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Transition-Metal Hydride Catalysis Meets Nitrenoid Transfer: Design Principles for Precision C−N Bond Formation

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Cite This: *Acc. Chem. Res.* 2026, 59, 1215−1226
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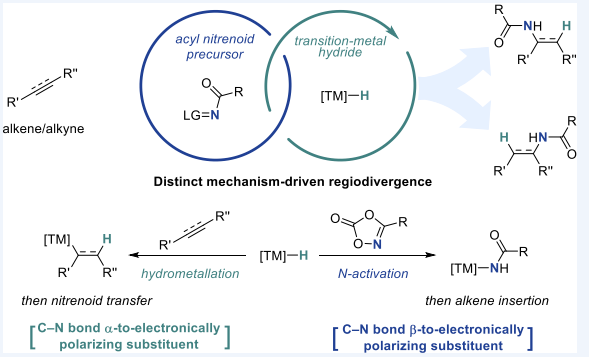
CONSPECTUS: Transition-metal hydride (TMH) catalysis has become a powerful strategy for hydroamination reactions, enabling direct C−N bond formation from simple alkenes and alkynes under mild conditions. In conventional TMH-catalyzed hydroamination, a metal hydride first engages a π system through hydrometalation or related hydrogen-atom-transfer processes to generate organometallic intermediates, wherein stabilization of the incipient carbon center dictates regioselectivity. As a consequence, subsequent coupling with a nitrogen electrophile intrinsically favors C−N bond formation at electronically activated positions. Accordingly, regioselectivity patterns such as α-amination adjacent to electronically polarizing substituents, directing-group-controlled sites, or sterically accessible terminal positions following migration are well-established, whereas complementary β-selective amination remains challenging to achieve.



This Account summarizes our efforts to merge TMH catalysis with nitrenoid transfer chemistry and, in doing so, to uncover two distinct and mechanistically orthogonal hydroamidation regimes governed by the ordering of elementary steps. Using bench-stable dioxazolones as acyl nitrenoid precursors, we first established a canonical TMH manifold in which hydrometalation precedes inner-sphere nitrenoid transfer. In this regime, regioselectivity is programmed at the metal hydride insertion stage and can be predictably controlled across a wide range of TMH catalytic systems, enabling regioselective hydroamidation of alkynes and alkenes with broad scope and high functional-group compatibility.

A conceptual turning point emerged from mechanistic studies of NiH catalysis, where an unexpected β-selective intramolecular hydroamidation exposed a fundamentally different reaction manifold. Rather than initiating with hydrometalation, NiH was found to activate the nitrenoid precursor first, generating a Ni-amido intermediate that subsequently engages the alkene through polarity-matched amidonickelation. This transposed hydroamidation regime inverts the selectivity-determining step, shifting control from alkene hydrometalation to C−N bond formation. As a result, regioselectivity patterns inaccessible under conventional TMH logic, including β-lactam formation, intermolecular β-amidation of conjugated carbonyls, and homobenzylic hydroamidation of vinylarenes, become attainable with high enantioselectivity.

Together, these studies establish step order as a central design parameter in TMH-catalyzed hydroamidation. By deliberately choosing whether hydride delivery or nitrenoid generation occurs first, complementary regio- and stereochemical outcomes can be accessed from the same classes of unsaturated substrates. Beyond nitrenoid chemistry, extension of this transposed logic to carbene transfer processes further underscores its generality. We anticipate that continued mechanistic elucidation and expansion of this framework will transform TMH−nitrenoid synergy from a collection of reactions into a predictive platform for precision C−N bond construction.

KEY REFERENCES

- 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.[1] *This work establishes the merger of NiH catalysis with inner-sphere nickel-nitrenoid transfer, enabling umpolung hydroamidation of alkynes.*
- 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.[2]

Received: January 13, 2026
Revised: March 2, 2026
Accepted: March 5, 2026
Published: March 18, 2026

https://doi.org/10.1021/acs.accounts.6c00040
Acc. Chem. Res. 2026, 59, 1215−1226

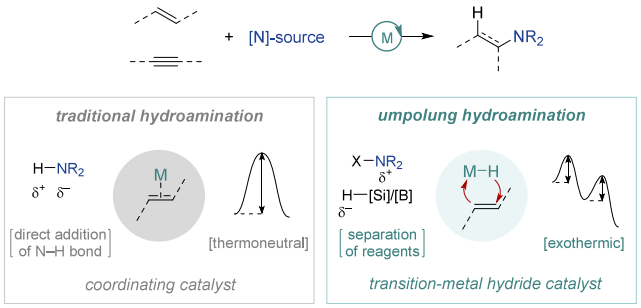
This work introduces transposed NiH catalysis, in which initial N-activation of dioxazolones precedes hydride insertion, enabling enantioselective β-lactam formation through amidonickelation pathways inaccessible under conventional transition-metal hydride catalysis.

- Lyu, X.; Jung, H.; Kim, D.; Chang, S. Enantioselective Access to β-Amino Carbonyls via a Ni-Catalyzed Formal Olefin Hydroamidation. *J. Am. Chem. Soc.* **2024**, *146*, 14745−14753.[3] *This work extends transposed NiH catalysis to α,β-unsaturated carbonyl compounds, enabling enantioselective β-amidation and overcoming the intrinsic limitations of amide Michael addition.*
- 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.[4] *This work demonstrates that transposed NiH catalysis enables regioreversed and enantioselective homobenzylic C−N bond formation through amidonickelation.*

1. INTRODUCTION

The formation of carbon−nitrogen bonds is central to the synthesis of pharmaceuticals, agrochemicals, and functional materials, motivating sustained interest in catalytic hydroamination reactions that directly convert abundant unsaturated feedstocks into value-added amine derivatives.[5−7] Classical hydroamination refers to the direct addition of an N−H bond across a carbon−carbon π system without the need for prefunctionalized carbon electrophiles or stoichiometric activating agents (Scheme 1, left).[8,9] While elegant in principle, such direct hydroamination remains challenging because this process is typically thermoneutral and requires the simultaneous activation of both the alkene/alkyne and the amine, each of which is intrinsically electron rich.[10] As a result, achieving broad substrate scope and high selectivity under mild conditions has proven difficult.

