Tackling Remote sp^3 C–H Functionalization via Ni-Catalyzed "chain-walking" Reactions

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This manuscript is dedicated to Stephen L. Buchwald and John F. Hartwig on winning the 2019 Wolf Prize in Chemistry

Abstract: Nickel catalysts have recently played an important role for rapidly and reliably converting feedstock chemicals into valuable compounds of interest for both pharmaceutical and academic laboratories. Herein, we summarize the recent advances on the ability of nickel catalysts to trigger olefin isomerization via "chain-walking", causing a displacement of the nickel catalyst throughout the alkyl chain while opening up new grounds for forging C–C and C-heteroatom linkages at remote, yet unfunctionalized, sp^3 C–H bonds.

Keywords: Remote functionalization • Catalysis • Nickel • "chain-walking" • Organometallic chemistry

1. Introduction

During the last decades, transition metal-catalyzed C–H functionalization has gained significant momentum at the scientific community for forging C–C and C–heteroatom bonds.[1] While sp^2 C–H functionalization has evolved into a mature tool for advanced organic synthesis, extensions to sp^3 C–H bond linkages has shown to be not as straightforward as one might initially anticipate.[2] This is likely due to the observation that sp^3 C–H bonds are considerably less acidic than sp^2 C–H linkages, and that these motifs lack proximal empty low-energy or filled high-energy orbitals that interact with the d orbitals of the transition metal. In addition, site-selectivity principles come into play due to the presence of multiple, yet similar, sp^3 C–H bonds in regular alkyl side-chains.[3] Chemists have navigated this challenge via directing group protocols or carbene-mediated reactions.[2] However, the introduction and detachment of directing groups might not be particularly trivial, whereas the need for carbene precursors might hamper the implementation of other C–C bond-forming events, respectively. sp^3 C–H bond-cleavage can also be triggered via open-shell species or enzyme-mediated processes.[2] However, the former protocols are dictated by bond-dissociation energies whereas subtle changes in both the enzyme and on the substrate might hamper reactivity and site-selectivity in the latter. Despite the advances realized, C–C bond-formation at unactivated primary sp^3 C–H bonds, the strongest C–H bonds in the alkyl series is still particularly problematic. While originally designed for controlling polymer topology, the recent years have witnessed renewed interest in olefin isomerization as a vehicle for enabling bond-construction at remote, yet unfunctionalized, primary sp^3 C–H sites.[4] This process – oftentimes coined as "chain-walking" – operates via dynamic displacement of the catalyst throughout the alkyl chain. Although significant progress has been made with Zr, Ru, Rh, Co or Pd complexes,[4] the versatility and flexibility in synthetic design offered by Ni catalysts[5] have only been recognized recently in "chain-walking". From a mechanistic standpoint, these techniques operate via alkyl-Ni species obtained by (a) iterative migratory insertion/β-hydride elimination events or (b) [1,3]-hydride migration (Scheme 1).[4]
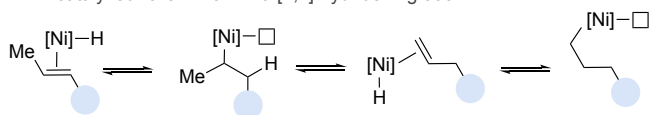
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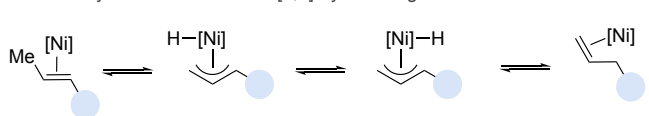   Barcelona, Spain
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■ Ni-catalyzed "chain-walk" via [1,2]-hydride migration

■ Ni-catalyzed "chain-walk" via [1,3]-hydride migration

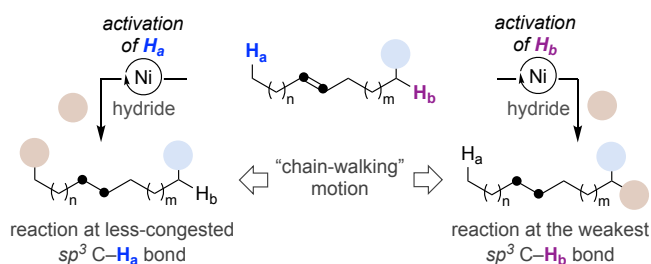**Scheme 1.** Ni-catalyzed "chain-walking" reactions.

Daniel Janssen-Müller studied chemistry at the Westfälische Wilhelms-Universität (WWU) Münster in Germany and received his B.Sc. degree in 2011. During his M. Sc. studies, he went as a visiting researcher to the University of Texas at Austin, USA. His PhD studies under the supervision of Prof. Frank Glorius (WWU Münster) focused on enantioselective NHC-Organocatalysis and metal-organic frameworks (MOFs). In 2017, he was awarded a Feodor Lynen-fellowship by the Alexander von Humboldt-foundation for a postdoctoral stay in the group of Prof. Ruben Martin at the Institute of Chemical Research of Catalonia (ICIQ), where his research focused on the development of Ni-catalyzed reductive cross-coupling reactions with CO_2 and the catalytic activation of C–N bonds.

Basudev Sahoo completed his MSc studies in chemistry at the Indian Institute of Technology (IIT) Kanpur in 2011. In 2015, he received his PhD degree from the Westfälische Wilhelms-Universität (WWU) Münster working under the supervision of Prof. Frank Glorius focusing on photocatalysis and metal-organic frameworks (MOFs). He then joined the group of Prof. Matthias Beller at the Leibniz-Institute for Catalysis (LIKAT) Rostock to work on heterogenous catalysis. In

2018, he was awarded with Marie Curie postdoctoral fellowship to join the group of Prof. Ruben Martin at the Institute of Chemical Research of Catalonia (ICIQ), where his research is focused on metallaphotoredox catalysis and catalytic functionalization of remote sp³ C–H sites.

Shang-Zheng Sun obtained his MSc degree in organic chemistry from Shanghai Institute of Organic Chemistry (SIOC) in 2016. During his MSc studies at SIOC (2013-2016), he focused his attention on designing new Cu-catalyzed C–H functionalization techniques under the supervision of Prof. Jin-Quan Yu and Prof. Hui-Xiong Dai. In November 2016, he joined the group of Prof. Ruben Martin at the Institute of Chemical Research of Catalonia (ICIQ) as a PhD student. His interests are primary focused on nickel-catalyzed reductive cross-coupling reactions as well as the development of catalytic functionalization of olefin feedstocks via functionalization at remote sp³ C–H sites.

Ruben Martin conducted his undergraduate studies at the University of Barcelona. He then received his PhD in 2003 from the University of Barcelona under the guidance of Prof. Antoni Riera. In 2004, he moved to the Max-Planck Institut für Kohlenforschung as a Humboldt postdoctoral fellow with Prof. Alois Fürstner. In 2005, he undertook further postdoctoral studies at MIT with Prof. Stephen L. Buchwald as a MEC-Fulbright fellow. In September 2008, he initiated his independent career as an assistant professor at the ICIQ (Tarragona). In July 2013, he was promoted to associate professor and subsequently to ICREA Research Professor. His research is focused on the development of new metal-catalyzed activation technologies of particularly strong σ-bonds. Among these, particular attention has been devoted to the catalytic fixation of carbon dioxide into organic matter, catalytic reductive cross-coupling reactions, and the functionalization of strong C–O, C–N bonds as well as remote sp³ C–H linkages.

In these transformations, "chain-walking" leads to the formal translocation of a double-bond (or alkyl-Ni intermediate) in a selective manner to the terminal position of the alkyl side-chain, presumably due to steric effects during the functionalization reaction (Scheme 2, *path a*), or to a resonance-stabilized position such as adjacent to an aromatic or a carbonyl group (Scheme 2, *path b*). In a formal sense, these observations stand as a testament that the "chain-walking" motion might a priori be controlled by either subtle modification of the catalyst or the nature of the functional groups within the alkyl side-chain.[4]

Scheme 2. Multidirectionality of Ni-catalyzed "chain-walking" reactions.

As judged by the recent literature data, Ni-catalyzed "chain-walking" techniques have received considerable attention, becoming powerful tools for the organic synthesis chemist's arsenal for enabling C–C and C–heteroatom formation at remote sp³ C–H bonds. While significant advances have been reported in "chain-walking" polymerizations or sequential isomerization-functionalization strategies,[6] the purpose of this account is to summarize the most recent and important advances in Ni-catalyzed "chain-walking" reactions, including mechanistic considerations and synthetic applications, when appropriate.

