amides (**4l**–**4m**), delivering adducts in up to 89% yield. Secondary amides with an acidic N–H unit (**4l**) are tolerated, and 1,1-disubstituted C=C bonds (**4h**) also participated in remote hydrophosphination. The exclusive generation of **4n** as the β-isomer from the corresponding long-chain alkene underscores the remarkable fidelity of the reaction. Dialkylphosphine oxide **L5** was also competent in promoting regiocontrolled chain-walking/phosphinyl addition, giving rise to the corresponding product **4o** in 81% yield.

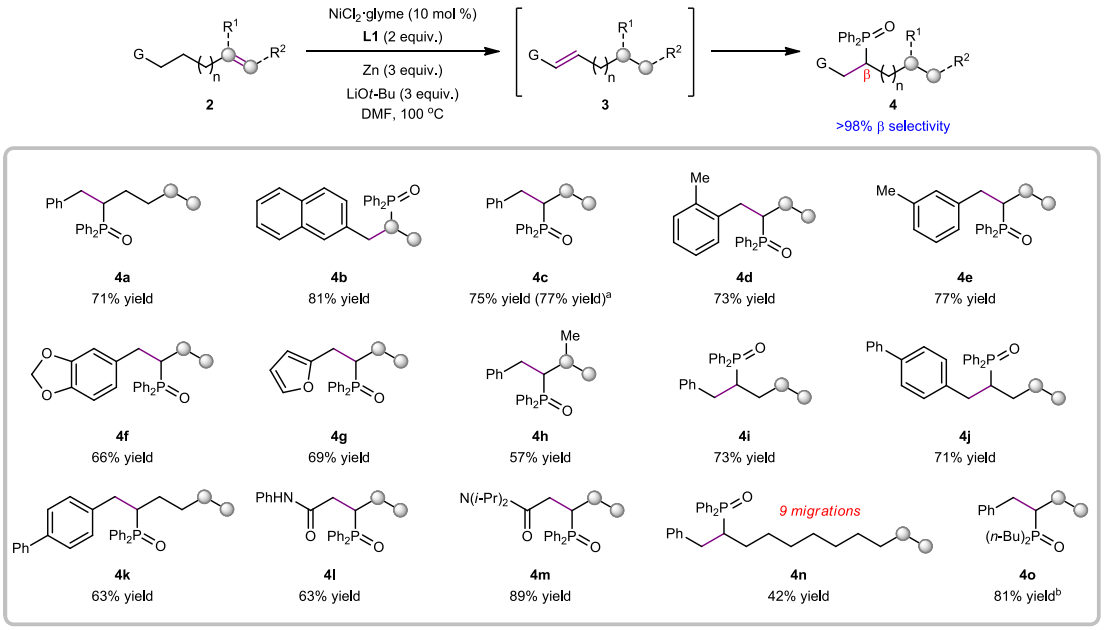


Fig. 3. β-Selective remote hydrophosphination. Reactions were carried out on 0.2 mmol scale. Regioisomeric ratios were determined by ^{1}H NMR analysis of the isolated and purified products. Yields are for isolated and purified products. [a]The reaction was conducted on 10 mmol scale. [b]The reaction was conducted with di(*n*-butyl)phosphine oxide **L5** instead of **L1**.

Mechanistic investigations. ^{1}H and ^{31}P NMR studies were conducted to obtain information on the in situ-generated organonickel species (Fig. 4a). Specifically, we sought to acquire evidence

for the formation of a catalytically active nickel-hydride complex responsible for olefin transposition.

