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NiH-Catalyzed Homobenzylic Hydroalkylation of Aryl Alkenes Using Sulfoxonium Ylides

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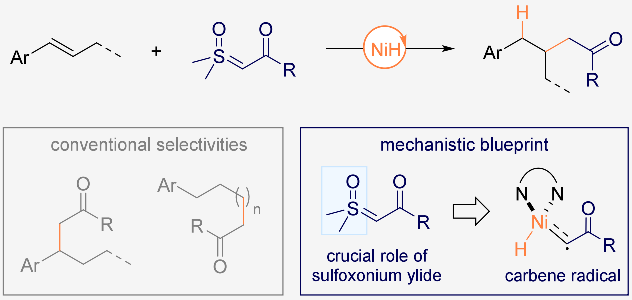
ABSTRACT: We present here the first example of NiH-catalyzed homobenzylic hydroalkylation of aryl alkenes mediated by a nickel carbene radical, achieving the elusive β-selectivity with excellent regiocontrol. Mechanistic investigations suggest that this transformation is enabled by the preferential engagement of NiH with bench-stable sulfoxonium ylides, whose unique chelation properties promote carbene activation prior to alkene insertion. The resulting nickel carbene radical is proposed to undergo selective β-addition, followed by intramolecular metal hydride transfer and protodemetalation. The reaction exhibits broad scope across aryl, heteroaryl, and complex bioactive alkene derivatives, as well as diverse sulfoxonium ylides. This work establishes a new mechanistic platform for NiH catalysis, expanding the synthetic repertoire for site-selective alkene functionalization.



INTRODUCTION

The development of synthetic strategies to diversify molecular frameworks through regioselective hydrofunctionalization of alkenes has been a longstanding objective in synthetic chemistry, as such transformations enhance both the synthetic utility and structural complexity of ubiquitous olefin substrates.[1−11] In this context, transition metal hydride-catalyzed hydroalkylation of aryl-containing alkenes has been actively explored as a powerful strategy to access structurally valuable sp^3-rich fragments (Scheme 1a, left).[12−16] Among the notable advances, alkylation at the benzylic position has been the most prevalent.[17−21] Elegant studies have shown that *in situ* generated NiH species, derived from nickel salts and hydride donors, can catalyze formal hydroalkylation of vinylarenes at the benzylic position through umpolung strategies employing electrophilic alkyl sources. In parallel, terminal alkylation has been achieved via olefin chain-walking under redox neutral conditions.[8] This approach to remote formal hydroalkylation, particularly with alkenes bearing aryl groups, has been independently demonstrated by the Zhu,[22,23] Martin,[24,25] Qi,[26] and Shang[27] groups.

Despite the substantial body of these works, regioselective internal alkene hydroalkylation at the *homobenzylic* site remains elusive (Scheme 1a, right). This scarcity is likely attributable to two intrinsic features of transition metal hydrides: the kinetic preference for hydrometalation at the α-position[28−31] as well as thermodynamic preference of the metal center for the benzylic[28,29,32−37] or terminal positions,[34,37−39] where chain walking is more feasible. Indeed, beyond hydroalkylation across the broader field of hydrofunctionalization, only a handful of examples exhibiting homobenzylic selectivity have been reported. For instance, metal hydride-mediated hydroborylation at this position was independently demonstrated by the Koh[40] and Zhang[41] groups. Our group has also contributed to this area by developing a formal NiH-catalyzed enantioselective hydroamidation of vinylarenes, in which C−N bond formation occurs at the homobenzylic position via olefin insertion into a proposed amidonickel intermediate.[42]

An emerging strategy for hydroalkylation leverages transition metal hydrides in conjunction with inner-sphere carbenoid transfer.[43−45] Notably, our group reported a regioselective remote C−H alkylation of internal olefins via iridium hydride catalysis, combining olefin chain-walking with carbenoid migratory insertion from sulfoxonium ylides (Scheme 1b, left).[43] In contrast, Gevorgyan and co-workers more recently demonstrated that nickel catalysis can reverse the regioselectivity toward the benzylic position using diazo compounds (Scheme 1b, right).[44] In both cases, the observed selectivities reflect the intrinsic behaviors of metal hydrides described above, leaving alternative regioselectivities largely unexplored.

To this end, we envisioned developing a new hydroalkylation platform for aryl alkenes that will deliver *homobenzylic* selectivity by harnessing carbenoid transfer. A major hurdle in this realm is the inherent propensity of

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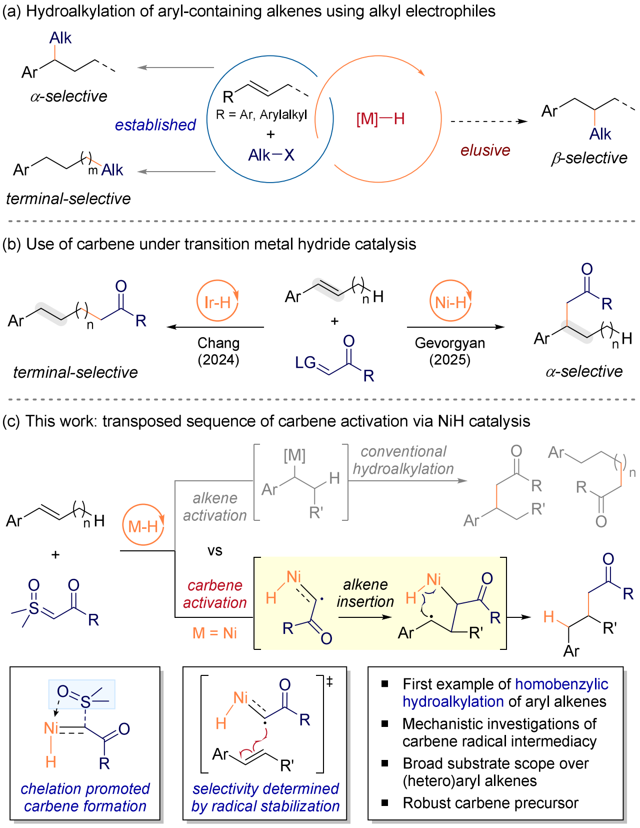
Scheme 1. Transition Metal Hydride-Catalyzed Hydroalkylation of Aryl Alkenes



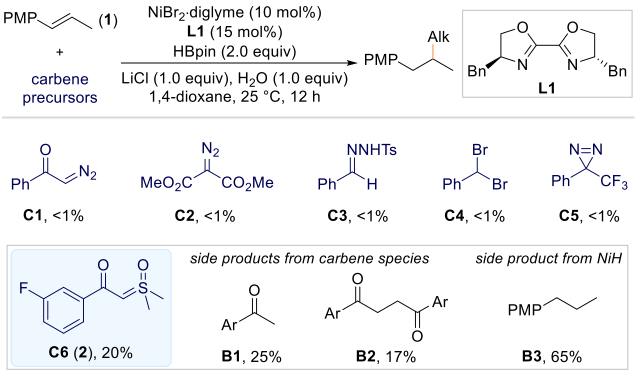
transition metal hydrides to undergo rapid hydrometalation with alkenes, leading to the more conventional hydroalkylation products (Scheme 1c, top).[43,44] An alternative strategy would selectively activate the carbene precursor *prior* to alkene engagement, thereby enabling subsequent carbene insertion at the homobenzylic position. Crucially, accessing a carbene species with radical character would select the bond-forming carbon being controlled by radical stabilization,[46−49] thus making homobenzylic carbene insertion highly predictable. While metal carbene radicals have recently emerged as powerful intermediates for C−C bond-forming reactions,[50] we posited that our previously developed NiH systems,[51−54] capable of nitrenoid activation and engaging in paramagnetic species, would engender controlled access to carbene radical intermediates. Furthermore, the stepwise radical addition of a carbenoid via NiH catalysis is anticipated to proceed with suppression of undesired carbene reactivities such as olefin cyclopropanation[55−72] and hydride-mediated carbene reduction,[73−76] since intramolecular NiH-mediated hydride transfer would be highly facile under these conditions.[77−80]

Herein, we report the first example of NiH-catalyzed homobenzylic hydroalkylation of aryl alkenes using convenient, bench-stable sulfoxonium ylides[81−86] as key carbene precursors (Scheme 1c, bottom). Combined experimental and computational studies reveal that NiH species preferentially engage the carbene precursor first, crucially facilitated by chelation, to generate nickel carbene radicals. This intermediate subsequently undergoes regioselective olefin radical addition, intramolecular metal hydride transfer, and protodemetalation.