2. Ni-catalyzed remote sp³ functionalization

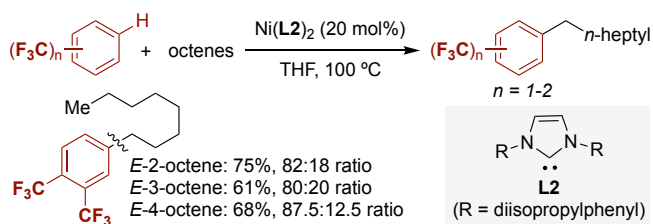### 2.1. Ni-catalyzed remote hydroarylation of olefins and alkyl halides

In 2013, Lee reported an intriguing hydroarylation of allylbenzenes at remote sp³ C–H bonds with Ni(COD)₂ (COD = 1,4-cyclooctadiene) as precatalyst in combination with *N*-heterocyclic carbenes (NHC) as ligands (Scheme 3).[7] Although no mechanistic studies were conducted, the authors proposed a pathway consisting of [1,3]-hydride migration. In this manner, an intermediate styrene is generated via π-allyl nickel hydrides, thus facilitating a subsequent hydroarylation

event at the benzylic site with heteroarene coupling partners. Particularly interesting was the lack of olefin isomerization with AlMe₃, leading to linear arylation instead. Although a wide range of heteroarenes could be employed, generally possessing low pK_a values, it is worth noting that a rather specific set of olefin partners could be employed as substrates. For instance, excellent site-selectivities could only be found for sp^3 C–H sites adjacent to an olefin partner, thus showing the inherent limitations of this rather appealing "chain-walking" scenario when elongating the alkyl side-chain.
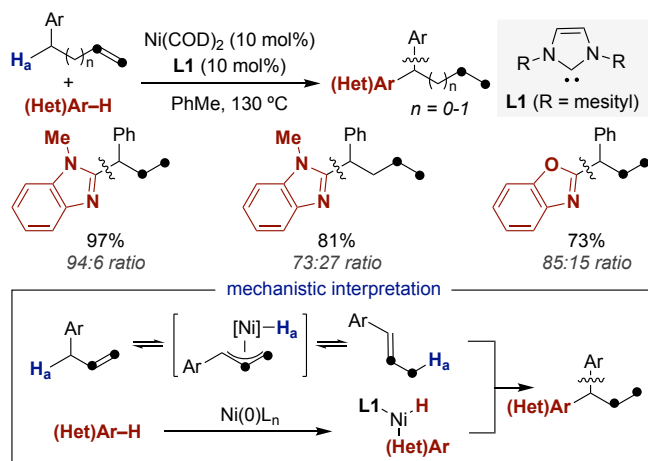
Scheme 3. Ni/**L1**-catalyzed remote hydroarylation of olefins

A related transformation was reported by Hartwig with trifluoromethylarenes as counterparts and internal olefins, resulting in C–C bond-formation at the terminal, primary sp^3 C–H site (Scheme 4).[8] In analogy with Lee's protocol,[7] a regime based on Ni(COD)₂ and NHC ligand, and arenes possessing low pK_a values were critical for success. Although the authors only showed the viability of this method with octene as the olefin partner, one might have expected a similar outcome to that of Lee's if a phenyl substituent was incorporated adjacent to the olefin motif.[7] The observed site-selectivity at terminal, primary sp^3 C–H sites was attributed to the steric hindrance imposed by the bulky NHC ligand. Notably, reaction without NHC led to mixture of olefins, thus suggesting that forging C–C bonds via "chain-walking" was due to the intermediacy of Ni(**L2**). Although the authors favoured a [1,2]-hydride migration pathway, it is worth noting that no mechanistic investigations were pursued; therefore, other conceivable scenarios might come into play.

**Scheme 4**. Ni/**L2**-catalyzed isomerization/hydroalkylation

Prompted by these precedents, Zhu's group reported a hydroarylation of olefins with (hetero)aryl iodides with C–C bond-formation occurring at distal, benzylic sp^3 C–

H sites and polymethylhydrosiloxane (PMHS) as hydride precursor (Scheme 5).[9] As for other Ni-catalyzed cross-coupling reactions via discrete alkyl nickel species,[10] it was found that 2,2'-bipyridine ligands possessing substituents adjacent to the nitrogen motif were critical for success. The reaction exhibited a broad scope and excellent site-selectivity at the sp^3 benzylic site. As expected, a regioconvergent arylation was within reach with statistical mixtures of phenyloctenes. While no mechanistic studies were performed, the authors favoured a mechanism consisting of an initial olefin migration via nickel hydrides followed by oxidative addition of (hetero)aryl iodides to *in situ* generated benzyl nickel species. Whether this outcome indicates that "chain-walking" occurs via Ni(II)Lₙ or Ni(I)Lₙ species still remains speculative.
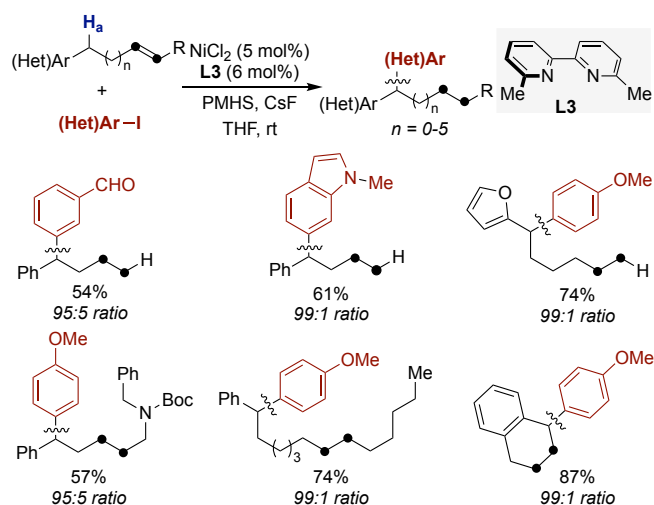
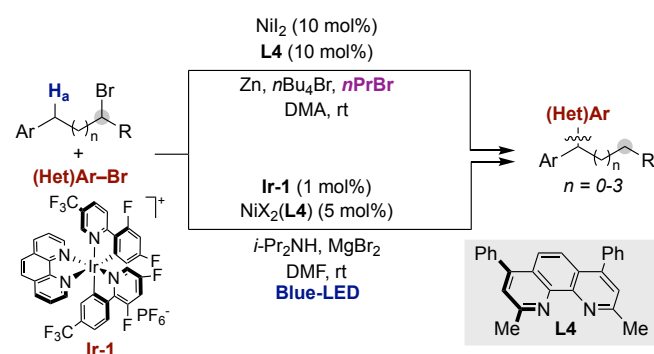

Scheme 5. Ni-catalyzed remote hydroarylation of olefins with ArI.

Prompted by a "chain-walking" protocol of alkyl halides developed by Martin,[11] Zhu extended the generality of their Ni-catalyzed arylation at remote sp^3 C–H sites by using aryl- and alkyl bromide counterparts with Mn as reductant under otherwise similar Ni/**L3** regime (Scheme 6).[12] In analogy with a recent reductive alkyne hydroamidation,[13] the authors found that 1-bromopropane could be used as a masked hydride source via β-hydride elimination. Notably, this protocol did not require CsF or expensive (hetero)aryl iodides, thus constituting a bonus from a synthetic standpoint when compared to the results summarized in Scheme 5.[9] The site-selectivity followed an identical outcome to that shown in Scheme 5, with C–C bond-formation occurring predominantly at the benzylic sp^3 C–H site.
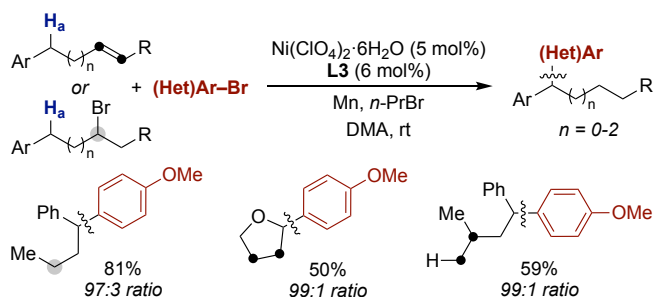
Scheme 6. Ni-catalyzed reductive arylation at benzylic sp^3 C–H sites.