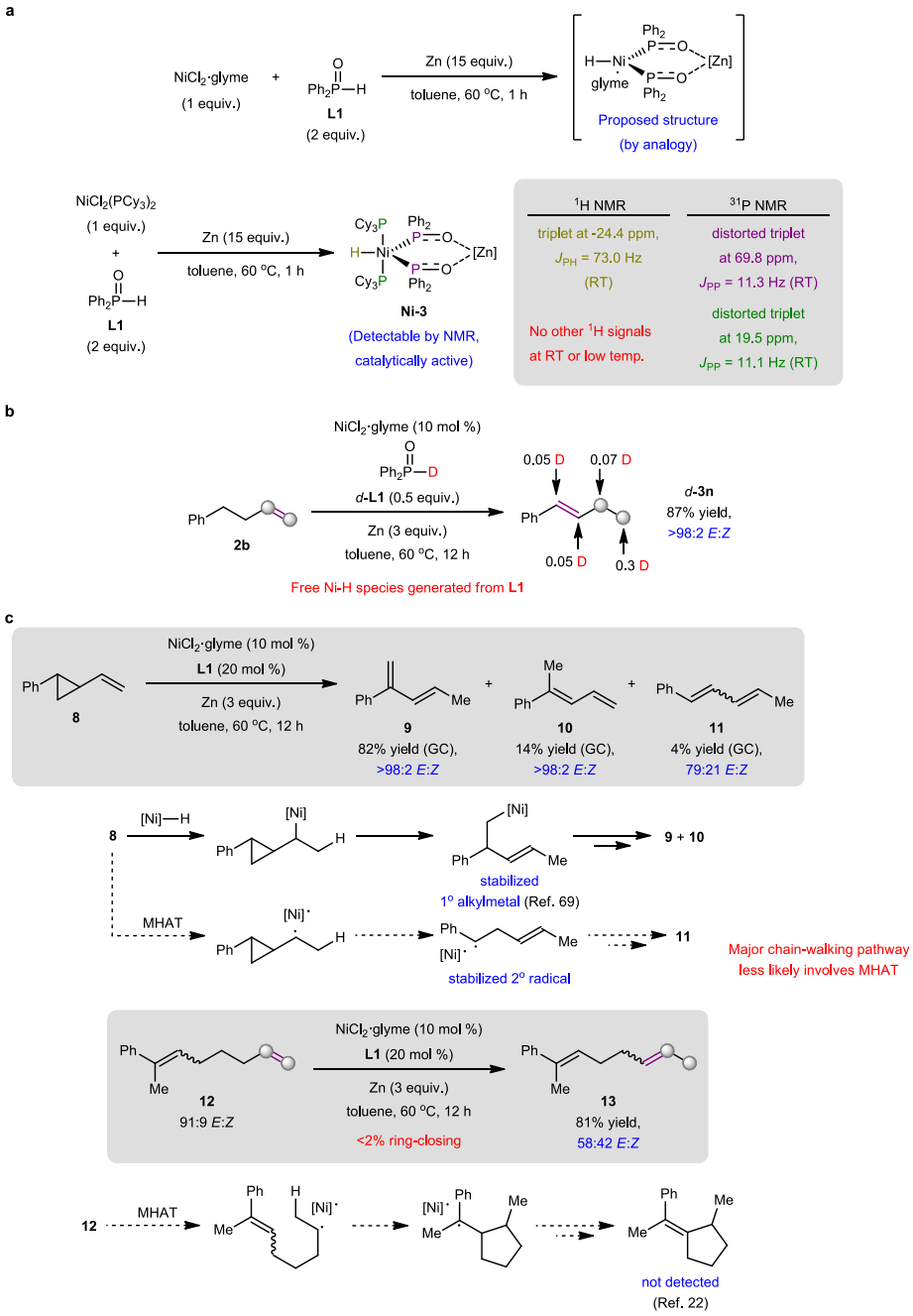


Fig. 4. Mechanistic studies. a, NMR studies to probe the nature of the in situ-generated nickel-hydride species. **b**, Deuterium labeling experiment. **c**, Radical clock experiments. Reactions were carried out on 0.1 mmol scale. *E*:*Z* ratios were determined by GC analysis with *n*-decane as an internal standard. Yields are for isolated and purified products, unless otherwise stated.

However, initial attempts to decipher through spectroscopic analysis by treating a 1:2 mixture of $NiCl_2$·glyme and **L1** in toluene with excess Zn at various temperatures were unsuccessful, which

might be attributed to the instability and short lifetime[41,43,63-65] of the putative nickel species. In order to derive meaningful data, we selected $NiCl_2(PCy_3)_2$ with strongly coordinating tricyclohexylphosphine ligands (vs. glyme) as the nickel precursor, which was also reasonably efficient in promoting chain-walking (Table 1 entry 2). In contrast to Han's disclosure[43] in which a phosphine-nickel(0) complex was employed, our study utilized a Ni(II) pre-catalyst which we hypothesized, served as a stable precursor of an organonickel(0) species by reduction with Zn[59]. Gratifyingly, a sufficiently stable nickel-hydride intermediate **Ni-3** that is postulated to adopt a symmetric five-coordinate geometry similar to **Ni-1**[43] (cf. Fig. 1b) was detected. **Ni-3** was surmised to derive from oxidative addition of an equivalent of **L1** and coordination by another equivalent of its tautomer[35-43].