■ RESULTS AND DISCUSSION

Initial Investigation. We commenced our study of olefin hydroalkylation using (*E*)-1-methoxy-4-(prop-1-en-1-yl)-benzene (**1**) as a model substrate in reactions with various carbene precursors, aiming to identify a suitable precursor for the transposed carbenoid activation (Scheme 2). For the initial screening, we employed a well-defined NiH catalytic system comprising $NiBr_2$·diglyme and bioxazoline ligand **L1**, in combination with HBpin as the hydride source. Additives were included to promote reactivity: LiCl to activate the reaction components and H_2O as a proton source.

Scheme 2. Initial Investigation on Carbene Precursors[a]



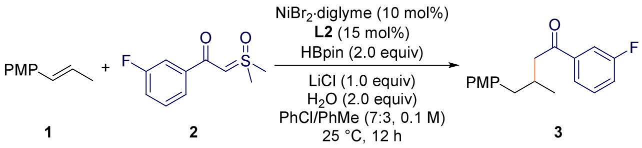
[a] Yields determined by ^1H NMR using 1,1,2-trichloroethane as an internal standard; PMP, *para*-methoxyphenyl; Ar, 3-fluorophenyl.

A survey of carbene precursors revealed that representative diazo compounds[46,47,55,56,58,61,67,72,75] (**C1**, **C2**) failed to produce any alkylated product under the initial conditions. Likewise, other common carbene precursors, including hydrazone[49,59,60,68] (**C3**), *gem*-dibromide[62−66,69,70] (**C4**), and diazirine[87] (**C5**), were unreactive. Gratifyingly, when sulfoxonium ylide[81−86] (**C6**) was examined, the *β*-alkylated product was obtained as a single regioisomer in 20% yield. Importantly, no isomeric *α*-alkylated product was detected in this transformation. Sulfoxonium ylides are attractive surrogates for *α*-diazocarbonyl compounds: they are typically bench-stable, readily prepared from the corresponding carboxylic acids, and compatible with a broad range of reaction conditions.[81−86]

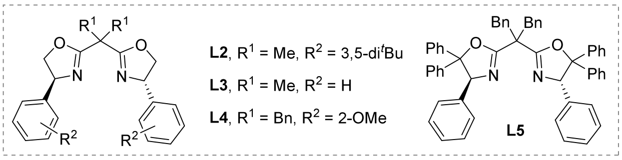
Along with the modest yield of the desired product from the reaction of alkene **1** and sulfoxonium ylide **C6**, several side products arising from carbene reactivity were also observed. These side products included the protonated acetophenone **B1** (25%) and the carbene dimeric adduct **B2** (17%). In addition, saturated alkane **B3** was obtained in 65% yield, presumably originating from nickel hydride reactivity. In fact, protonation at the carbene carbon to form a metal−alkyl species is well documented, as evidenced by Fogg and Baker, who showed that hydrated carbene species can undergo dimerization via alkyl−alkyl coupling.[88] Consistent with this precedent, when **C6** was subjected to the NiH reaction conditions in the absence of the alkene substrate, the C−C dimerization product **B2** was formed (63%), supporting the potential involvement of a Ni−carbene intermediacy under these conditions (see Supporting Information for details).

Reaction Optimization. With the promising initial results in hand, we carried out further optimization studies using aryl alkene **1** and sulfoxonium ylide **C6** (**2**) as shown in Table 1.

Table 1. Reaction Optimization[a]



entry	deviation from the reaction conditions	3 (%)
1	none	**79 (76[b])**
2	HCO_2H/Et_3N instead of HBpin	<1
3	$(MeO)_3SiH$ instead of HBpin	67
4	**L3** instead of **L2**	54
5	**L4** instead of **L2**	75
6	**L5** instead of **L2**	74
7	w/o **L2**	<1
8	w/o LiCl	52
9	CsF instead of LiCl	<1
10	K_2CO_3 instead of LiCl	21
11	^{i}PrOH instead of H_2O	70
12	PhCl as solvent	59
13	PhMe as solvent	34
14	w/o $NiBr_2$·diglyme	<1
15	w/o H_2O	21
16	w/o HBpin	<1



[a] Reaction conditions: **1** (0.1 mmol), **2** (2.0 equiv), $NiBr_2$·diglyme (10 mol %), **L2** (15 mol %), HBpin (2.0 equiv), LiCl (1.0 equiv), H_2O (2.0 equiv), and PhCl/PhMe (7:3, 1.0 mL) at 25 °C for 12 h under N_2 atmosphere; >20:1 regioselectivity was obtained; yields determined by ^1H NMR using 1,1,2-trichloroethane as an internal standard. [b] Isolated yield.

After extensive screening of reaction parameters (see Supporting Information for details), the β-selective hydroalkylation product **3** was obtained in 79% yield with excellent regioselectivity (>20:1) when employing $NiBr_2$·diglyme (10 mol %) supported by bisoxazoline ligand **L2** (15 mol %), in the presence of HBpin (2.0 equiv) as the hydride source, LiCl (1.0 equiv) as an additive, and H_2O (2.0 equiv) as the proton source, at 25 °C in a PhCl/PhMe (7:3) cosolvent system (entry 1).

Changing the hydride source to HCO_2H/Et_3N completely suppressed product formation (entry 2), whereas using $(MeO)_3SiH$ instead afforded 67% yield of **3** (entry 3). Additional modifications to the ligand structure failed to improve the yield (entries 4−6; see Supporting Information for further details), and no reaction occurred in the absence of ligand (entry 7). Given that sulfoxonium ylides can be converted to carbenes more effectively in the presence of certain additives,[43,82,84−86] we next examined alternative species. In the absence of LiCl, the yield dropped to 52% (entry 8), and other additives such as CsF and K_2CO_3 proved less effective (entries 9 and 10, respectively). Notably, replacing water with isopropanol as the proton source delivered a comparable yield (entry 11). Using either PhCl or PhMe as a single solvent resulted in diminished yields (entries 12 and 13). Control experiments confirmed that the reaction required both the nickel catalyst and HBpin, and that water as proton source was essential for efficient conversion (entries 14−16).