Recently, Yin and co-workers reported an otherwise similar arylation event to that shown in Scheme 6 by using bathocuproine (**L4**) and Zn as reductant (Scheme 7).[14] The observed induction period in the presence of TEMPO (TEMPO = (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) contributed to the perception that a radical chain-type mechanism was involved in. It is worth noting that a redox-neutral protocol based on PhB(OH)$_2$/LiOMe led to the targeted arylation event, albeit in lower yields. In analogy with related Ni-catalyzed cross-electrophile coupling reactions,[15] the authors suggested a pathway consisting of an initial oxidative addition of the aryl bromide to Ni(0)(**L4**) followed by recombination with *in situ* generated alkyl radical species. "Chain-walking" was proposed to occur via [1,2]-hydride migrations from (aryl)(alkyl)Ni(III) species followed by final C–C bond-formation at the benzylic *sp³* site. This hypothesis tacitly suggests that β-hydride elimination should occur at a significantly faster rate than C–C bond reductive elimination, a rather provocative observation if one takes into consideration the known literature data on Ni-catalyzed cross-coupling reactions.[5] Shortly after, Yin described that the merger of Ni catalysis with photoredox catalysis might constitute a powerful alternative for enabling a remote functionalization of benzylic *sp³* C–H sites.[16] This result is particularly noteworthy, as stoichiometric amounts of Zn or Mn could be replaced by diisopropyl amine as terminal reductant;[17] although a bonus from a synthetic standpoint, it is worth mentioning that these reactions require a photoreactor to operate.

Scheme 7. Ni-catalyzed remote reductive benzylic arylation of (hetero)aryl bromides with alkyl bromides.

2.2. Ni-catalyzed remote benzylic alkenylation of alkyl bromides with 1,1,-difluoroalkenes.

Inspired by a series of related Ni-catalyzed remote functionalization techniques with a different set of electrophilic partners,[4,9-12,14] Feng's group recently described the means to forge C–C bonds by combining unactivated alkyl bromides with *gem*-difluoroalkenes as coupling counterparts (Scheme 8).[18] As for Zhu[10,12] and Yin's protocols,[14,16] the reaction took place at the benzylic *sp³* C–H site. Although a longer distance between the initial prefunctionalized motif and the targeted remote *sp³* C–H site might a priori influence site-selectivity of the C–C bond-forming event,[19] the reaction proved to be equally effective four carbons away from the initial C–Br bond. The use of ytterbium (III) triflate (Yb(OTf)$_3$) was crucial for improved reactivity. Among various scenarios, the authors

proposed a "chain-walking" based on Ni(I) intermediates followed by insertion into the difluoroolefin backbone and β-fluoride elimination to give rise to the targeted product. This assumption is certainly intriguing, particularly if one takes into account that "chain-walking" reactions have been proposed to operate via Ni(II) cationic species instead.[4] Particularly interesting was the ability to use the resulting fluoroalkene products for further manipulation via subsequent epoxidation, bromination, dioxygenation, or hydrogenation, among others.
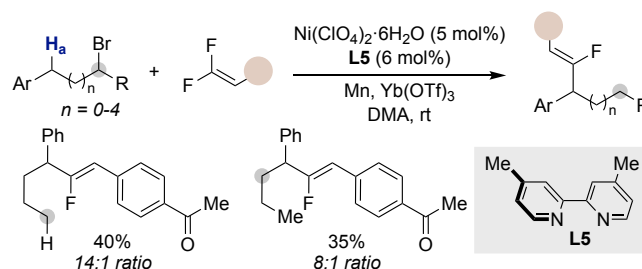
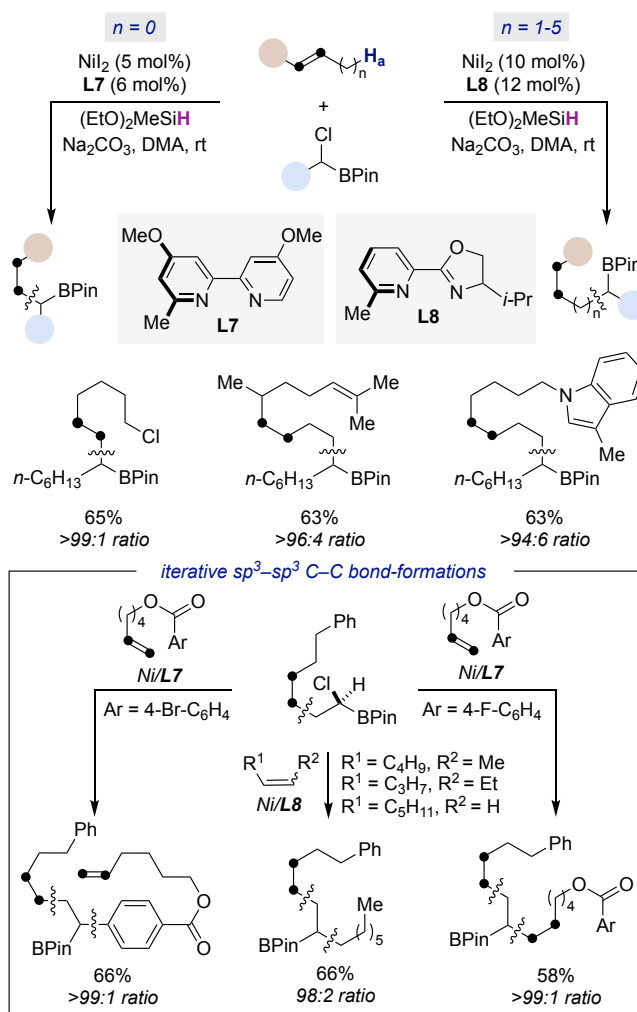**Scheme 8.** Ni-catalyzed remote alkenylation with difluoroalkenes.

2.3. Ni-catalyzed remote *sp³* C–H alkylation of olefins

Although metal-catalyzed cross-coupling reactions of organometallic reagents with organic (pseudo)halides have emerged as indispensable tools for forging C–C bonds,[20] the need for prefunctionalized and stoichiometric C–metal bonds might hamper the application profile of these procedures, thus reinforcing a change in strategy. Driven by this observation, chemists have been challenged to come up with alternate partners with improved flexibility, practicality and generality. Among these, the catalytic addition of a hydrogen atom across an unsaturated bond has received considerable attention as a powerful alternative to classical C–C bond-formations based on stoichiometric organometallic reagents or organic halides, as it generates a latent nucleophile that can further be elaborated in the presence of a suitable functional group.[21] In line with this notion Zhu and co-workers reported a catalytic remote *sp³* C–H alkylation of alkyl iodides with internal alkenes via Ni-catalyzed reductive "chain-walking" and sequential alkylation relay process via Ni-hydride intermediate species (Scheme 9).[22]
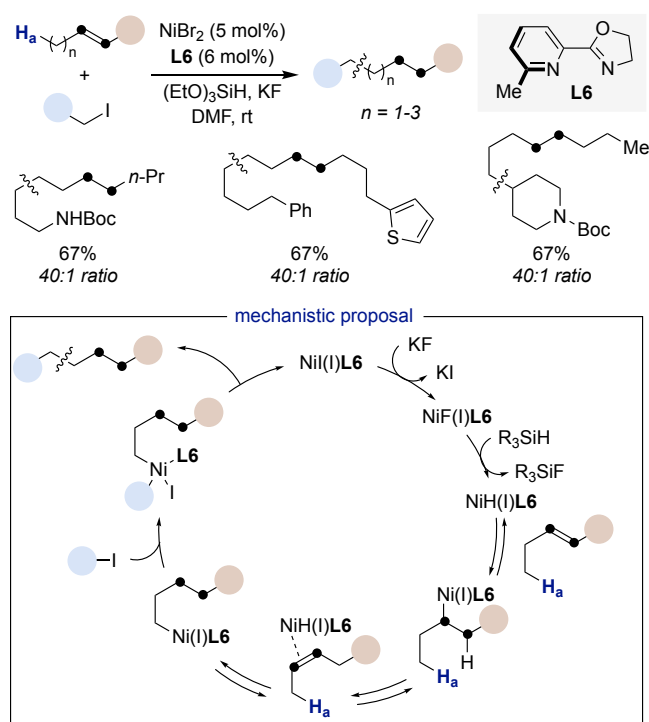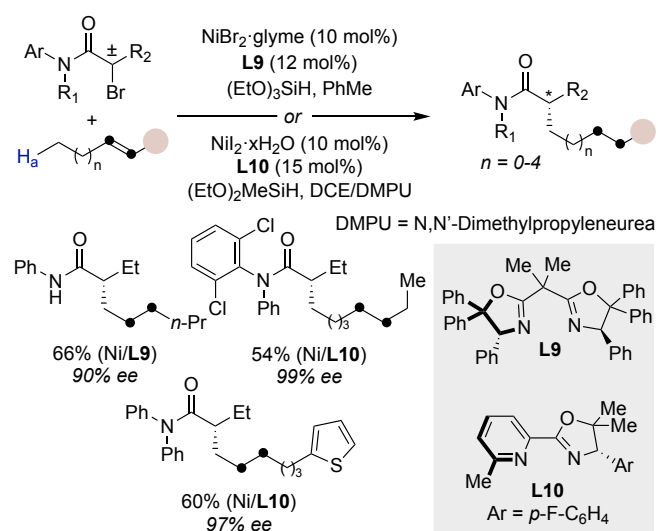
Scheme 9. Ni-catalyzed remote hydroalkylation of internal olefins.