At ambient temperature, the NMR signals arising from **L1** disappeared and were subsequently replaced with new signals: a triplet at -24.4 ppm (J_{PH} = 73.0 Hz) in the ^{1}H NMR spectrum (Ni–H) and two distorted triplets (J_{PP} ~ 11.2 Hz; integration ratio ~1:1) at 69.8 (P=O) and 19.5 ppm (PCy_3) in the ^{31}P NMR spectrum were recorded; these signals were assigned by comparison with reported spectroscopic data[43]. Unexpectedly, no other ^{1}H signals were detected at ambient or cryogenic temperatures, suggesting the apparent absence of a proton bridge that exists in **Ni-1** or **Ni-2**. Instead, the acidic proton could be replaced by a Zn(II) species[41,66-68] generated during the course of $NiCl_2(PCy_3)_2$ reduction. Control experiments showed that mixing *d*-**L1** with $ZnCl_2$ led to disappearance of the P–D signal in the ^{2}H NMR spectrum (see SI Section 7b for details). Unfortunately, crystals of **Ni-3** that are suitable for X-ray crystallographic analysis were not obtained. Nevertheless, the mixture that presumably contains **Ni-3** was shown to be catalytically active by subjecting it to a terminal olefin, which furnished the fully isomerized product. By analogy, we presumed that a similar monomeric **L1**-activated nickel-hydride was also generated from $NiCl_2$·glyme through preliminary mass spectrometry analysis, although the formation of oligomeric species could not be completely excluded. Further investigations are underway to elucidate more insights on these in situ-generated organonickel species.

Isomerization of **2b** with *d*-**L1** resulted in deuterium incorporation and scrambling across the entire hydrocarbon skeleton, providing additional support that the hydride source required to form the active nickel-hydride catalyst originates from the phosphine oxide (Fig. 4b). Radical clock studies were performed with **8** and **12** (Fig. 4c). In the event, **9** (82% yield) and **10** (14% yield) were predominantly obtained from **8**[69], whereas **12** was converted to the monoisomerization product **13** in 81% yield and 58:42 *E*:*Z* ratio (<2% ring-closing detected).[22] These observations

intimate that olefin migration involving metal-hydride atom transfer (MHAT)[33,34] via long-lived radical intermediates is less likely. To summarize, alkene transposition probably proceeds through sequential Ni–H olefin insertions/β-H eliminations[1,5-8] instead of 1,3-hydride shift[5-8,70] or MHAT.

Control experiments further showed that hydrophosphination likely proceeded by nucleophilic addition of a deprotonated hydroxyphosphine tautomer across the C=C bond to give an electronically stabilized carbanion[44], which could either abstract a proton from hydroxyphosphine or undergo adventitious protonolysis with trace *t*-BuOH formed in solution. The reaction of a 1,2-disubstituted aryl alkene with *d*-**L1** in the presence of LiO*t*-Bu afforded the expected hydro(deutero)phosphination adduct (see SI Section 7c for details). Under the basic conditions, H/D exchange was detected at the acidic C_α–H site adjacent to the electron-withdrawing P=O group (i.e. *t*-BuOH is inadvertently generated[44,49]). Thus, the exceptional β selectivity observed in remote hydrophosphination could be rationalized by the lack of undesired phosphinyl additions during the course of chain-walking, since generation of destabilized alkyl-substituted carbanion intermediates is likely unfavorable.

Discussion

In conclusion, an operationally simple Ni-catalyzed reductive protocol for regio- and stereoselective alkene isomerization was devised. Beyond serving as an anciliary ligand, the secondary phosphine oxide underwent reaction to form the requisite nickel-hydride that promotes non-radical C=C bond shifts under mild conditions. The versatility of the present regime allows for regiocontrolled chain-walking/hydrophosphination to occur in one operation, furnishing prized organophosphorus compounds that are difficult to obtain by alternative means. The present work offers a new blueprint for olefin chain-walking that will likely facilitate efforts to tackle other unresolved challenges in site-selective remote alkene functionalization.

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Author contributions

L.H. and E.Q.L. developed the catalytic method and carried out the mechanistic studies. M.J.K. directed the investigations and wrote the manuscript with revisions provided by the other authors.