Scheme 1. Traditional and Umpolung Hydroamination of Unsaturated Bonds



More recent advances have therefore shifted toward stepwise catalytic manifolds, most notably those involving transition-metal hydride (TMH) catalysis (Scheme 1, right).[11,12] In these reactions, a metal hydride species first undergoes hydrometalation of the π system to generate a nucleophilic alkyl-/alkenylmetal intermediate, which is subsequently intercepted by a nitrogen electrophile. In principle, TMH catalysis provides an attractive platform for hydroamination because hydrometalation enables the controlled generation of well-defined organometallic intermediates, thereby offering a handle for regio- and chemoselectivity. This *umpolung* hydroamination strategy relies on the use of distinct, high-energy reagents for hydride and nitrogen transfer, separating the two elementary steps that are intrinsically coupled in classical hydroamination. Such stepwise separation replaces the classically thermoneutral hydroamination coordinate with energetically downhill hydride- and nitrogen-transfer steps, while also improving kinetic control and enabling hydroamination under remarkably mild conditions. Since the seminal contributions by Buchwald[13] and by Hirano and Miura,[14] TMH catalysis employing a diverse array of metals has been developed to enable hydroamination reactions with high selectivity and functional-group compatibility.

Despite this progress, extending these strategies to hydroamidation, the formal installation of hydrogen and an amide group across a π system, poses additional challenges. In conventional hydroamidation, the inherently lower nucleophilicity of amide derivatives compared to amines renders their addition to alkenes, which are poor π acceptors, particularly difficult. TMH-catalyzed hydroamidation, however, is uniquely positioned to address this limitation because it relies on electrophilic nitrogen reagents to engage hydrometalated intermediates. In this context, acyl nitrenoids represent appealing electrophiles owing to their high intrinsic reactivity and the availability of robust nitrene precursors, such as dioxazolones, which are readily accessible from carboxylic acids and exhibit excellent stability.[15] Nevertheless, in contrast to the extensive body of work on nitrenoid-mediated C−H amidation,[16−19] TMH-catalyzed hydroamidation reactions have remained comparatively underdeveloped.

Against this backdrop, and building on our group's long-standing interest in acyl nitrenoid transfer chemistry,[20,21] we initiated a research program aimed at merging TMH catalysis with acyl nitrenoid transfer to realize hydroamidation reactions (Scheme 2). Our initial discovery of NiH-catalyzed hydroamidation of alkynes established a canonical TMH-driven manifold in which regioselectivity is dictated by hydrometalation, leading to predictable C−N bond formation adjacent to electronically polarizing substituents. This reactivity paradigm was subsequently expanded to other transition-metal hydride systems. During these studies, however, we unexpectedly observed a reversed, β-selective regioselectivity in certain NiH-catalyzed reactions that contradicted established hydrometalation logic. This serendipitous deviation prompted detailed mechanistic investigation and ultimately revealed an inverted catalytic regime in which nitrenoid formation precedes hydrometalation, generating a Ni-amido intermediate capable of amidonickelation.

This Account surveys recent progress in TMH-catalyzed hydroamidation reactions based on nitrenoid transfer, with particular emphasis on how positional selectivity can be programmably controlled through catalyst design and reaction sequencing. We highlight the mechanistic foundations, selectivity-determining features, and synthetic implications of the bifurcation between canonical hydrometalation-first pathways and transposed, N-activation-first regimes, and we outline the broader opportunities that emerge from this merged catalytic paradigm.

2. CANONICAL TMH-CATALYZED HYDROAMIDATION VIA NITRENOID TRANSFER

The mechanistic foundation of this Account traces back to our discovery that NiH catalysis can be merged with inner-sphere acyl nitrenoid transfer to enable hydroamidation. This

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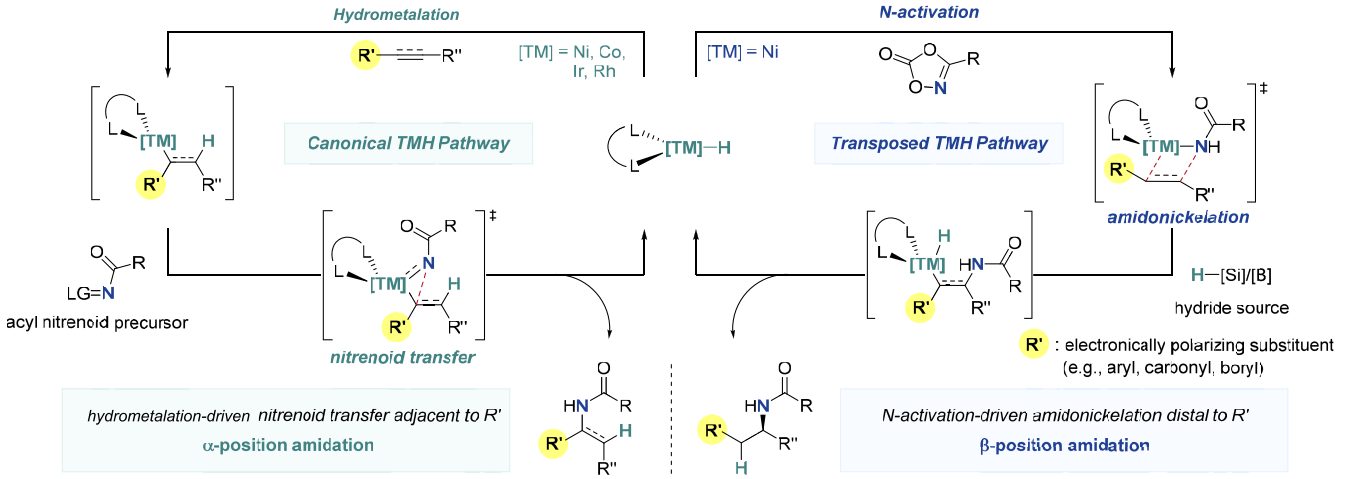
Scheme 2. Overview of Transition-Metal Hydride Catalysis Incorporating Nitrenoid Transfer