Scheme 10. Site-selective Ni-catalyzed reductive alkylation of unactivated olefins with α-haloboranes.

Unlike the previous olefin hydroarylation event,[10,12] the utilization of a pyrox-type ligand resulted in the C–C bond-formation at an unactivated primary sp^3 C–H bond. These results suggested the intermediacy of alkyl nickel complexes that undergo a rapid iterative series of β-hydride elimination/migratory insertions with a formal translocation of the nickel complex at a terminal, yet unactivated, sp^3 C–H site (Scheme 9, *bottom*).[4] Deuterium labelling studies revealed that a "chain-walking" was indeed operative, but the origin behind the selectivity at primary sp^3 C–H sites remains unclear. In addition, there exists a reasonable ambiguity on whether "chain-walking" occurs via Ni(I), as proposed by the authors, or Ni(II) intermediates, thus suggesting that further investigation will be needed to unravel the intricacies of this or related processes.

While the hydroboration of α-olefins has evolved as a mature tool for accessing organoboranes – one of the most versatile synthons in organic synthesis –, site-selectivity issues come into play with unbiased internal olefins as coupling partners.[23] Aiming at incorporating both a carbon and a boron fragment across an olefin in a site-selective manner, Martin recently described a site-selective reductive alkylation of α-olefin or internal olefin feedstocks with readily available α-haloboranes (Scheme 10).[24] Of particular importance was the ability to establish a platform to build up multiple sp^3–sp^3 bonds in an iterative fashion from simple building blocks (Scheme 10, *bottom*). Preliminary studies ruled out a pathway consisting of an addition of an in situ generated α-boryl radical to the olefin, suggesting that a hydrometallation via nickel hydrides precedes C–C bond-formation with the corresponding α-haloborane. As for other "chain-walkings", there exists a certain ambiguity on the nature and oxidation state of the putative nickel intermediates within the catalytic cycle.

Scheme 11. Enantioconvergent Ni-catalyzed hydroalkylation of olefins with racemic α-bromo amides.

Scheme 12. Remote hydroamination of alkenes with ArNO₂.

The available portfolio on "chain-walking" reactions suggested that the installation of chiral *sp³*–carbon centers should by no means be a chimera. Challenged by this observation, Fu and Zhu independently described a Ni-catalyzed enantioconvergent coupling of racemic secondary or tertiary α-bromo amides with olefin partners in which C–C bond-formation occurred at remote C–H sites, thus giving rise to the targeted products in good yields and high enantioselectivities by using bisoxazolines or pyrox-type ligands (Scheme 11).[25,26] While undoubtedly an enormous step-forward in the field, it is worth noting that these technologies remain restricted to the utilization of activated organic halides (e.g, α-bromo amides), leaving ample room for future asymmetric transformations, particularly when utilizing unactivated electrophilic partners.

2.4. Ni-catalyzed remote amination of olefins

The ubiquity of (hetero)aryl amines in a myriad of pharmaceuticals or agrochemicals has prompted chemists to develop *de novo* catalytic techniques for forging *sp²* and *sp³* C–N bonds by using chemical feedstocks as precursors.[27] To such end, Zhu recently described a Ni-catalyzed amination of nitroarenes with olefins at remote benzylic *sp³* C–H sites operating via alkene isomerization followed by relay hydroamination (Scheme 12),[28] thus complementing existing methods for preparing *sp³* C–N linkages. If esters were employed as substrates, however, *sp³* C–N bond-formation took place at the α position instead, thus resulting in an intriguing route for preparing *N*-aryl amino acids. Undoubtedly, the synthetic potential of this protocol will encourage the development of alternate methods with improved atom economy or cheaper reductants to be employed in late-stage functionalization.
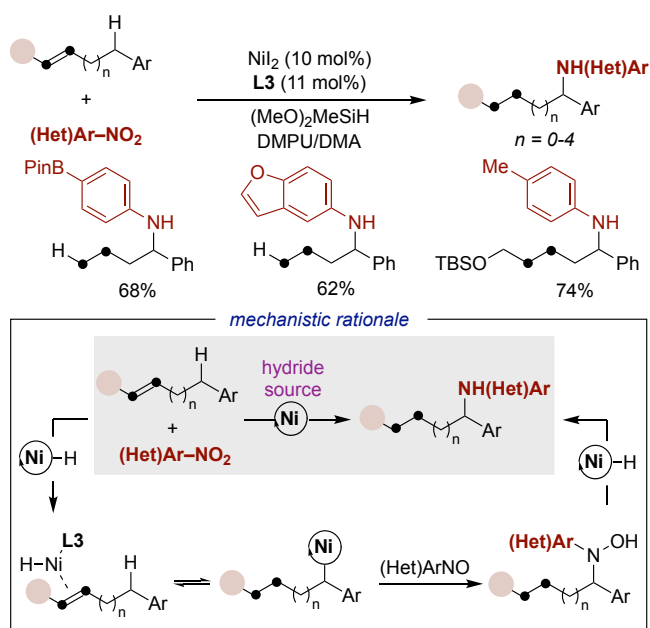
2.5. Ni-catalyzed remote hydrothiolation of olefins

The pivotal role of *sp³* C–S linkages in metabolites or bioactive molecules that are essential to life has prompted chemists to design new *sp³* C–S bond-forming reactions.[29] A particularly attractive, yet atom-economical, endeavour is the catalytic hydrothiolation of olefins. Very recently, Zhu described the merger of olefin isomerization via "chain-walking" with a subsequent *sp³* C–S bond-formation at either remote benzylic sites or adjacent to ether motifs (Scheme 13).[30] In sharp contrast to previous reductive remote hydrofunctionalization of olefins, this reaction does not require sophisticated electrophilic reagents, but rather simple and commercially available alkyl or aryl thiols. The utilization of phenanthroline ligands possessing groups adjacent to the nitrogen motif – a common feature found in Ni-catalyzed "chain-walking" reactions and reductive couplings –[4,10] and pinacolborane as hydride source was found to be critical for success. Interestingly, the utilization of alkynes as counterparts was equally effective, delivering the targeted benzylic hydrothiolation while reinforcing the notion that the reaction is initiated by insertion of a nickel hydride across the unsaturated backbone. A subtle modification of the reaction conditions resulted in a site-selectivity switch, favoring the anti-Markovnikov hydrothiolation of terminal alkenes. Preliminary studies revealed the formation of RSBPin species that act as the corresponding pronucleophile, whereas the nature of the solvent had a non-negligible impact on the formation of the propagating nickel hydride species.

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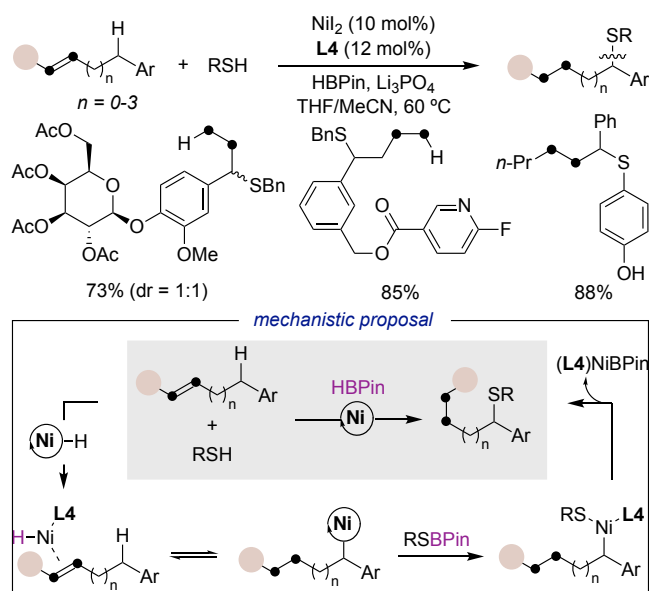
Scheme 13. Ni-catalyzed hydrothiolation of alkenes or alkynes at remote benzylic *sp³* sites.