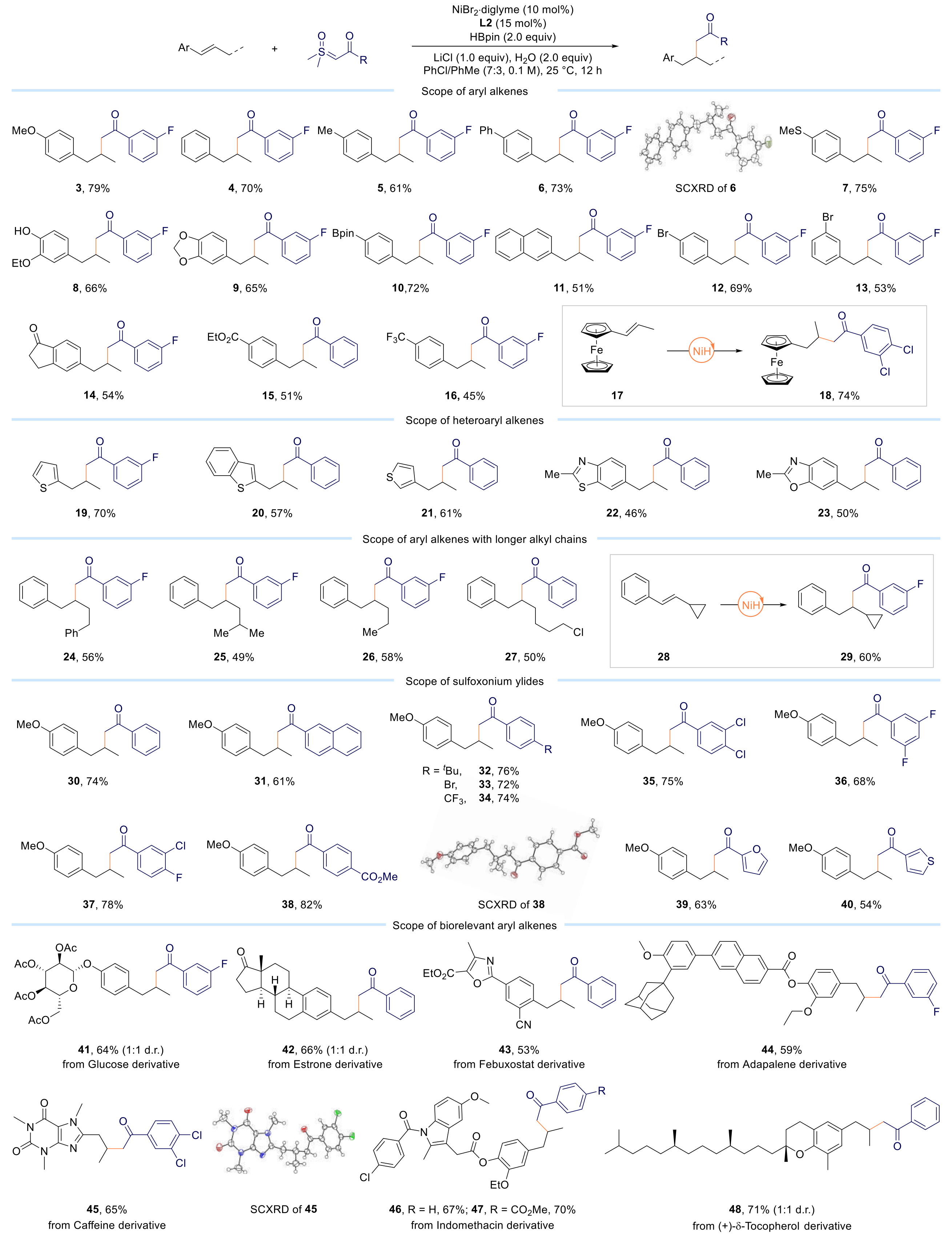
Reaction Scope. Having established the optimized reaction conditions, we next explored the scope of the regioselective homobenzylic hydroalkylation of aryl alkenes (Scheme 3). All substrates tested delivered excellent regioselectivity (>20:1), favoring hydroalkylation at the homobenzylic position over both benzylic hydroalkylation and olefin cyclopropanation pathways. Vinylarenes bearing electron-donating or neutral substituents on the aryl ring, including alkoxy (**3**, **9**), hydrogen (**4**), methyl (**5**), phenyl (**6**), methylthio (**7**), hydroxy (**8**), and Bpin (**10**) groups, were well tolerated, affording the corresponding ketone products in high yields. The structure of product **6** was unambiguously confirmed by single-crystal X-ray diffraction (SCXRD) analysis. Naphthyl-substituted olefins also furnished the desired product in moderate yield (**11**). Electron-withdrawing substituents, such as bromo (**12**, **13**), acyl (**14**), ester (**15**), and trifluoromethyl (**16**) groups, were likewise compatible, delivering the corresponding products in moderate to good yields. Interestingly, a ferrocene derivative **17**, representing a distinct class of organometallic framework, also participated successfully to give product **18** in good yield with high regioselectivity.

Furthermore, heteroaryl alkenes featuring medicinally relevant scaffolds,[89,90] including thiophenes (**19**, **21**), benzothiophene (**20**), benzothiazole (**22**), and benzoxazole (**23**), underwent smooth hydroalkylation to furnish the corresponding products with consistently high regioselectivity. Vinylarenes bearing extended alkyl chains were also amenable to the transformation, affording the corresponding products in moderate yields with excellent regioselectivity. Indeed, substrates containing alkyl chains with additional functional groups, such as phenyl (**24**), alkyl (**25**, **26**), and chloro (**27**) substituents, were well tolerated. Notably, vinylarenes bearing a cyclopropyl group at the β-position underwent alkylation smoothly, delivering the desired products without opening of the cyclopropane ring (**29**).

As sulfoxonium ylides are readily prepared from the corresponding carboxylic acids in two steps and in high yields, we next examined the scope of these carbene precursors by employing various derivatives (**30**−**40**). Benzoyl sulfoxonium ylides bearing diverse substituents on the aryl ring, such as benzofused (**31**), alkyl (**32**), trifluoromethyl (**34**), halides (**33**, **35**−**37**), and ester (**38**) groups, were well accommodated, affording the corresponding ketone products in high yields with excellent regioselectivity. Furthermore, sulfoxonium ylides tethered to heterocycles, such as furan (**39**) and thiophene (**40**), were also tolerable under the optimized conditions. However, the reaction was ineffective with sulfoxonium ylides bearing aliphatic acyl groups (see Supporting Information for details on unsuccessful substrates).

Next, we evaluated the applicability of the present homobenzylic hydroalkylation approach to alkene substrates derived from complex or biologically relevant molecules (**41**−**48**). Significantly, a range of ketone analogues of drugs and natural products were obtained in high yields and with excellent regioselectivity, including derivatives of glucose (**41**), estrone (**42**), febuxostat (**43**), adapalene (**44**), caffeine (**45**), indomethacin (**46**, **47**), and (+)-δ-tocopherol (**48**), thereby demonstrating the high synthetic utility of the current homobenzylic hydroalkylation. The structure of the ketone

Scheme 3. Reaction Scope of NiH-Catalyzed Hydroalkylation of Aryl Alkenes[a]



[a] Reaction conditions: alkene (0.1 mmol), sulfoxonium ylide (2.0 equiv), NiBr$_2$·diglyme (10 mol %), **L2** (15 mol %), HBpin (2.0 equiv), LiCl (1.0 equiv), H$_2$O (2.0 equiv), and PhCl/PhMe (7:3, 1.0 mL) at 25 °C for 12 h under N$_2$ atmosphere; isolated yields are reported; >20:1 regioselectivity was obtained.

product obtained from the caffeine derivative (**45**) was further confirmed by SCXRD analysis.