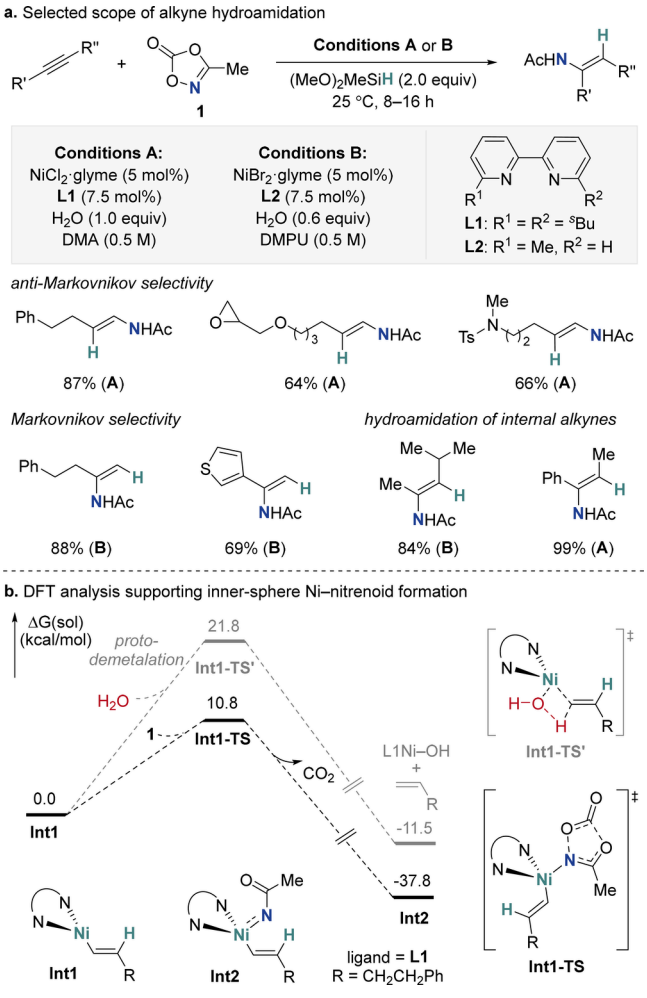
reactivity defines a canonical TMH-driven manifold in which hydrometalation of a π system precedes interception by an electrophilic acyl nitrenoid, resulting in regioselectivity governed by the intrinsic preferences of metal hydride insertion. On this basis, a series of hydroamidation reactions were subsequently developed across distinct metal hydride systems, as discussed in the following sections.

2.1. NiH-Catalyzed Alkyne Hydroamidation

While Buchwald demonstrated that dioxazolones can engage in CuH-catalyzed hydroamidation of vinylarenes, proposed to proceed through N−O bond oxidative addition followed by C−N reductive elimination,[22] the rapid development of NiH-catalyzed hydrofunctionalization positioned nickel hydrides as a particularly attractive platform for exploring alternative modes of nitrogen incorporation.[23−28] In this regard, we sought to develop a NiH-catalyzed hydroamidation reaction based on electrophilic nitrenoid precursors. Initial attempts toward alkyne hydroamidation employing common nitrene precursors, such as organic azides and *N*-benzoyloxyamides, were unsuccessful, leading predominantly to unreacted starting materials or competitive alkyne reduction. A key breakthrough emerged with the identification of dioxazolones as uniquely competent nitrogen-transfer reagents, enabling productive coupling without excessive reduction or catalyst deactivation.

In 2021, using this strategy, we disclosed the NiH-catalyzed hydroamidation of alkynes that proceeds through a canonical hydrometalation-triggered, inner-sphere nitrenoid transfer pathway (Scheme 3a).[1] In this reaction manifold, regioselectivity is established during *syn* hydrometalation of the alkyne, and steric modulation of the ligand environment enables access to both *anti*-Markovnikov- and Markovnikov-selective enamide products. Density functional theory (DFT) calculations supported the proposed mechanism, revealing that the in situ generated vinylnickel intermediate preferentially activates the dioxazolone rather than undergoing protodemetalation (Scheme 3b). This behavior contrasts sharply with previously reported Cu- or Co-based systems,[29,30] which proceed through cascade alkyne semireduction followed by hydroamination to afford alkylamines, and rationalizes the feasibility of inner-sphere acyl nitrenoid transfer under NiH catalysis. Consistent with this proposal, the intermediacy of a Ni-nitrenoid species

Scheme 3. NiH-Catalyzed Hydroamidation of Alkynes



was further supported by nitrenoid-trapping experiments using phosphine additives.

While the reaction proceeds under mild conditions, the presence of water was found to be essential for achieving high catalytic turnover. Given that protic additives are frequently employed in TMH catalysis but often play poorly defined

https://doi.org/10.1021/acs.accounts.6c00040
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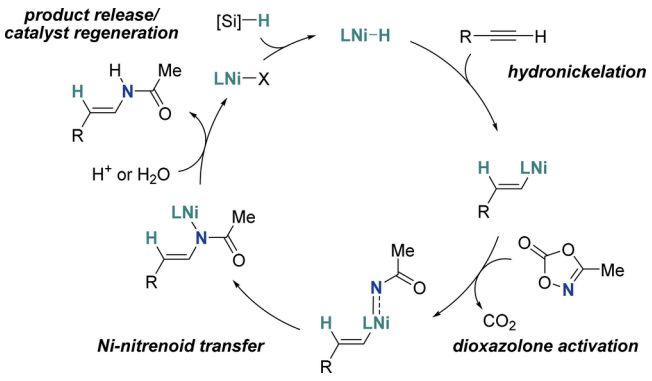
roles, we conducted a detailed investigation into the function of H_2O in this system. Electron paramagnetic resonance (EPR) analysis revealed that Ni(I) species form more rapidly in the presence of water, suggesting that H_2O promotes catalyst activation. More importantly, combined experimental and computational studies indicated that irreversible Si−O bond formation provides a significant thermodynamic driving force for catalyst regeneration, thereby facilitating efficient turnover of the NiH species. Altogether, a catalytic cycle was proposed in which generation of a Ni(I)H species is followed by alkyne hydronickelation to form a vinylnickel intermediate, subsequent interception of the dioxazolone, decarboxylation to generate a putative Ni-nitrenoid, and inner-sphere C−N bond formation (Scheme 4). In this cycle, the H_2O additive

Scheme 4. Proposed Catalytic Cycle for NiH-Catalyzed Alkyne Hydroamidation via Nitrenoid Transfer