2.6. Ni-catalyzed remote *sp³* C–H acylation of alkenes or alkyl halides
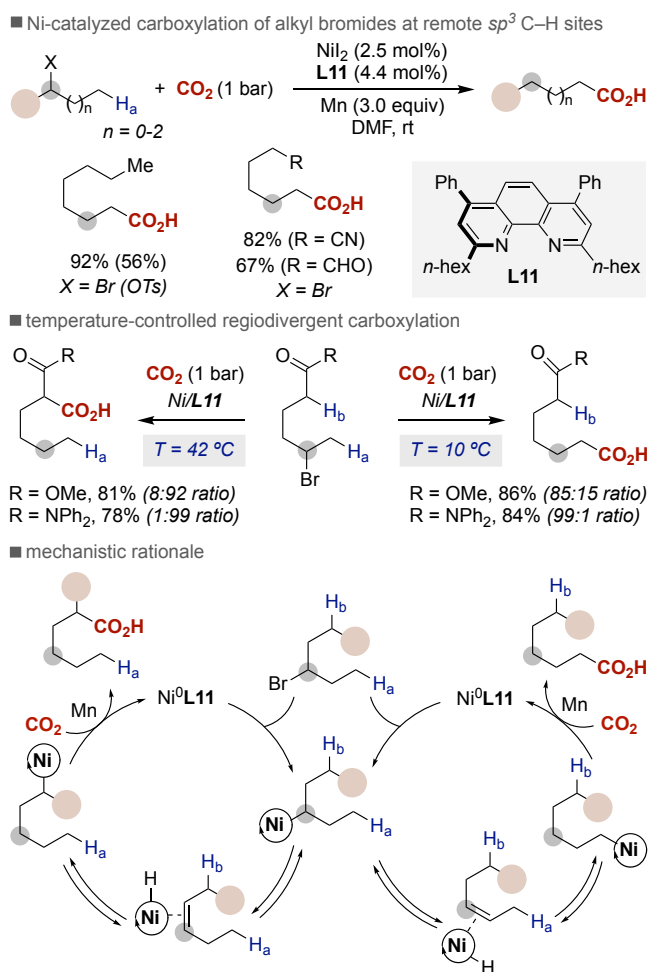
The natural occurrence of carboxylic acids makes them ideal counterparts for building up molecular complexity via C–C bond-forming reactions. Among various scenarios, the ability to convert carboxylic acids into their corresponding ketone congeners constitutes a powerful alternative to classical acylation techniques based on toxic reagents.[31] Unlike classical *ipso*-acylation of carboxylic acids,[31] Zhu and Wang recently described the use of the latter as electrophilic partners in the context of "chain-walking" reactions with either alkyl halides or alkene counterparts,[32] resulting in a site-selective acylation event at remote benzylic *sp³* C–H sites (Scheme 14). The authors proposed a similar mechanistic rationale to that shown in previous "chain-walking" reactions via olefin migration[4] triggered by nickel hydrides followed by C–C bond-formation with *in situ* generated Boc-anhydride as the carbonyl source.
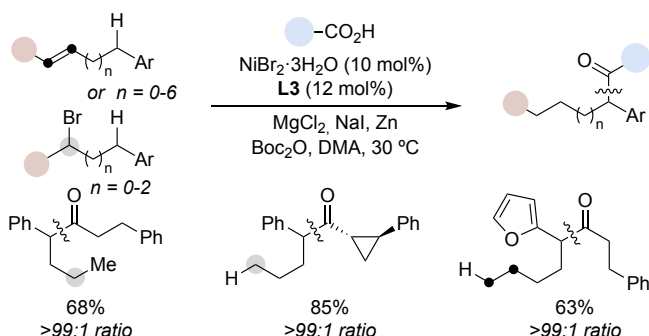
Scheme 14. Ni-catalyzed reductive remote acylation of alkyl halides and alkenes.

The transformation outlined above merits some further discussion. As for other related "chain-walking" events,[10] substituents adjacent to the nitrogen atom on the ligand backbone were found to be critical for the

dynamic displacement of the catalyst throughout the side-chain. Likewise, the inclusion of NaI and $NiBr_2 \cdot 3H_2O$ had a non-negligible impact on reactivity; while a Filkenstein-type reaction might account for the former, the presence of water in the latter might facilitate the formation of the key nickel hydride intermediate. In addition, $MgCl_2$ and Boc_2O were required to activate the carboxylic acid by forming an acid anhydride that precedes C–C bond-formation.[33] As judged by the data provided, a wide range of carboxylic acids with a diverse set of substitution patterns or sensitive functional groups were equally effective. As initially anticipated, regioconvergency was within reach by using statistical mixtures of olefins. Unlike related Ni-catalyzed *ipso*-acylation techniques, this protocol remains unfortunately limited to aliphatic acids, and the nature of the nickel intermediates remains speculative.

■ Ni-catalyzed carboxylation of alkyl bromides at remote *sp³* C–H sites

■ temperature-controlled regiodivergent carboxylation

■ mechanistic rationale

Scheme 15. Site-selective Ni-catalyzed reductive carboxylation of alkyl halides at remote *sp³* C–H sites.

2.7. Ni-catalyzed remote *sp³* C–H carboxylation of alkyl halides and alkenes

Ni-catalyzed reductive carboxylations have recently gained momentum as powerful alternatives to existing methods for accessing carboxylic acids,[34] privileged motifs in a wide variety of compounds that display important biological activities.[35] Despite the significant advances realized, the available carboxylation portfolio contributed to the perception that prefunctionalization

was required for the reaction to occur. Challenged by this notion, Martin reported a catalytic carboxylation at remote sp^3 C–H sites via "chain-walking" (Scheme 15, *top*).[11] In line with their knowledge on reductive cross-couplings, bipyridine or phenanthroline ligands with substituents adjacent to the nitrogen atom were absolutely critical for the reaction to occur,[10] an observation that has rapidly been embraced in other C–C bond-formations (Schemes 5-14). A plethora of alkyl (pseudo)halides with sensitive functional groups were converted to carboxylic acids, constituting a bonus when compared to conventional carboxylations based on stoichiometric and highly reactive organometallics. Particularly intriguing was the preservation of the chiral integrity of carbon centers, an observation that tacitly suggests that the nickel catalyst does not get disengaged from the olefin.[36] Importantly, site-selectivity could be controlled and switched by a subtle control of the temperature, enabling C–C bond-formation at different sp^3 sites (Scheme 15, *middle*) while challenging the perception that multidirectional "chain-walking" motions could not be implemented.[4] As expected, regioconvergent strategies could be within reach by converting abundant alkanes or mixtures of alkenes into single carboxylic acids. In addition, related protocols could be implemented by converting carboxylic acids into their corresponding isotope-labelling analogues by using $^{13}CO_2$ or $^{14}CO_2$.[10a] Although metal reductants (Mn) are required to turn over the Ni catalyst, Martin, König and Crespi recently designed a photoredox protocol based on the utilization of Hantzsch esters (HEH = Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) as reductants under Blue-LED irradiation with 4CzIPN (4CzIPN = 1,2,3,5-Tetrakis(carbazole-9-yl)-4,6-dicyanobenzene) as photocatalyst (Scheme 16).[37] While one might argue that a similar ligand set should be employed regardless of whether a photochemical event[37] or a protocol based on Mn is utilized,[11] this was not the case; indeed, benzylic carboxylation was found for a protocol based on Ni/**L12** whereas CO_2 insertion takes place at primary sp^3 site via Ni/**L3** regimes. Spectroelectrochemical studies supported a CO_2 insertion into C–Ni(I) whereas theoretical calculations ruled out a "chain-walking" based on alkyl-Ni(I); the latter is particularly important, reinforcing the relevance of cationic alkyl-Ni(II) species in β-hydride elimination while arguing against olefin migration occurring via alkyl-Ni(I), an argument that has been drawn in numerous "chain-walking" reactions.
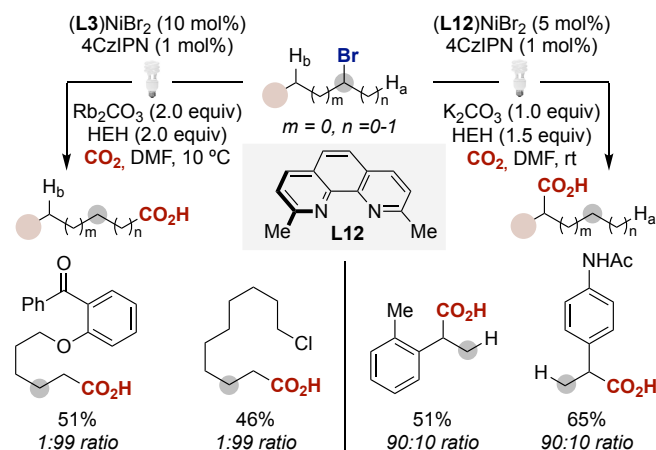
Scheme 16. Site-selective photochemical Ni-catalyzed carboxylation of alkyl halides at remote sp^3 C–H bonds.