Mechanistic Investigations. With the broad generality of the NiH-catalyzed homobenzylic hydroalkylation, we next wished to substantiate our proposed mechanistic blueprint. For this investigation, we first performed density functional theory (DFT) calculations based on a catalytic cycle in which Ni(I)−H serves as the active species (Figure 1a), guided by previously reported mechanisms for NiH-catalyzed hydrofunctionalization reactions.[21,22,32−35,39,42,51−54] In fact, consistent with precedents, the calculated energy barrier for direct hydrometalation of NiH into the alkene (**Int1′-TS**, 13.4 kcal/mol) was markedly lower than that for nickel carbenoid formation (**Int1-TS**, 27.7 kcal/mol), favoring a benzylnickel intermediate, in line with the regioselectivity typically observed from NiH insertion into vinylarenes.[20,44] However, in light of the critical role of the sulfoxonium ylide as the carbene precursor, our computational analysis suggests that it may possess a unique chelating property: upon rotation of the sulfoxide moiety toward the nickel center, the sulfoxide oxygen can stabilize the otherwise high-energy transition state for carbene formation. This chelation-promoted carbene activation was predicted to proceed with an energy barrier of 5.9 kcal/mol,[91] indicating that prior activation of the sulfoxonium ylide is also feasible under the current mild conditions. Although activation of either olefin or sulfoxonium ylide was estimated to occur readily, we propose that the excess equivalents and zwitterionic nature of the latter will render nickel carbene formation to be more probable and irreversible. Indeed, multiple literature precedents have documented the coordinating ability of sulfoxonium ylides through their innate resonance-stabilized donor sites.[83,92−94]

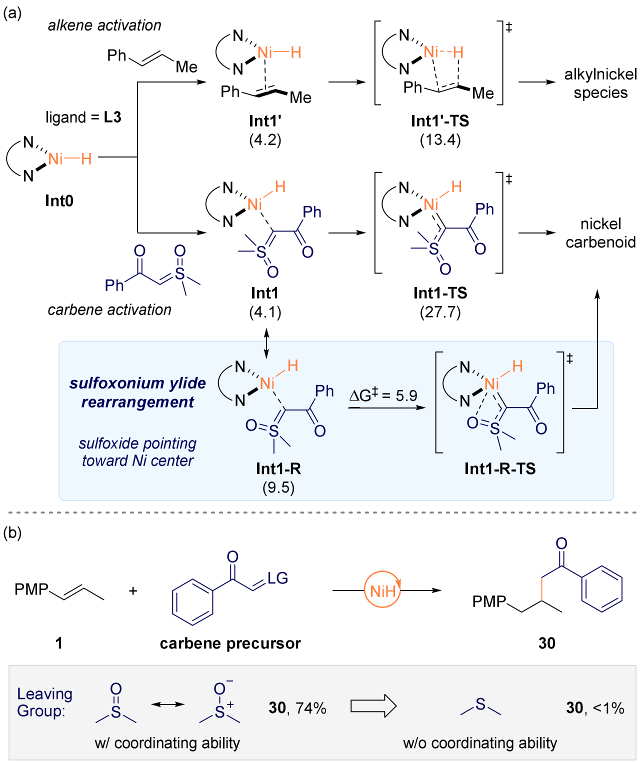


Figure 1. (a) Proposed initial activation modes by NiH, and related energies calculated at the M06/def2-TZVPP+SMD(PhCl)//M06/def2-SVP level of theory (ΔG in kcal/mol). (b) Dependency of carbene precursor leaving group on the reactivity.

To support this proposition, we examined the dependence of the carbene precursor's nature on the desired reactivity (Figure 1b). As with the other well-known carbene precursors that were unsuccessful (Scheme 2), removal of the oxygen atom from the sulfoxide moiety completely suppressed the current reaction. Considering that sulfonium ylides are also frequently employed as carbene precursors,[81−83,86] this leaving-group dependence further supports the importance of a plausible coordination-assisted carbene activation, which indeed enables the transposed sequence.

Having pinpointed the Ni-carbenoid intermediate with radical character as an essential mechanistic element that enables the key regioselective carbene insertion, we sought to experimentally validate this radical nature. Initially, introduction of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) under the standard reaction conditions completely suppressed the formation of the desired product, indicating that the reaction likely proceeds via a radical pathway (Figure 2a). Furthermore, spin-trapping experiments with 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) were performed to detect radical-trapped intermediates by electron paramagnetic resonance (EPR) spectroscopy (Figure 2b). In this case, multiple species were observed, consistent with trapping of a hydride-derived species from NiH or formation of an alkyl-trapped species via the carbene radical. These results corroborate earlier EPR detections of spin-trapped carbene radical species[59,95,96] or analogous intermediates in NiH systems involving alkyl halides.[97]

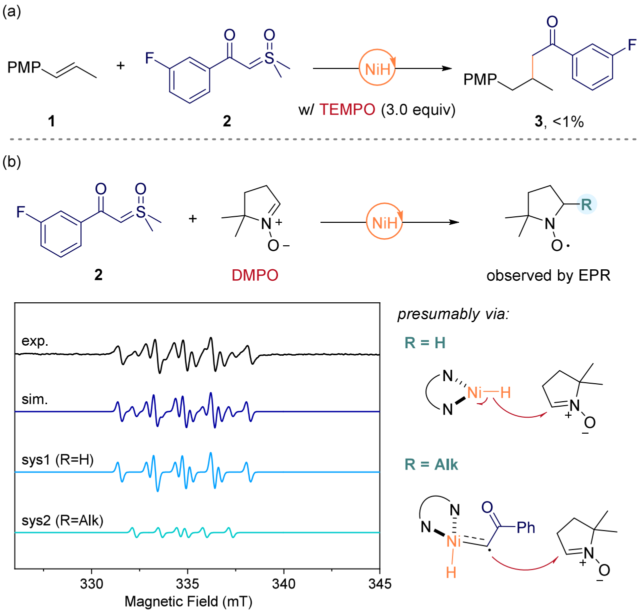
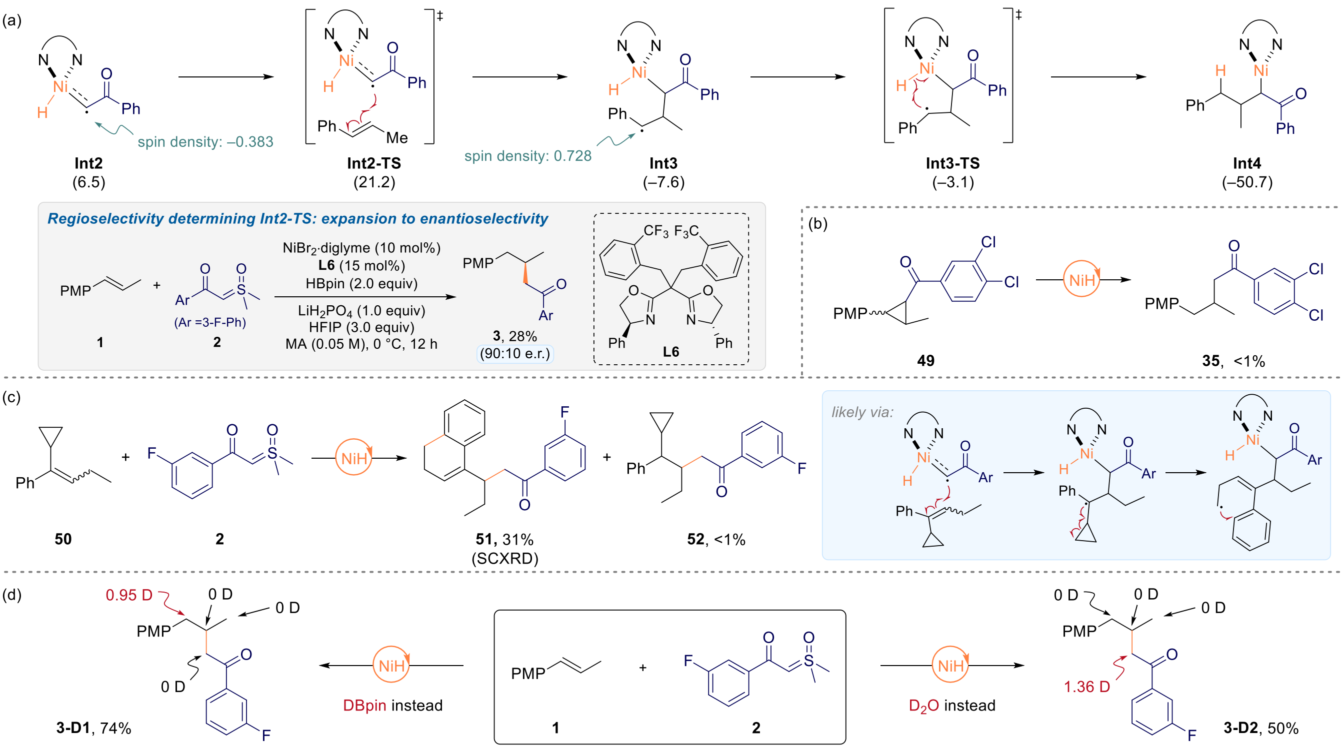