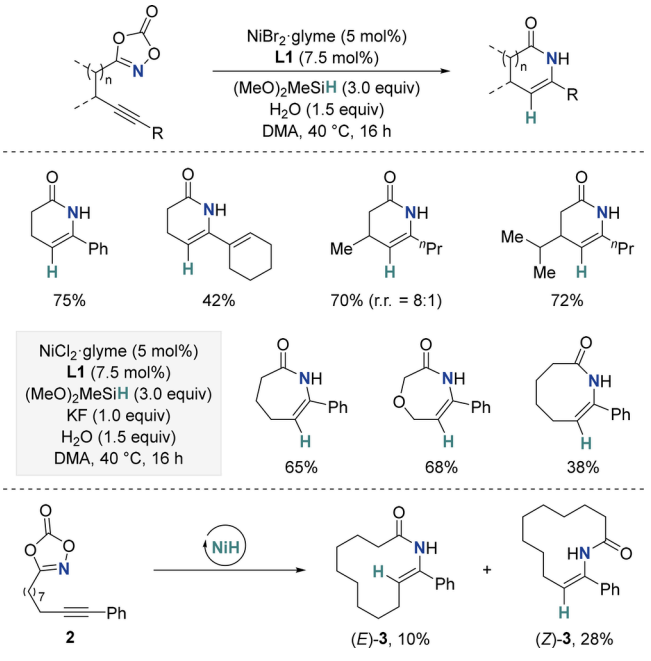


facilitates catalyst turnover by promoting regeneration of the catalytically active Ni(I) species, ultimately enabling formation of the enamide product.

Building on this foundation, we subsequently extended the NiH/dioxazolone platform to intramolecular alkyne hydroamidation, enabling *endo*-selective cyclization to form nitrogen-containing heterocycles (Scheme 5).[31] Regiocontrol in amide cyclization is generally unpredictable, as competing *exo* and *endo* pathways are often critically affected by reactant structures.[32] Leveraging the established canonical hydrometalation-initiated nitrenoid transfer manifold, we sought to dictate cyclization regioselectivity at the hydronickelation stage, thereby enabling the otherwise disfavored *endo* cyclization.

Under this design, endocyclic enamides were obtained with high selectivity when the alkyne substrate incorporated either an electronically polarizing substituent distal to the dioxazolone or a sterically demanding substituent proximal to it, both of which bias the site of Ni−H insertion. While regioselectivity is thus established during hydronickelation, *syn* insertion inherently misaligns the resulting alkenylnickel intermediate with the tethered dioxazolone, rendering direct nitrenoid capture geometrically inaccessible. Productive C−N bond formation therefore requires subsequent geometric reorganization of the alkenylnickel species. Evidence for such alkenylnickel isomerization emerged from reactions of substrate **2** forming 12-membered endocyclic enamides. In this substrate, the increased tether length partially alleviates geometric constraints, making *endo* cyclization possible even without isomerization, albeit still challenging. Consistent with this picture, the reaction furnished a mixture of (*E*)- and (*Z*)-

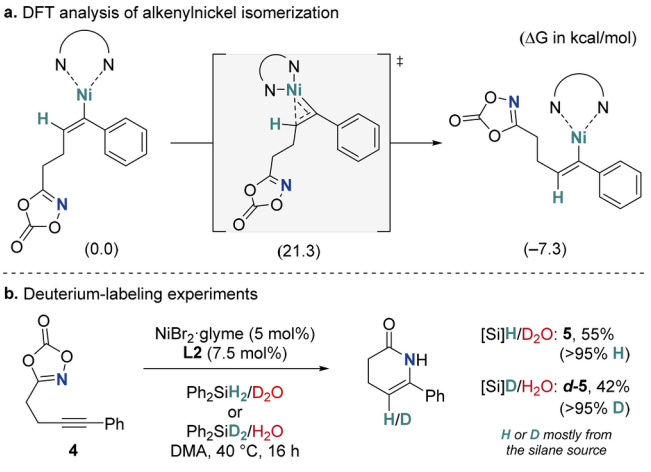
Scheme 5. *Endo*-Selective Intramolecular Alkyne Hydroamidation



enamides: formation of (*E*)-**3** is consistent with direct *syn*-hydronickelation followed by cyclization, whereas the observation of (*Z*)-**3** provides compelling evidence for alkenylnickel isomerization prior to nitrenoid transfer.

To further elucidate the nature of this isomerization process, DFT calculations were performed and identified an η^2-vinyl isomerization transition state, supporting a mechanism involving geometric reorganization of the alkenylnickel intermediate after regioselectivity has been set (Scheme 6a).

Scheme 6. Mechanistic Investigations of Alkenylnickel Isomerization



An alternative isomerization pathway involving reversible β-protonation was also considered; however, deuterium crossover experiments ruled out this possibility (Scheme 6b). If protonation-mediated isomerization were operative, comparable isotope incorporation would be expected under both Ph_2SiH_2/D_2O and Ph_2SiD_2/H_2O conditions. Instead, each experiment overwhelmingly retained the isotopic identity of

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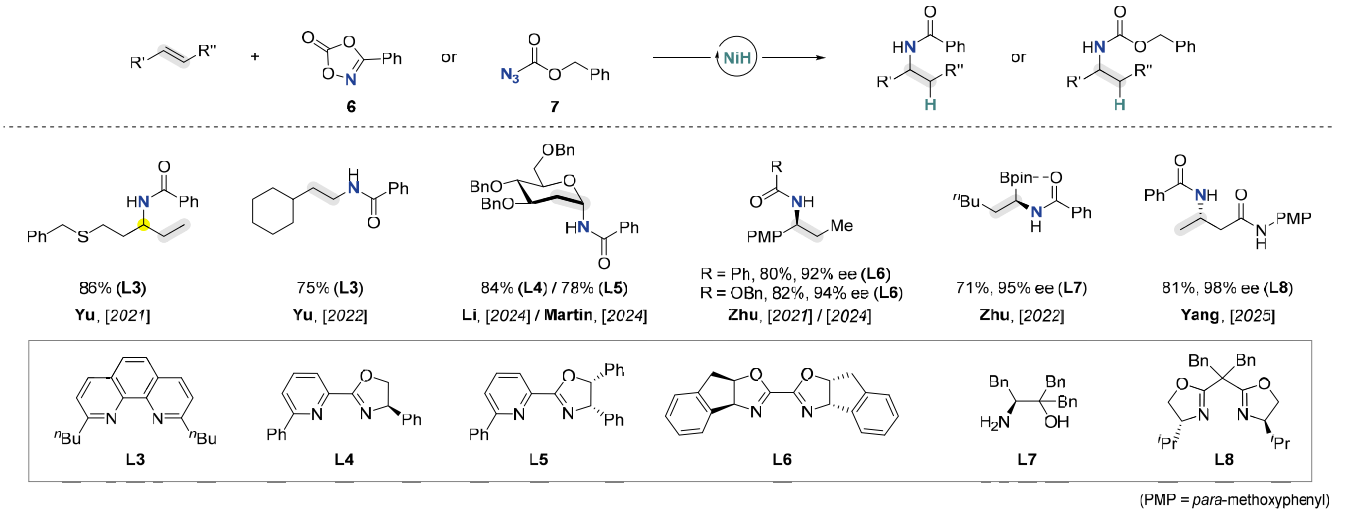
Scheme 7. Recent Developments in NiH-Catalyzed Hydroamidation via Nitrenoid Transfer