Following up his interest in remote carboxylation techniques,[10,11] Martin showed the ability to promote CO_2 insertion at remote sp^3 sites with olefin feedstocks and by simply using water as hydride source with a protocol based on Ni/**L4** (Scheme 17).[38] This result is particularly noteworthy, as it represents an opportunity to repurpose three abundant feedstocks (water, CO_2 and olefins). As expected, regioconvergency from unrefined mixtures of olefins was portrayed for site-selective carboxylation at a single, remote sp^3 C–H site. In this context, preliminary mechanistic experiments did not only confirm water as hydride source, but also revealed a non-negligible role of the substituents proximal to the nitrogen donor, an aspect worth considering for future mechanistic studies that unravel the intricacies exerted by the ligand backbone.
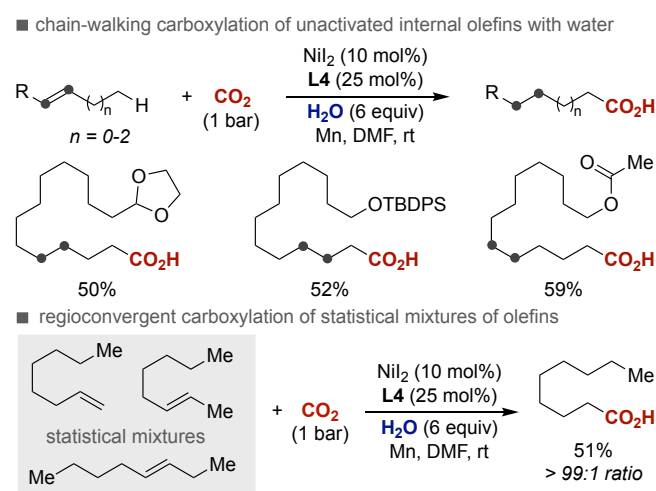

Scheme 17. Site-selective Ni-catalyzed carboxylation of olefins at remote sp^3 C–H sites with water as hydride source.

2.8. Ni-catalyzed remote sp^3 C–H silylation of olefins

Catalytic hydrosilylation of olefins constitutes one of the most widely applied methods in the silicones industry for preparing monomers containing C–Si linkages and cross-linking polymers.[39] These processes are oftentimes catalyzed by noble platinum catalysts such as the silicon-soluble Karstedt's catalyst.[40] In recent years, non-precious transition metal catalysts has gained considerable momentum in these endeavors.[41] However, nickel-based protocols have not yet been fully adopted in hydrosilylation techniques due to some issues related to their versatility, chemoselectivity or generality beyond α-olefins.[41c] In 2015, Hu showed that pincer-type Nickamine complexes (**L13**)NiX (X = Cl, OMe) do not only promote the anti-Markovnikov hydrosilylation of α-olefins with diarylsilanes, but also silylation of internal olefins at remote primary sp^3 sites via "chain-walking" strategies (Scheme 18).[42] Although the use of trialkoxysilanes might furnish industrially-relevant silicones, this process remained particularly problematic. To such end, Hu developed a simple, stable and recyclable Ni-based nanocatalyst Ni(O^{t}Bu)$_2$.xKCl that turned out to outperform previous
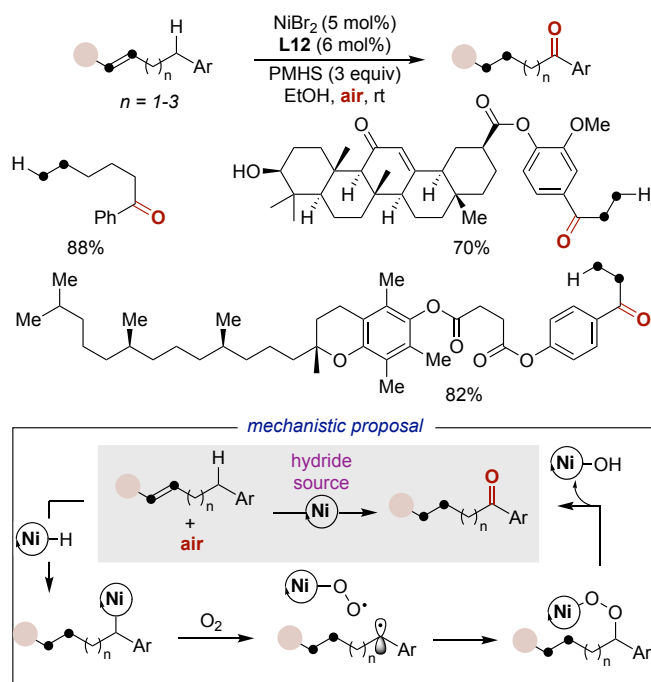
Ni-based methods and particularly applicable to the coupling of α-olefins and internal alkenes, the latter via "chain-walking" at remote *sp³* sites.[43] As expected, this heterogeneous protocol could be applied in regioconvergent techniques with unrefined mixture of olefins to deliver linear silicones in high site-selectivity.
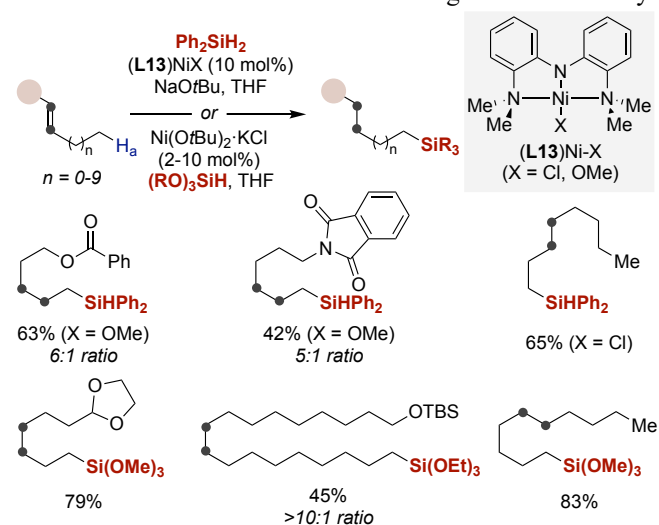
Scheme 18. Ni-catalyzed remote hydrosilylation of olefins

Scheme 19. Ni-catalyzed Wacker oxidation at remote, benzylic *sp³* C–H bonds.

## 2.9 Ni-catalyzed remote Wacker-type oxidation of alkenes

Beyond any reasonable doubt, the Wacker oxidation of olefins ranks amongst the most direct and applicable methods for accessing high value-added ketones.[44] At present, these protocols primarily rely on Pd catalysts, invariably forging a C–O bond at the prefunctionalized alkene terminus. Recently, Han reported a rather intriguing Ni-catalyzed Wacker oxidation-type protocol that results in the functionalization of remote benzylic sites via "chain-walking", thus allowing to convert olefins substituted with aryl groups into the corresponding alkyl aryl ketones (Scheme 19).[45] As for other Ni-catalyzed "chain-walking" reactions,[10] the nature of the ligand was critical for success, with nitrogen-containing ligands containing substituents adjacent to the nitrogen atom providing the best results (**L12**). From a mechanistic standpoint, the method seems to operate via the canonical olefin migration enabled by nickel hydrides followed by homolysis of the C–Ni bond in the presence of oxygen, ultimately leading to the oxidation at the benzylic site. Among the many interesting aspects behind this hypothesis, the ability to trigger a dynamic displacement of the nickel hydride throughout the side-chain under oxidative conditions is undoubtedly noteworthy, and might open new avenues in remote functionalization by means of Ni catalysis.

2.10. Stereoselective transition metal-catalyzed olefin isomerization

Stereoselective olefin isomerization is particularly interesting for the practice of organic synthesis, as the precise location and geometry of the C=C bond often defines the physical and chemical characteristics of the molecule.[46] Not surprisingly, considerable attention has been devoted to enable catalytic stereoselective olefin isomerization in an efficient and regioselective manner. While nickel-based protocols have shown to be suited for such purposes, the low efficiency and selectivity of these processes reinforced the need for alternate protocols with improved flexibility and generality.[47] Recently, Schoenebeck and co-workers have disclosed the olefin isomerization of industrially relevant olefins catalyzed by a chloro-bridged dimeric nickel complex supported by electron-rich NHC ligand **L2** (Scheme 20).[48] Control experiments and DFT calculations ruled out the intervention of either (**L2**)₂Ni(0) or (**L2**)Ni(II)(H)Cl and suggested a pathway consisting of a radical-based [1,n]–H shift via open shell, monomeric (**L2**)Ni(I)Cl species instead. Unfortunately, the non-negligible effect exerted by the ligand on both reactivity and selectivity remains to be elucidated. As judged by the data provided, the reaction exhibited a broad substrate scope and excellent *E*-selectivity profile for a wide number of differently substituted olefins, including challenging combinations such as long-chain olefin isomerization.
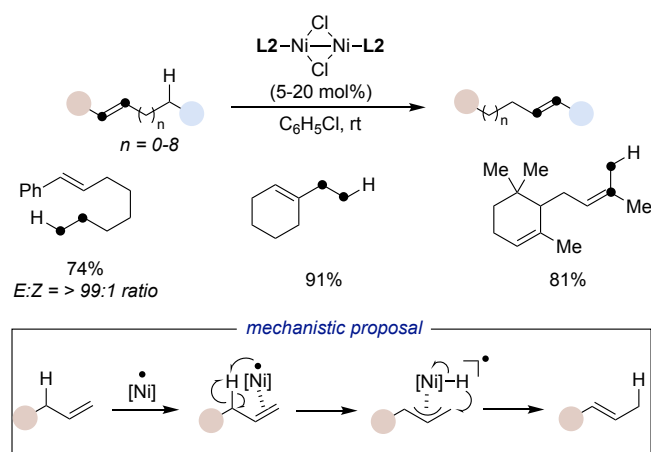
Scheme 20. Stereoselective Ni-catalyzed isomerisation of unactivated olefins.