Figure 2. (a) Radical-trap experiment using TEMPO. (b) Experimental EPR spectra of spin-trapped intermediates; simulation parameters for sys1: g_{iso} = 2.007, a^N = 42 MHz, a^H = 52 MHz, a^H = 52 MHz; simulation parameters for sys2: g_{iso} = 2.007, a^N = 38 MHz, a^H = 65 MHz.

Scheme 4. Mechanistic Investigations on Nickel Carbenoid Insertion^a



^{a}(a) Computed pathways of nickel carbenoid insertion and subsequent hydride transfer calculated at the M06/def2-TZVPP+SMD(PhCl)//M06/def2-SVP level of theory (ΔG in kcal/mol); MA, methyl acetate. (b) Radical clock experiment. (c) Investigation on involvement of cyclopropane ring-opening. (d) Deuterium experiments.

On the basis of the proposed nickel carbenoid intermediate possessing radical character, we next scrutinized the subsequent carbene insertion step, where the regioselectivity is established (Scheme 4a). DFT calculations revealed that the nickel carbenoid intermediate **Int2** indeed exhibits radical character, with a spin density of −0.383 on the carbene carbon. Radical insertion of **Int2** into the olefin was calculated to be feasible (**Int2-TS**), with an energy barrier of 14.7 kcal/mol. The resulting Ni−alkyl species **Int3** displays a spin density of 0.728 on the benzylic carbon, indicating that the observed regioselectivity arises from radical stabilization at the benzylic position as expected. Subsequently, the metal hydride transfer process of Ni−H is predicted to occur rapidly, owing to its small energy barrier (**Int3-TS**, 4.5 kcal/mol), to furnish the hydroalkylated nickel species **Int4**.

Providing additional evidence for the regioselectivity-determining step of the nickel carbene radical addition (**Int2-TS**), we sought to examine whether certain chiral ligands may induce enantioselectivity at the homobenzylic carbon center (Scheme 4a, bottom). To evaluate this plausibility, a series of chiral ligands were screened using alkene **1** and sulfoxonium ylide **2** as model substrates under slightly modified conditions. The standard bisoxazoline ligand **L2** provided the desired product in 65% yield with 30% ee, whereas ligand **L6** improved enantioselectivity (90:10 e.r.), but giving rise to low reactivity (28%). These preliminary results support our proposal that olefin insertion of the putative nickel carbene radical intermediate governs both regio- and enantioselectivity. On the other hand, to exclude an alternative pathway of involving cyclopropanation and subsequent ring-opening, when cyclopropane **49** was subjected to the standard conditions, no desired product was detected (Scheme 4b). This observation suggests that the conventional cyclopropanation process is not operative in our present system.

The above-mentioned reaction pathway was corroborated by experimental mechanistic studies. For instance, subjecting aryl alkene **50**, bearing a cyclopropyl group at the styrenyl α-position, to the standard reaction conditions with sulfoxonium ylide **2** afforded the radical ring-opened product **51** in 31% yield (see Supporting Information for its SCXRD analysis), while no product retaining the cyclopropyl group (**52**) was observed (Scheme 4c). This outcome suggests that the reaction will proceed via selective addition of a nickel carbene radical to the styrenyl β-position, generating a benzylic radical intermediate that, in this case, undergoes cyclopropyl ring-opening, radical cyclization, and aromatization (highlighted in blue box).

To further elucidate the proposed mechanistic steps, we performed control experiments with deuterated reagents (Scheme 4d). Substitution of the hydride source with deuterated DBpin resulted in selective deuterium incorporation solely at the benzylic position of the corresponding ketone product **3-D1**. This observation rules out olefin hydronickelation of NiH prior to carbene activation and, therefore, it suggests that the reaction proceeds via an intramolecular metal hydride transfer process. In contrast, using D_2O as the proton source led to exclusive deuterium incorporation at the α-keto position (**3-D2**), indicative of product release through protodemetalation of the postulated Ni-alkyl intermediate (**Int4** in Scheme 4a) in the final step.

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CONCLUSION

In summary, we disclose herein the first example of NiH-catalyzed hydroalkylation of aryl alkenes mediated by a nickel carbene radical, achieving the elusive β-selective hydroalkylation with excellent regioselectivity. The key to this transformation is the preferential engagement of the NiH species with sulfoxonuim ylides to generate a nickel carbene radical, which selectively adds to the styrenyl β-position of the aryl alkene, followed by intramolecular metal hydride transfer and protodemetalation. Using sulfoxonium ylides as bench-stable carbene precursors, the reaction displays broad applicability to diverse alkenes under mild, operationally simple conditions. Combined experimental and computational studies reveal the key mechanistic features of carbene radical intermediacy underlying this transformation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c14594.

> Experimental procedures, characterization data, spectra for all new compounds, crystallographic data, and Cartesian coordinates of all computed structures (PDF)

Accession Codes

Deposition Numbers 2481786−2481788, 2481792, and 2481804 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.

(2) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912−9000.

(3) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A. The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628−2640.

(4) Li, Y.; Lu, X.; Fu, Y. Recent Advances in Cobalt-Catalyzed Regio- or Stereoselective Hydrofunctionalization of Alkenes and Alkynes. *CCS Chem.* **2024**, *6*, 1130−1156.

(5) Liu, L.-X.; Bhat, M.-u.-S.; Li, Y.-L.; Shu, W. Co-catalyzed sp3-sp3 coupling enabled by hydrofunctionalization of alkenes with nucleophiles. *Tetrahedron Chem.* **2025**, *15*, 100142.

(6) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229−1243.

(7) Sun, X.-Y.; Yao, B.-Y.; Xuan, B.; Xiao, L.-J.; Zhou, Q.-L. Recent advances in nickel-catalyzed asymmetric hydrofunctionalization of alkenes. *Chem. Catal.* **2022**, *2*, 3140−3162.

(8) Wang, Y.; He, Y.; Zhu, S. NiH-Catalyzed Functionalization of Remote and Proximal Olefins: New Reactions and Innovative Strategies. *Acc. Chem. Res.* **2022**, *55*, 3519−3536.

(9) Wang, Y.; He, Y.; Zhu, S. Nickel-Catalyzed Migratory Cross-Coupling Reactions: New Opportunities for Selective C-H Functionalization. *Acc. Chem. Res.* **2023**, *56*, 3475−3491.