the silane, thereby excluding proton-assisted isomerization and supporting direct alkenylnickel rearrangement.

Collectively, these two studies establish the fundamental design principles of canonical NiH-catalyzed hydroamidation: (i) regioselectivity is set by hydrometalation of the π system, (ii) dioxazolones serve as uniquely compatible acyl nitrenoid precursors under reducing NiH conditions, and (iii) downstream manipulation of alkenylnickel intermediates can be leveraged to expand structural complexity without altering the core mechanistic sequence. These insights laid the groundwork for subsequent generalization to other TMH systems involving nitrenoid transfer.[33,34]

2.2. NiH-Catalyzed Alkene Hydroamidation

Further extending the establishment of NiH-mediated nitrenoid transfer, parallel advances applying this reactivity to alkenes have emerged across the synthetic community (Scheme 7). In these systems, regioselectivity is likewise determined at the hydronickelation stage and can be modulated through directing, electronic, or steric effects. For example, Yu and co-workers demonstrated that NiH catalysis can promote chain-walking along alkenes,[35] enabling thioether-directed γ-C(sp^3)−H hydroamidation or, through ligand-controlled steric effects, formation of linear *N*-alkyl amides from terminal alkenes.[36] Additionally, Li[37] and Martin[38] concurrently reported NiH-catalyzed hydroamidation of alkenes using tailored pyridine-oxazoline ligands, enabling site-selective amide installation in complex glycol-derived substrates, with regioselectivity favoring positions α to oxygen substituents.

Beyond regioselective control alone, substantial progress has also been made toward enantioselective alkene hydroamidation under NiH catalysis. Zhu and co-workers reported enantioselective NiH-catalyzed hydroamidation reactions using dioxazolones that deliver chiral benzylic amides[39] or α-aminoboronates,[40] demonstrating that stereochemical information can be embedded into the hydrometalation−nitrenoid transfer sequence through judicious ligand design. In subsequent work, the same group expanded the repertoire of nitrenoid precursors to include organic azides, enabling access to α-branched amides from styrenyl substrates and linear amides from unactivated alkenes.[41] More recently, Yang and co-workers employed chiral bisoxazoline ligands to achieve asymmetric formation of vicinal diamines and β-amino amide through coordination-assisted hydroamidation.[42] Complementing these intermolecular examples, Kong and co-workers reported an enantioselective reductive cyclization−amidation of 1,6-enynes,[43] highlighting the versatility of NiH catalysis and the compatibility of alkylnickel intermediates with intermolecular nitrenoid transfer following intramolecular cyclization.

2.3. IrH- and RhH-Catalyzed Hydroamidation

Drawing on our established expertise in Ir-nitrenoid-mediated C−H amidation,[44,45] we sought to translate related metal-nitrenoid reactivity into an IrH-catalyzed hydroamidation regime. In our early study, this conceptual bridge was established under borrowing-hydrogen conditions, wherein in situ generated IrH species enable nondissociative chain walking to preorganize alkyl-iridium intermediates (Scheme 8).[46] In this system, chain walking positions the metal α to a carbonyl group, generating an enolate that subsequently engages an Ir-bound nitrenoid, with hydrogen bonding proposed to assist C−N bond formation.

We subsequently advanced to a more canonical IrH-catalyzed hydroamidation manifold by employing external hydride sources.[47] This platform operates through sequential hydrometalation, reversible chain walking, and nitrenoid transfer, uniquely accommodating both unactivated and heteroatom-substituted alkenes while still delivering terminal amide products (Scheme 9). DFT calculations revealed that, although Ir-alkyl intermediates generated upon hydrometalation undergo rapid and reversible chain walking, regioselectivity is ultimately determined at the nitrenoid formation step. Among the accessible Ir-alkyl species, the terminal Ir-alkyl intermediate exhibits the lowest barrier for dioxazolone activation, as the sterically less encumbered terminal site more readily accommodates binding and decarboxylative activation of the nitrenoid precursor.

Parallel advances employing RhH catalysis further underscore the generality of this selectivity paradigm. Rovis and co-workers reported RhH-catalyzed hydroamidation reactions that similarly favor terminal functionalization through hydrometalation−nitrenoid sequences (Scheme 10).[48,49] In complementary work, Huang and co-workers developed RhH-catalyzed *ipso* and remote hydroamidation of alkenyl carboxylic