3. Summary and Outlook

As judged by the wealth of literature data, it is evident that the functionalization of olefins and the metal-catalyzed cross-coupling reactions of alkyl halides has led to new knowledge in retrosynthetic analysis, significantly improving our ever-expanding synthetic arsenal for forging sp^3 linkages. Ironically, however, the success of these methodologies has contributed to the perception that bond-construction should only occur at a previously functionalized site. Fortunately, the recent years have witnessed a dramatic progress in earth-abundant nickel catalysts, allowing to establish new design principles that seek new chemical knowledge instead of following traditional or preconceived ideas. Among these, particularly attractive is the ability of a catalyst to trigger a dynamic displacement throughout the alkyl side-chain coined as "chain-walking", allowing to promote bond-forming reactions at remote sp^3 C–H sites. While originally designed for controlling polymer topology, the recent years have witnessed considerable progress on nickel-catalyzed "chain-walking" reactions of olefins or alkyl halides, allowing to promote not only new, yet counterintuitive, bond-disconnections but also providing new vistas for sp^3 C–H functionalization. Although the use of nickel-catalyzed "chain-walking" reactions is still at its infancy when compared with the traditional cross-coupling reactions of alkyl halides or olefin counterparts, the widespread use of this new technology holds great promise to change logics in organic synthesis.

Despite the preparative advances realized in nickel-catalyzed "chain-walking" reactions for forging C–C and C–heteroatom bonds at remote sp^3 sites, a number of daunting challenges remain in these rather appealing scenarios: (1) while the functionalization of benzylic or primary sp^3 C–H bonds is routine in these techniques, the means to develop "*a la carte*" "chain-walking" reactions at different sp^3 C–H bonds within an alkyl side-chain with reliable and predictable site-selectivity – including the always elusive methylene sp^3 C–H bonds–, is still considered *terra incognita*; (2) although regioconvergent scenarios from statistical mixtures of olefins or alkyl halides have been implemented, the ability to reliably switch the site-selectivity via the regiodivergent scenarios remains largely underexplored;

(3) "chain-walking" reactions are still substrate-specific. Indeed, the inclusion of branched substituents within the alkyl side-chain typically hinders the dynamic displacement of the catalyst throughout the hydrocarbon side-chain and a general solution to trigger "chain-walking" reactions of tri- or tetrasubstituted olefins still remains rather problematic; (4) catalytic asymmetric "chain-walking" reactions are scarce; (5) a non-negligible number of "chain-walking" reactions still require stoichiometric metal reductants or high-molecular weight silanes; while the adoption of photoredox catalysis might bring new chemical spaces in these endeavors, these strategies are still at their infancy; (6) undoubtedly the major challenge in "chain-walking" techniques lies on the ambiguity behind the putative nickel species within the catalytic cycle, the enigmatic role exerted by the ligand backbone and whether Ni(I), Ni(II) or even Ni(III) are responsible for the motion throughout the alkyl side-chain. At present, progress in this field is based on empirical discoveries, and the lack of mechanistic data on "chain-walking" reactions might prevent the field to reach the maturity required to change new paradigms in organic synthesis. Taking into consideration the new knowledge acquired in catalytic endeavors, particularly on catalyst design, it is fair to look at the field with certain optimism. We are certainly convinced that many of the challenges highlighted above will be addressed in the not so distant future. Particular attention should be devoted to unravel the mechanistic intricacies of these processes in order to understand all elementary steps in Ni-catalyzed "chain-walking" reactions at the molecular level, serving as the basis to design future cross-coupling techniques in this intellectually rewarding field of expertise.

Acknowledgements

References

[1] For selected reviews on C–H functionalization, see: a) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900–2936; b) R. H. Crabtree, A. Lei, *Chem. Rev.* **2017**, *117*, 8481–8482; c) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) H. M. L. Davies, D. Morton, *J. Org. Chem.* **2016**, *81*, 343

[2] For selected reviews: a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. –Q. Yu, *Chem. Rev.* **2017**, *117*, 8754; b) H. Li, B. –J. Li; Z. –J. Shi, *Catal. Sci. Technol.* **2011,** *1*, 191; c) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O.

Baudoin, *Chem. –Eur. J.* **2010**, *16*, 2654; d) P. Herrmann, T. Bach, *Chem. Soc. Rev.* **2011**, *40*, 2022; e) H. M. L. Davies, D. Morton, *ACS Cent. Sci.* **2017**, *3*, 936; f) J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281; g) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62.

[3]   R. G. Bergman, *Nature* **2007**, *446*, 391.

[4]   a) H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* **2018**, *4*, 153; b) A. Vasseur, J. Bruffaerts, I. Marek, *Nat. Chem.* **2016**, *8*, 209; c) I. Franzoni, C. Mazet, *Org. Biomol. Chem.* **2014**, *12*, 233; d) F. H. Jardine, *Hydrogenation & Isomerization of Alkenes* in *Encycl. Inorg. Chem.*, John Wiley & Sons, Ltd, Chichester, UK, **2006.**

[5]   a) V. P. Ananikov, *ACS Catal.* **2015**, *5*, 1964; b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; c) E. Richmond, J. Moran, *Synthesis* **2018**, *50*, 499.

[6]   Selected references: a) K. Johnson, C. M. Killian, M. Brookhart, *J. Am. Chem. Soc.* **1995**, *117*, 6414; b) F. Wang, C. Chen, *Polym. Chem.* **2019**, *10*, 2354; c) J. Wang, L. Wang, H. Yu, R. S. Ullah, M. Haroon, Z. –U. Abdin, X. Xia, R. U. Khan, *Eur. J. Inorg. Chem.* **2018**, *13*, 1450; d) C. J. Stephenson, J. P. McInnis, C. Chen, M. P. Weberski, A. Motta, M. Delferro, T. J. Marks, *ACS Catal.* **2014**, *4*, 999; e) L. Guo, S. Dai, X. Sui, C. Chen, *ACS Catal.* **2016**, *6*, 428; f) K. S. O' Connor, J. R. Lamb, T. Vaidya, I. Keresztes, K. Klimovica, A. M. Lapointe, O. Daugulis, G. W. Coates, *Macromolecules* **2017**, *50*, 7010; g) D. N. Vaccarello, K. S. O' Connor, P. Iacono, J. M. Rose, A. E. Cherian, G. W. Coates, *J. Am. Chem. Soc.* **2018**, *140*, 6208.

[7]   W. C. Lee, C. H. Wang, Y. H. Lin, W. C. Shih, T. G. Ong, *Org. Lett.* **2013**, *15*, 5358–5361.

[8]   J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 13098.

[9]   Y. He, Y. Cai, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 1061.

[10]   See for example: a) A. Tortajada, Y. Duan, B. Sahoo, G. Toupalas, A. Sallustrau, O. Loreau, D. Audisio, R. Martin, *ACS Catal.* **2019**, *9*, 5897; b) M. Börjesson, T. Moragas, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 7504; c) T. Moragas, M. Gaydou, R. Martin, *Angew. Chem. Int. Ed.* **2016**, *55*, 5053; d) K. Nogi, T. Fujihara, J. Terao, Y. Tsuji, *J. Org. Chem.* **2015**, *80*, 11618; e) Q. -Y. Meng, S. Wang, B. König *Angew. Chem. Int. Ed.* **2017**, *56*, 13426; f) Y. Liu, J. Cornella, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 11215; g) A. Correa, T. León, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 1062; h) Q. -Y. Meng, S. Wang, G. S. Huff, B. König, *J. Am. Chem. Soc.* **2018**, *140*, 3198; i) V. R. Yatham, Y. Shen, R. Martin, *Angew. Chem. Int. Ed.* **2017**, *56*, 10915; j) H. Seo, A. Liu, T. F. Jamison, *J. Am. Chem. Soc.* **2017**, *139*, 13969.