(10) Yin, X.; Li, S.; Guo, K.; Song, L.; Wang, X. Palladium-Catalyzed Enantioselective Hydrofunctionalization of Alkenes: Recent Advances. *Eur. J. Org. Chem.* **2023**, *26*, No. e202300783.

(11) Pang, X.; Zhao, Z.-Z.; Wei, X.-X.; Qi, L.; Xu, G.-L.; Duan, J.; Liu, X.-Y.; Shu, X.-Z. Regiocontrolled Reductive Vinylation of Aliphatic 1,3-Dienes with Vinyl Triflates by Nickel Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 4536−4542.

(12) Zhang, Z.; Bera, S.; Fan, C.; Hu, X. Streamlined Alkylation via Nickel-Hydride-Catalyzed Hydrocarbonation of Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 7015−7029.

(13) Yang, P.-F.; Shu, W. Asymmetric alkyl-alkyl cross-coupling enabled by earth-abundant metal-catalyzed hydroalkylations of olefins. *Chem. Catal.* **2023**, *3*, 100508.

(14) Li, Y.; Liu, D.; Hu, X.; Zhang, J.-Y.; Zhu, Q.-W.; Men, B.; Gao, G.-W.; Chen, P.-W.; Tong, Y.-Z.; Chang, Z.; Li, Z.; Lu, X.; Fu, Y. Enantioselective alkene hydroalkylation overcoming heteroatom constraints via cobalt catalysis. *Nat. Synth.* **2024**, *3*, 1134−1144.

(15) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *MedChemComm* **2013**, *4*, 515−519.

(16) Caplin, M. J.; Foley, D. J. Emergent synthetic methods for the modular advancement of sp^3-rich fragments. *Chem. Sci.* **2021**, *12*, 4646−4660.

(17) Wang, Y.-M.; Buchwald, S. L. Enantioselective CuH-Catalyzed Hydroallylation of Vinylarenes. *J. Am. Chem. Soc.* **2016**, *138*, 5024−5027.

(18) Dong, Y.; Shin, K.; Mai, B. K.; Liu, P.; Buchwald, S. L. Copper Hydride-Catalyzed Enantioselective Olefin Hydromethylation. *J. Am. Chem. Soc.* **2022**, *144*, 16303−16309.

(19) You, Y. e.; Pham, Q. V.; Ge, S. Copper-Catalyzed Asymmetric Formal Hydroaminomethylation of Alkenes with N,O-Acetals to Access Chiral β-Stereogenic Amines: Dual Functions of the Copper Catalyst. *CCS Chem.* **2019**, *1*, 455−463.

(20) Kong, L.; Gan, X.-c.; van der Puyl Lovett, V. A.; Shenvi, R. A. Alkene Hydrobenzylation by a Single Catalyst That Mediates Iterative Outer-Sphere Steps. *J. Am. Chem. Soc.* **2024**, *146*, 2351−2357.

(21) Wang, J.-W.; Zhu, Q.-W.; Liu, D.; Chen, P.-W.; Chen, H.-Z.; Lu, X.; Fu, Y. Nickel-Catalyzed α-selective Hydroalkylation of Vinylarenes. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202413074.

(22) Zhou, F.; Zhu, J.; Zhang, Y.; Zhu, S. NiH-Catalyzed Reductive Relay Hydroalkylation: A Strategy for the Remote C(sp^{3})-H Alkylation of Alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 4058−4062.

(23) Zhou, F.; Zhang, Y.; Xu, X.; Zhu, S. NiH-Catalyzed Remote Asymmetric Hydroalkylation of Alkenes with Racemic α-Bromo Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 1754−1758.

(24) Sun, S.-Z.; Börjesson, M.; Martin-Montero, R.; Martin, R. Site-Selective Ni-Catalyzed Reductive Coupling of α-Haloboranes with Unactivated Olefins. *J. Am. Chem. Soc.* **2018**, *140*, 12765−12769.

(25) Zhang, L.; Wang, H.; Santiago, T. G.; Yue, W.-J.; Martin, R. Photoinduced nickel-catalysed enantioconvergent sp^3-sp^3 coupling of unactivated olefins and aziridines. *Nat. Catal.* **2025**, *8*, 348−356.

(26) Gao, Y.; Yang, C.; Bai, S.; Liu, X.; Wu, Q.; Wang, J.; Jiang, C.; Qi, X. Visible-Light-Induced Nickel-Catalyzed Cross-Coupling with Alkylzirconocenes from Unactivated Alkenes. *Chem.* **2020**, *6*, 675−688.

(27) Sun, S.-Z.; Cai, Y.-M.; Zhang, D.-L.; Wang, J.-B.; Yao, H.-Q.; Rui, X.-Y.; Martin, R.; Shang, M. Enantioselective Deaminative Alkylation of Amino Acid Derivatives with Unactivated Olefins. *J. Am. Chem. Soc.* **2022**, *144*, 1130−1137.

(28) Liu, J.; Gong, H.; Zhu, S. Nickel-Catalyzed, Regio- and Enantioselective Benzylic Alkenylation of Olefins with Alkenyl Bromide. *Angew. Chem., Int. Ed.* **2021**, *60*, 4060−4064.

(29) Jiang, X.; Han, B.; Xue, Y.; Duan, M.; Gui, Z.; Wang, Y.; Zhu, S. Nickel-catalysed migratory hydroalkynylation and enantioselective hydroalkynylation of olefins with bromoalkynes. *Nat. Commun.* **2021**, *12*, 3792.

(30) Xiao, L.-J.; Cheng, L.; Feng, W.-M.; Li, M.-L.; Xie, J.-H.; Zhou, Q.-L. Nickel(0)-Catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoboron Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 461−464.

(31) Du, Y.-M.; Chen, X.-Y.; Li, Y.; Koh, M. J.; Shu, W. Rapid assembly of enantioenriched α-arylated ketones via Ni-catalyzed asymmetric cross-hydrocarbonylation enabled by alkene sorting. *Nat. Commun.* **2025**, *16*, 4163.

(32) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C-H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1061−1064.

(33) Zhang, Y.; Xu, X.; Zhu, S. Nickel-catalysed selective migratory hydrothiolation of alkenes and alkynes with thiols. *Nat. Commun.* **2019**, *10*, 1752.

(34) Zhang, Y.; He, J.; Song, P.; Wang, Y.; Zhu, S. Ligand-Enabled NiH-Catalyzed Migratory Hydroamination: Chain Walking as a Strategy for Regiodivergent/Regioconvergent Remote sp^{3}C−H Amination. *CCS Chem.* **2021**, *3*, 2259−2268.

(35) He, Y.; Ma, J.; Song, H.; Zhang, Y.; Liang, Y.; Wang, Y.; Zhu, S. Regio- and enantioselective remote hydroarylation using a ligand-relay strategy. *Nat. Commun.* **2022**, *13*, 2471.

(36) He, J.; Song, P.; Xu, X.; Zhu, S.; Wang, Y. Migratory Reductive Acylation between Alkyl Halides or Alkenes and Alkyl Carboxylic Acids by Nickel Catalysis. *ACS Catal.* **2019**, *9*, 3253−3259.

(37) Du, Y.-M.; Lin, J.-N.; Li, Y.-L.; Yu, Q.; Shu, W. Nickel-Catalyzed Adaptive Migration-Enabled Asymmetric Cross-Hydrocarbonylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2025**, *147*, 18944−18952.

(38) Sun, S.-Z.; Romano, C.; Martin, R. Site-Selective Catalytic Deaminative Alkylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 16197−16201.