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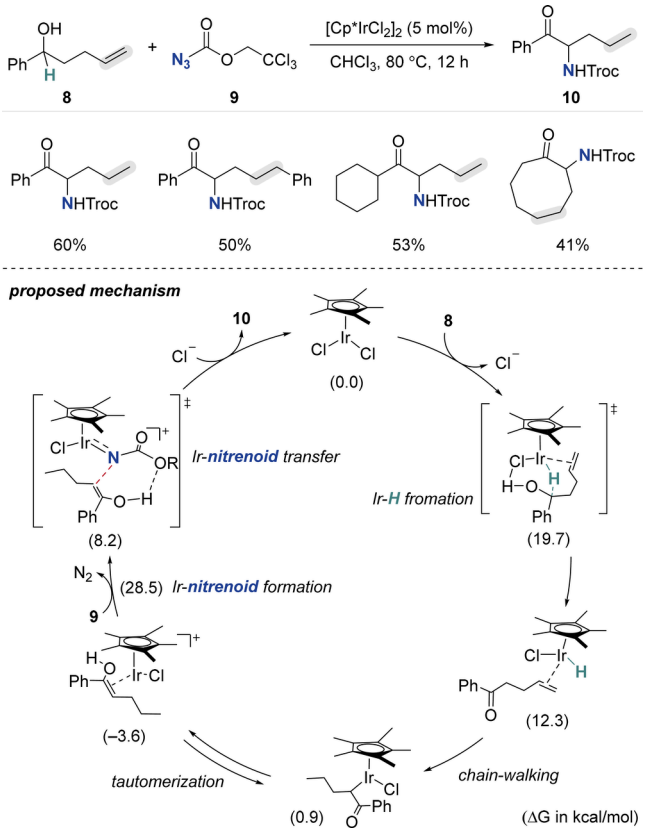
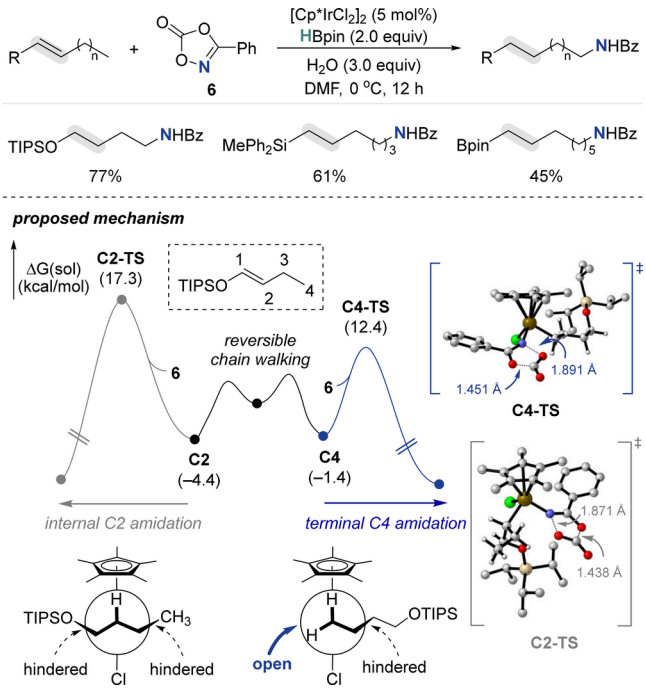
Scheme 8. IrH-Catalyzed Hydroamidation via a Borrowing-Hydrogen Strategy



Scheme 9. IrH-Catalyzed Migratory Hydroamidation

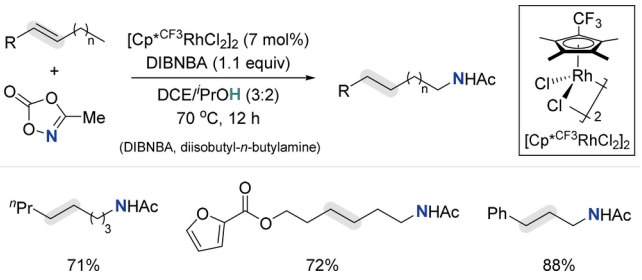


acids, wherein regioselectivity is dictated by the directing effect of the carboxylate group rather than by chain walking alone.[50]

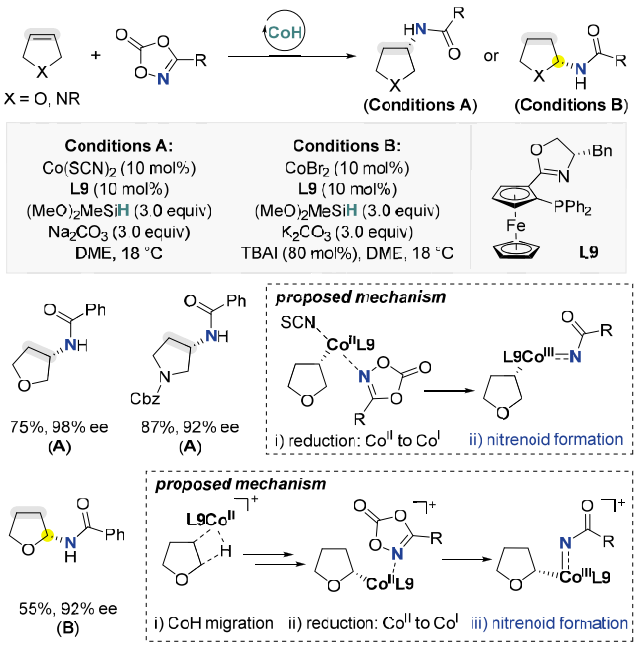
2.4. CoH-Catalyzed Hydroamidation

Expanding the range of TMHs compatible with nitrenoid transfer, Lu, Fu, and Liu recently introduced CoH catalysis as a complementary platform for alkene hydroamidation.[51] Building on the established versatility of CoH systems in alkene hydrofunctionalization,[52−54] this approach enables regiodivergent and enantioselective hydroamidation of heterocyclic alkenes, with regioselectivity governed by the coordination environment of the cobalt center (Scheme 11). Mechanistic

Scheme 10. RhH-Catalyzed Migratory Hydroamidation



Scheme 11. CoH-Catalyzed Regiodivergent Hydroamidation



studies indicated that this regiodivergence originates from the coordinating ability of the counteranion. In the presence of strongly coordinating anions such as SCN^-, hydrocobaltation generates a neutral Co(II)-alkyl species, which undergoes reduction followed by oxidative decarboxylation of the dioxazolone to form a Co(III)-nitrenoid intermediate. Subsequent inner-sphere C−N bond formation delivers *ipso*-selective amidation. In contrast, under conditions employing weakly coordinating anions, facile anion dissociation produces a cationic Co(II)-alkyl manifold. This species exhibits a reduced barrier for β-hydride elimination, enabling migratory chain walking prior to nitrenoid transfer and ultimately leading to remote amidation. Furthermore, within the same catalytic platform, CoH catalysis was also shown to enable benzylic- and terminal-selective hydroamidation of styrenes and terminal alkenes.