[11]   F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* **2017**, *545*, 84.

[12]   F. Chen, K. Chen, Y. Zhang, Y. He, Y. M. Wang, S. Zhu, *J. Am. Chem. Soc.* **2017**, *139*, 13929.

[13]   X. Wang, M. Nakajima, E. Serrano, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 15531.

[14]   L. Peng, Y. Li, Y. Li, W. Wang, H. Pang, G. Yin, *ACS Catal.* **2018**, *8*, 310.

[15]   a) J. Gu, X. Wang, W. Xue, H. Gong, *Org. Chem. Front.*

2015, *2*, 1411; b) J. D. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767; c) T. Moragas, A. Correa, R. Martin, *Chem. Eur. J.* **2014**, *20*, 8242; d) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828.

[16]   L. Peng, Z. Li, G. Yin, *Org. Lett.* **2018**, *20*, 1880.

[17]   For reviews on dual catalysis in photochemical events: a) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, *1*, 0052; b) M. D. Levin, S. Kim, F. D. Toste, *ACS Cent. Sci.* **2016**, *2*, 293; c) M. N. Hopkinson, B. Sahoo, J. –L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; d) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035; e) L. Marzo, S. K. Pagore, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018***, 57*, 2; f) N. A. Romero, D. A. Nicewicz, *Chem. Rev.*, **2016**, *116*, 10075; g) M. D. Kärkäs, J. A. Porco, C. R. J. Stephenson, *Chem. Rev.*, **2016**, *116*, 9683.

[18]   L. Zhou, C. Zhu, P. Bi, C. Feng, *Chem. Sci.* **2019**, *10*, 1144.

[19]   L. Lin, C. Romano, C. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 10344.

[20]   A. De Meijere, S. Brase, M. Oestreich, *In Metal-catalyzed cross-coupling reactions;* Wiley-VCH: Weinheim, Germany, 2004.

[21]   For selected reviews on hydrofunctionalization reactions, see: a) K. D. Nguyen, B. Y. Park, T. Luong, H. Sato, V. J. Garza, M. J. Krische, *Science* **2016**, *354*, 300; b) S. W. M. Crossley, C. Obradors, R. M. Martinez, R. A. Shenvi, *Chem. Rev.* **2016**, *116*, 8912; c) K. A. Margrey, D. A. Nicewicz, *Acc. Chem. Res.* **2016**, *49*, 1997; d) J. R. Coombs, J. P. Morken, *Angew. Chem., Int. Ed.* **2016**, *55*, 2636. (e) V. P. Ananikov, M. Tanaka, *Top. Organomet. Chem.* **2014**, 34.

[22]   F. Zhou, J. Zhu, Y. Zhang, S. Zhu, *Angew. Chem. Int. Ed.* **2018**, *57*, 4058–4062.

[23]   K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179.

[24]   S. –Z. Sun, M. Börjesson, R. Martin-Montero, R. Martin, *J. Am. Chem. Soc.* **2018**, *140*, 12765.

[25]   Z. Wang, H. Yin, G. C. Fu, *Nature* **2018**, *563*, 379

[26]   F. Zhou, Y. Zhang, X. Xu, S. Zhu, *Angew. Chem. Int. Ed.* **2018**, *58*, 1754.

[27]   S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451.

[28]   J. Xiao, Y. He, F. Ye, S. Zhu, *Chem* **2018**, *4*, 1645.

[29]   a) J. O. Jeppesen, M. B. Nielsen, J. Becher, *Chem. Rev.* **2004**, *104*, 5115; b) K. Takimiya, I. Osaka, T. Mori, M. Nakano, *Acc. Chem. Res.* **2014**, *47*, 1493; c) E. A. Ilardi, E. Vitakuand, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832.

[30]   Y. Zhang, X. Xu, S. Zhu, *Nat. Commun.* **2019**, *10*, 1752.

[31]   For selected references on the use of carboxylic acids and/or derivatives as acylating agents: a) C. Zhao, X. Jia, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2014**, *136*, 17645; b) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442; c) H. Yin, C. Zhao, H. You, K. Lin, H. Gong, *Chem. Commun.* **2012**, *48*, 7034; d) F. Wu, W. Lu, Q. Qian, Q. Ren, H. Gong, *Org. Lett.* **2012**, *14*, 3044. e) A. C. Wotal, D. J. Weix, *Org. Lett.* **2012**, *14*, 1476; f) M. Onaka, M. Yoshio, M. Teruaki, *Chem. Lett.* **1981**, *10*, 531.

[32] J. He, P. Song, X. Xu, S. Zhu, Y. Wang, *ACS Catal.* **2019**, 3253.

[33] G. Bartoli, M. Bosco, A. Carlone, R. Dalpozzo, E. Marcantoni, P. Melchiorre, L. Sambri, *Synthesis* **2007**, 3489.

[34] a) A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas, R. Martin, *Angew. Chem. Int. Ed.* **2018**, *57*, 15948; b) F. Juliá-Hernández, M. Gaydou, E. Serano, M. van Gemmeren, R. Martin, *Top. Curr. Chem.* **2016**, 374, 45; c) M. Börjesson, T. Moragas, D. Gallego, R. Martin, *ACS Catal.* **2016**, *6*, 6739; d) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933; e) Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956; f) L. Zhang, Z. Hou, *Chem. Sci.* **2013**, *4*, 3395; g)

[35] H. Maag, *Prodrugs of Carboxylic Acids,* Springer, New York, **2007**.

[36] For other non-nickel based chain-walking reactions that result in the preservation of the intrinsic chirality of alkyl side-chains, see: a) T. –S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340; b) S. Singh, J. Bruffaerts, A. Vasseur, I. Marek, *Nat. Commun.* **2017**, *545*, 84.

[37] B. Sahoo, P. Bellotti, F. Juliá-Hernández, Q. –Y. Meng, S. Crespi, B. König, R. Martin, *Chem. Eur. –J.* **2019**, DOI:10.1002/chem.201902095.

[38] M. Gaydou, T. Moragas, F. Juliá-Hernández, R. Martin, *J. Am. Chem. Soc.* **2017**, *139*, 12161.

[39] a) B. Marciniec, *Hydrosilylation: A Comprehensive Review on Recent Advances*, Springer, Berlin, **2009**; b) S. Putzien, O. Nuyken, F. Kühn, *Prog. Polym. Sci.* **2010**, *35*, 687.

[40] P. B. Hitchcock, M. F. Lappert, N. J. W. Warhurst, *Angew. Chem. Int. Ed.* **1991**, *30*, 438.

[41] For selected examples: a) J. Chen, B. Cheng, Z. Lu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4661; b) J. Sun, L. Deng, *ACS Catal.* **2016**, *6*, 290; c) V. Srinivas, Y. Nakajima, W. Ando, K. Sato, S. Shimada, *J. Organomet. Chem.* **2016**, *809*, 57; d) V. Srinivas, Y. Nakajima, W. Ando, K. Sato, S. Shimada, *Catal. Sci. Technol.* **2015**, *5*, 2081; e) D. Peng, Y. Zhang, X. Du, L. Zhang, X. Leng, M. D. Walter, Z. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 19154; f) A. M. Tondreau, C. C. H. Atienza, K. J. Weller, S. A. Nye, K. M. Lewis, J. G. P. Delis, P. J. Chirik, *Science* **2012**, *335*, 567; g) S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794.

[42] I. Buslov, J. Becouse, S. Mazza, M. Montandon-Clerc, X. Hu, *Angew. Chem. Int. Ed.* **2015**, *54*, 14523.

[43] I. Buslov, F. Song, X. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 12295.

[44] J. A. Keith, P. M. Henry, *Angew. Chem. Int. Ed.* **2009**, *48*, 9038.

[45] B. Liu, P. Hu, F. Xu, L. Cheng, M. Tan, W. Han, *Nat. Commun.* **2019**, *2*, 1.

[46] C. R. Larsen, D. B. Grotjahn "*The value and application of transition metal catalyzed alkene isomerization in industry"* in *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook.* Cornils, W. A. Herrmann, M. Beller, R. Paciello, Eds. Wiley, **2017**, pp. 1365.

[47] a) H. J. Lim, C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **2009**, *74*, 4565; b) A. Wille, S. Tomm, H. Frauenrath, *Synthesis* **1998**, *1998*, 305.

[48] A. Kapat, T. Sperger, S. Guven, F. Schoenebeck, *Science* **2019**, *363*, 391.