(39) Wang, Z.-Y.; Wan, J.-H.; Wang, G.-Y.; Wang, R.; Jin, R.-X.; Lan, Q.; Wang, X.-S. Terminal C(sp^{3})H alkylation of internal alkenes via Ni/H-catalyzed isomerization. *Tetrahedron Lett.* **2018**, *59*, 2302−2305.

(40) Yu, X.; Zhao, H.; Xi, S.; Chen, Z.; Wang, X.; Wang, L.; Lin, L. Q. H.; Loh, K. P.; Koh, M. J. Site-selective alkene borylation enabled by synergistic hydrometallation and borometallation. *Nat. Catal.* **2020**, *3*, 585−592.

(41) Zhang, Q.; Wang, S.; Yin, J.; Xiong, T.; Zhang, Q. Remote Site-Selective Asymmetric Protoboration of Unactivated Alkenes Enabled by Bimetallic Relay Catalysis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202202713.

(42) Lyu, X.; Jeon, E.; Seo, C.; Kim, D.; Chang, S. Nickel-Catalyzed Asymmetric Homobenzylic Hydroamidation of Aryl Alkenes to Access Chiral β-Arylamides. *J. Am. Chem. Soc.* **2025**, *147*, 8928−8938.

(43) Wang, Q.; Kweon, J.; Kim, D.; Chang, S. Remote Catalytic C(sp^{3})H Alkylation via Relayed Carbenoid Transfer upon Olefin Chain Walking. *J. Am. Chem. Soc.* **2024**, *146*, 31114−31123.

(44) Kvasovs, N.; Iziumchenko, V.; Sterling, A. J.; Gevorgyan, V. Nickel-Catalyzed Branched Hydroalkylation of Alkenes with Diazo Compounds. *J. Am. Chem. Soc.* **2025**, *147*, 8093−8100.

(45) Karmakar, U.; Bae, J.; Kim, J. A.; Kim, S.; Yang, W.-G.; Cho, E. J. Nickel-Catalyzed Regio- and Stereoselective Hydroalkylation of Allenes: Exploiting the Unique Reactivity of Diazo Compounds as an Alkylating Source. *ACS Catal.* **2024**, *14*, 16570−16576.

(46) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. Experimental Evidence for Cobalt(III)-Carbene Radicals: Key Intermediates in Cobalt(II)-Based Metalloradical Cyclopropanation. *J. Am. Chem. Soc.* **2011**, *133*, 8518−8521.

(47) Giedyk, M.; Goliszewska, K.; ó Proinsias, K.; Gryko, D. Cobalt(i)-catalysed CH-alkylation of terminal olefins, and beyond. *Chem. Commun.* **2016**, *52*, 1389−1392.

(48) Epping, R. F. J.; Hoeksma, M. M.; Bobylev, E. O.; Mathew, S.; de Bruin, B. Cobalt(II)-tetraphenylporphyrin-catalysed carbene transfer from acceptor-acceptor iodonium ylides via N-enolate-carbene radicals. *Nat. Chem.* **2022**, *14*, 550−557.

(49) Das, B. G.; Chirila, A.; Tromp, M.; Reek, J. N. H.; de Bruin, B. CoIII-Carbene Radical Approach to Substituted 1H-Indenes. *J. Am. Chem. Soc.* **2016**, *138*, 8968−8975.

(50) Epping, R. F. J.; Vesseur, D.; Zhou, M.; de Bruin, B. Carbene Radicals in Transition-Metal-Catalyzed Reactions. *ACS Catal.* **2023**, *13*, 5428−5448.

(51) Lyu, X.; Zhang, J.; Kim, D.; Seo, S.; Chang, S. Merging NiH Catalysis and Inner-Sphere Metal-Nitrenoid Transfer for Hydroamidation of Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 5867−5877.

(52) Choi, H.; Lyu, X.; Kim, D.; Seo, S.; Chang, S. Endo-Selective Intramolecular Alkyne Hydroamidation Enabled by NiH Catalysis Incorporating Alkenylnickel Isomerization. *J. Am. Chem. Soc.* **2022**, *144*, 10064−10074.

(53) Lyu, X.; Seo, C.; Jung, H.; Faber, T.; Kim, D.; Seo, S.; Chang, S. Intramolecular hydroamidation of alkenes enabling asymmetric synthesis of β-lactams via transposed NiH catalysis. *Nat. Catal.* **2023**, *6*, 784−795.

(54) Lyu, X.; Jung, H.; Kim, D.; Chang, S. Enantioselective Access to β-Amino Carbonyls via Ni-Catalyzed Formal Olefin Hydroamidation. *J. Am. Chem. Soc.* **2024**, *146*, 14745−14753.

(55) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-amino Acid. *J. Am. Chem. Soc.* **1996**, *118*, 6897−6907.

(56) Davies, H. M. L.; Antoulinakis, E. G. Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. In *Organic Reactions*; 2001; pp 1−326.

(57) Morandi, B.; Carreira, E. M. Iron-Catalyzed Cyclopropanation in 6 M KOH with in Situ Generation of Diazomethane. *Science* **2012**, *335*, 1471−1474.

(58) Xu, X.; Zhu, S.; Cui, X.; Wojtas, L.; Zhang, X. P. Cobalt(II)-Catalyzed Asymmetric Olefin Cyclopropanation with α-Ketodiazoacetates. *Angew. Chem., Int. Ed.* **2013**, *52*, 11857−11861.

(59) Lee, W.-C. C.; Wang, D.-S.; Zhu, Y.; Zhang, X. P. Iron(III)-based metalloradical catalysis for asymmetric cyclopropanation via a stepwise radical mechanism. *Nat. Chem.* **2023**, *15*, 1569−1580.

(60) Ke, J.; Lee, W.-C. C.; Wang, X.; Wang, Y.; Wen, X.; Zhang, X. P. Metalloradical Activation of In Situ-Generated α-Alkynyldiazomethanes for Asymmetric Radical Cyclopropanation of Alkenes. *J. Am. Chem. Soc.* **2022**, *144*, 2368−2378.

(61) Chan, K.-H.; Guan, X.; Lo, V. K.-Y.; Che, C.-M. Elevated Catalytic Activity of Ruthenium(II)-Porphyrin-Catalyzed Carbene/Nitrene Transfer and Insertion Reactions with N-Heterocyclic Carbene Ligands. *Angew. Chem., Int. Ed.* **2014**, *53*, 2982−2987.

(62) Pal, S.; Zhou, Y.-Y.; Uyeda, C. Catalytic Reductive Vinylidene Transfer Reactions. *J. Am. Chem. Soc.* **2017**, *139*, 11686−11689.

(63) Berger, K. E.; Martinez, R. J.; Zhou, J.; Uyeda, C. Catalytic Asymmetric Cyclopropanations with Nonstabilized Carbenes. *J. Am. Chem. Soc.* **2023**, *145*, 9441−9447.

(64) Liu, M.; Le, N.; Uyeda, C. Nucleophilic Carbenes Derived from Dichloromethane. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202308913.

(65) Liu, M.; Uyeda, C. Redox Approaches to Carbene Generation in Catalytic Cyclopropanation Reactions. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202406218.

(66) Janabel, J.; Kumar, D.; Kanale, V. V.; Liu, M.; Uyeda, C. Catalytic Asymmetric Synthesis of Axially Chiral Methylenecyclopropanes. *J. Am. Chem. Soc.* **2025**, *147*, 23270−23276.

(67) Caló, F. P.; Zimmer, A.; Bistoni, G.; Fürstner, A. From Serendipity to Rational Design: Heteroleptic Dirhodium Amidate Complexes for Diastereodivergent Asymmetric Cyclopropanation. *J. Am. Chem. Soc.* **2022**, *144*, 7465−7478.