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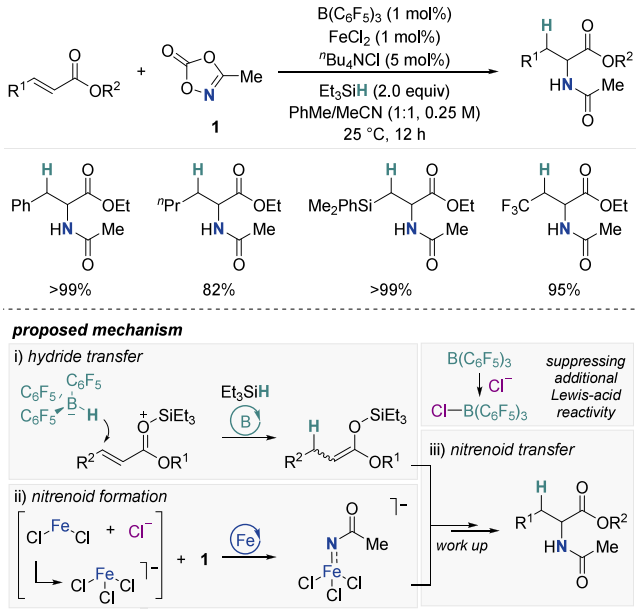
Acc. Chem. Res. 2026, 59, 1215−1226

2.5. Borane/Iron Relay-Catalyzed Hydroamidation

Whereas regioselectivity in TMH-catalyzed hydroamidation is typically dictated by the intrinsic electronic properties of the alkene, substrates bearing multiple electronically competing substituents often pose a fundamental selectivity challenge. To address this limitation, we formulated a borane/iron relay catalytic system for the hydroamidation of α,β-unsaturated esters. While finely tuned CuH catalysis can achieve α-selective amination of electronically biased α,β-unsaturated esters,[55] the present dual-catalytic system enables α-amidation even when additional electronically polarizing substituents are present at the β-position through decoupled catalysts for hydride delivery and nitrenoid transfer (Scheme 12).[56]

Scheme 12. Lewis Acid/Iron Relay Catalysis for Sequential Hydride and Nitrenoid Transfer



The central design principle of this dual-catalytic platform exploits the strong Lewis acidity of $B(C_6F_5)_3$ to abstract hydride from the hydrosilane, generating a silylium species that activates the ester carbonyl and promotes selective 1,4-hydride addition to form a silyl ketene acetal intermediate. In prior studies, we established that under typical $B(C_6F_5)_3$-catalyzed conditions, such silyl ketene acetals undergo rapid silyl migration to form α-silyl esters.[57] However, by appropriate steric tuning of the hydrosilane, we identified that triethylsilane significantly retards this silyl migration. Moreover, the addition of chloride anions effectively suppresses Lewis acid-mediated silyl transfer, thereby stabilizing the silyl ketene acetal intermediate. With the silyl ketene acetal thus preserved, regioselectivity of C−N bond formation is fixed at the α-position of the ester. This nucleophilic intermediate can then engage an in situ generated iron nitrenoid to forge the C−N bond, completing the hydroamidation sequence. Notably, the chloride additive plays a dual role in this relay system: in addition to inhibiting silyl migration, it converts $FeCl_2$ into an anionic $FeCl_3^-$ species, which is uniquely competent for dioxazolone activation and subsequent nitrenoid transfer.

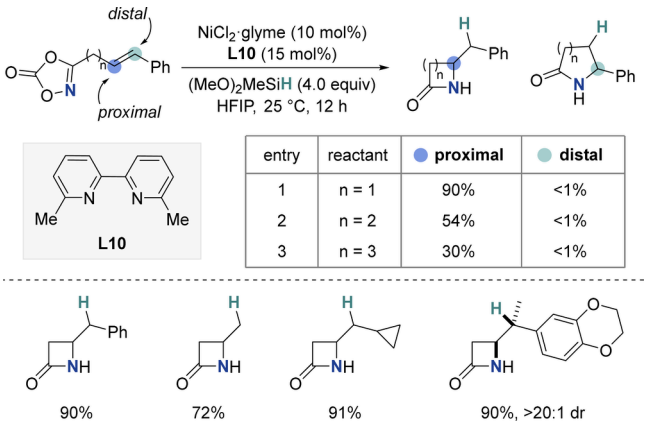
3. TRANSPOSED HYDROAMIDATION VIA NITRENOID TRANSFER

In the canonical hydroamidation manifolds described above, regioselectivity is established through hydrometalation of the π system prior to nitrenoid transfer. During our studies of NiH-catalyzed hydroamidation, however, we uncovered a fundamentally different regime in which this sequence of elementary steps is reversed. In this *transposed hydroamidation* pathway, initial nitrenoid formation precedes hydrometalation, generating a nickel-amido intermediate that subsequently engages the alkene. Reordering the catalytic sequence in this manner enables regioselectivity patterns that are inaccessible under conventional hydrometalation-initiated TMH catalysis and establishes a new design paradigm for hydroamidation.

3.1. Transposed NiH Catalysis: Intramolecular Access to β-Lactams

Our entry into transposed NiH catalysis arose serendipitously during studies of intramolecular hydroamidation of styrenyl dioxazolones (Scheme 13).[2] Instead of the distal, benzylic

Scheme 13. Discovery of Transposed NiH Catalysis via β-Selective Intramolecular Hydroamidation



entry	reactant	proximal	distal
1	n = 1	90%	<1%
2	n = 2	54%	<1%
3	n = 3	30%	<1%

amidation products expected from canonical hydrometalation logic,[58,59] substrates bearing a range of tether lengths consistently furnished lactam products with proximal selectivity. Notably, this preference extended across terminal, alkyl-substituted, and trisubstituted alkenes. Such behavior directly contradicts the established tendency of hydrometalation-controlled pathways to favor formation of less strained ring systems.