(68) Cai, B.-G.; Empel, C.; Jana, S.; Xuan, J.; Koenigs, R. M. Catalytic Olefin Cyclopropanation with In Situ-Generated Dialkyl Diazomethanes via Co(II)-Based Metalloradical Catalysis. *ACS Catal.* **2023**, *13*, 11851−11856.

(69) Liu, H.-L.; Wang, X.; Gao, K.; Wang, Z. Catalytic Diastereo- and Enantioselective Cyclopropanation of gem-Dihaloalkanes and Terminal Olefins. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305987.

(70) Wang, X.; Shi, Z.; Xu, M.; Lin, X.; Wang, Z. Asymmetric Radical Cyclopropanation of α,β-Unsaturated Amides with α-Boryl and α-Silyl Dibromomethanes via Cr(II)-Based Metalloradical Catalysis. *J. Am. Chem. Soc.* **2025**, *147*, 7282−7292.

(71) Sakurai, S.; Inagaki, T.; Kodama, T.; Yamanaka, M.; Tobisu, M. Palladium-Catalyzed Siloxycyclopropanation of Alkenes Using Acylsilanes. *J. Am. Chem. Soc.* **2022**, *144*, 1099−1105.

(72) Han, F.; Xie, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. Chiral-at-Ru Catalyst with Cyclometalated Imidazo[1,5-a]pyridin-ylidene for Enantioselective Intramolecular Cyclopropanations. *Synlett* **2023**, *34*, 1403−1408.

(73) Zhu, S.-F.; Zhou, Q.-L. Transition-Metal-Catalyzed Enantioselective Heteroatom-Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365−1377.

(74) Yang, J.-M.; Guo, F.-K.; Zhao, Y.-T.; Zhang, Q.; Huang, M.-Y.; Li, M.-L.; Zhu, S.-F.; Zhou, Q.-L. Insertion of Alkylidene Carbenes into B-H Bonds. *J. Am. Chem. Soc.* **2020**, *142*, 20924−20929.

(75) Yang, L.-L.; Evans, D.; Xu, B.; Li, W.-T.; Li, M.-L.; Zhu, S.-F.; Houk, K. N.; Zhou, Q.-L. Enantioselective Diarylcarbene Insertion into Si-H Bonds Induced by Electronic Properties of the Carbenes. *J. Am. Chem. Soc.* **2020**, *142*, 12394−12399.

(76) Zhao, X.; Wang, G.; Hashmi, A. S. K. Carbene B-H Insertion Reactions for C-B Bond Formation. *ChemCatChem.* **2021**, *13*, 4299−4312.

(77) Chen, F.; Zhang, Q.; Li, Y.; Yu, Z.-X.; Chu, L. Selective Hydrofunctionalization of Alkenyl Fluorides Enabled by Nickel-Catalyzed Hydrogen Atoms and Group Transfer: Reaction Development and Mechanistic Study. *J. Am. Chem. Soc.* **2024**, *146*, 11418−11431.

(78) Chen, F.; Zhao, X.; Miao, W.; Li, Y.; Yuan, Y.; Chu, L. Regio- and enantioselective hydrofluorination of internal alkenes via nickel-catalyzed hydrogen atom transfer. *Chin. Chem. Lett.* **2025**, *36*, 110239.

(79) Song, P.; Zhu, S. Nickel-Catalyzed Hydrofluorination of Unactivated Alkenes through a HAT Pathway. *ACS Catal.* **2020**, *10*, 13165−13170.

(80) Yao, C.; Wang, S.; Norton, J.; Hammond, M. Catalyzing the Hydrodefluorination of CF_3-Substituted Alkenes by $PhSiH_3$. H• Transfer from a Nickel Hydride. *J. Am. Chem. Soc.* **2020**, *142*, 4793−4799.

(81) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. Sulfoxonium and Sulfonium Ylides as Diazocarbonyl Equivalents in Metal-Catalyzed Insertion Reactions. *Eur. J. Org. Chem.* **2013**, *2013*, 5005−5016.

(82) Lu, L.-Q.; Li, T.-R.; Wang, Q.; Xiao, W.-J. Beyond sulfide-centric catalysis: recent advances in the catalytic cyclization reactions of sulfur ylides. *Chem. Soc. Rev.* **2017**, *46*, 4135−4149.

(83) Neuhaus, J. D.; Oost, R.; Merad, J.; Maulide, N. Sulfur-Based Ylides in Transition-Metal-Catalysed Processes. *Top. Curr. Chem.* **2018**, *376*, 15.

(84) Wu, X.; Sun, S.; Yu, J.-T.; Cheng, J. Recent Applications of α-Carbonyl Sulfoxonium Ylides in Rhodium- and Iridium-Catalyzed C-H Functionalizations. *Synlett* **2019**, *30*, 21−29.

(85) Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. Sulfoxonium ylides: simple compounds with chameleonic reactivity. *Org. Biomol. Chem.* **2020**, *18*, 8793−8809.

(86) Kumar, M.; Sadaf, I.; Pamidighantam, J.; Anamika; Kumar, S. Recent advance: Sulfur ylides in organic synthesis. *J. Heterocycl. Chem.* **2024**, *61*, 29−70.

(87) Moss, R. A. Diazirines: Carbene Precursors Par Excellence. *Acc. Chem. Res.* **2006**, *39*, 267−272.

(88) Cormier, S. K.; Foscato, M.; Ferguson, M. J.; Jensen, V. R.; Baker, R. T.; Fogg, D. E. Elementary Steps in Olefin Metathesis: Nickelacyclobutanes via Cycloaddition to Nickel Carbenes. *J. Am. Chem. Soc.* **2025**, *147*, 24225−24229.

(89) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(90) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348−1349.

(91) The energy barrier for the chelation-promoted carbene activation was estimated by a potential energy surface scan, which revealed that oxygen coordination to the nickel center occurs only along the activation pathway, but not in the ground or product states; see Supporting Information for details.

(92) Koezuka, H.; Matsubayashi, G.; Tanaka, T. Ylide-metal complex. Preparations and structures of palladium(II) and platinum(II) halide complexes with a stable sulfur ylide. *Inorg. Chem.* **1974**, *13*, 443−446.

(93) Fackler, J. P., Jr.; Paparizos, C. Trimethylgold(III) complexes of reactive sulfoxonium and sulfonium ylides. *J. Am. Chem. Soc.* **1977**, *99*, 2363−2364.

(94) Singh, A.; Kumar, S.; Volla, C. M. R. α-Carbonyl sulfoxonium ylides in transition metal-catalyzed C-H activation: a safe carbene precursor and a weak directing group. *Org. Biomol. Chem.* **2023**, *21*, 879−909.

(95) Li, F.; Xiao, L.; Liu, L. Metal-Diazo Radicals of α-Carbonyl Diazomethanes. *Sci. Rep.* **2016**, *6*, 22876.

(96) Tan, L.; Boehme, M.; Papworth, L.; Wu, K.; Qiu, Y.; Li, G. Highly Diastereoselective Radical Cyclopropanation of Olefins via Cobaloxime-Based Metalloradical Catalysis. *Eur. J. Org. Chem.* **2025**, *28*, No. e202401069.

(97) Wang, X.-X.; Yu, L.; Lu, X.; Zhang, Z.-L.; Liu, D.-G.; Tian, C.; Fu, Y. NiH-Catalyzed Reductive Hydrocarbonation of Enol Esters and Ethers. *CCS Chem.* **2022**, *4*, 605−615.