Mechanistic analysis revealed that, in this system, activation of the dioxazolone by NiH occurs with a lower kinetic barrier than alkene hydronickelation, leading to formation of a Ni-amido intermediate prior to alkenyl π-bond engagement (Scheme 14). Subsequent polarity-matched amidonickelation forges the proximal C−N bond, with hydride transfer occurring at a later stage of the catalytic cycle. Although a Ni-amido intermediate can arise from a sequence involving comproportionation and protonation of a Ni-nitrenoid species,[60,61] ligand exchange to form an amido-Ni(II)Cl complex is essential, as chloride anions play a critical role in stabilizing the catalytically competent Ni-amido species and enabling this inverted reactivity. Importantly, this transposed pathway not only accounts for the observed β-selectivity but also supports high levels of enantiocontrol when chiral ligands

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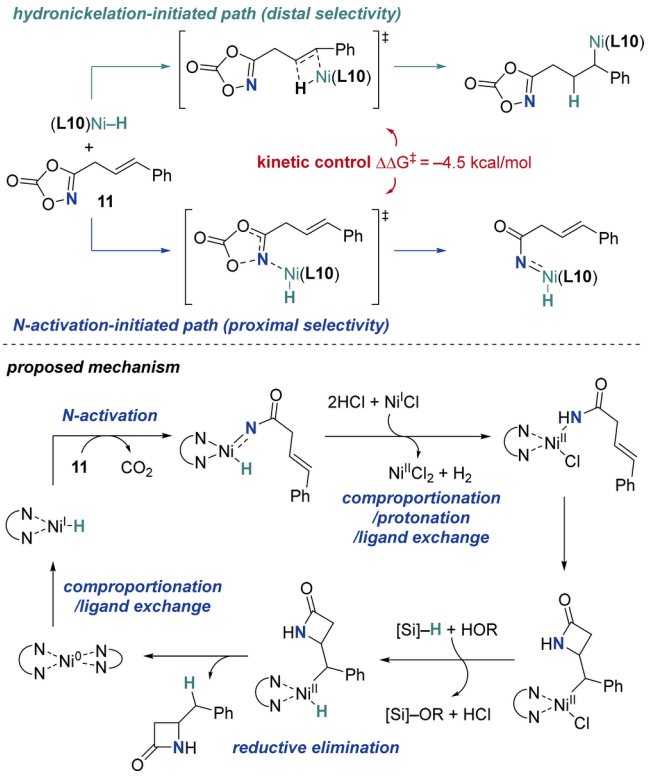
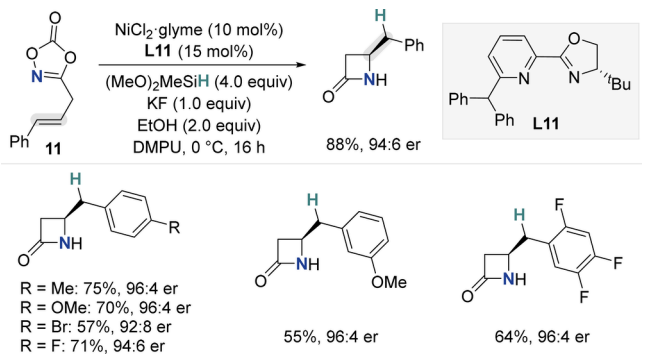
Scheme 14. Proposed Mechanistic Pathway for N-Activation-Initiated Hydroamidation



are employed, providing efficient access to enantioenriched β-lactams of significant synthetic value (Scheme 15).

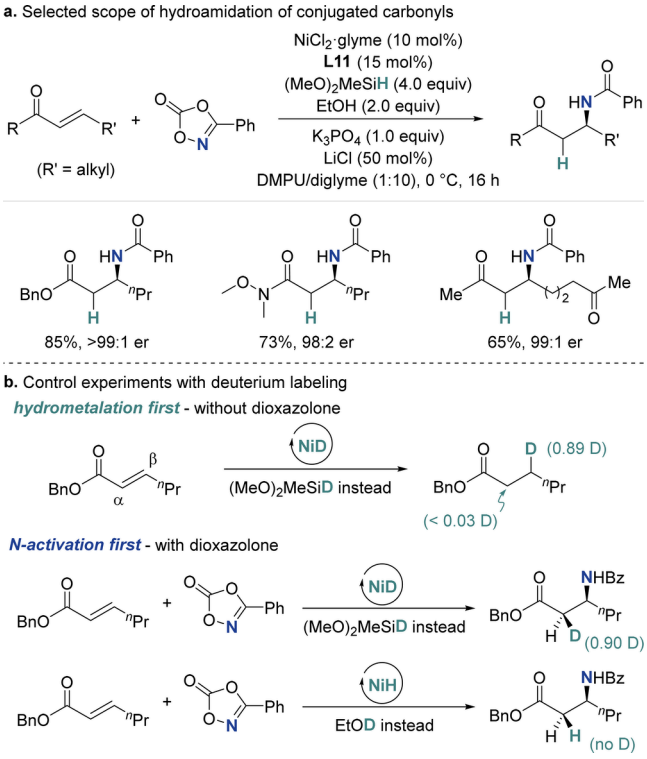
Scheme 15. Asymmetric β-Lactam Formation Enabled by Transposed NiH Catalysis



3.2. Transposed NiH Catalysis: Intermolecular Access to β-Amidated Carbonyls

Encouraged by these findings, we sought to extend N-activation-initiated NiH catalysis to intermolecular systems. Under conventional TMH catalysis, conjugated carbonyl compounds typically undergo α-functionalization, reflecting the inherent preference for hydrometalation for α-metalation. Although β-amidation of α,β-unsaturated carbonyls has been achieved in isolated cases by Buchwald[62] and Zhang,[63] this selectivity relies on *benzylic* activation at the β position. In contrast, transposed NiH catalysis enables direct β-amidation of α,β-unsaturated carbonyls bearing *β-alkyl* substituents through initial formation of a Ni-amido intermediate, thereby shifting the selectivity-determining step from hydrometalation to C–N bond formation (Scheme 16a).[3]

Scheme 16. Intermolecular Hydroamidation of Conjugated Carbonyls via Transposed NiH Catalysis



Isotopic labeling studies provided strong support for this mechanistic assignment (Scheme 16b). Under catalytic conditions employing a deuterated silane, deuterium was incorporated exclusively at the α position of the product. By contrast, in the absence of a nitrenoid precursor, reaction of the substrate with Ni–D resulted in selective β-deuteration, consistent with intrinsic 1,4-hydride addition. This complete inversion of deuterium incorporation rules out a hydrometalation-initiated pathway and instead supports a sequence in which N-activation precedes amidonickelation and subsequent α-hydride transfer. Further insight was obtained from kinetic isotope effect (KIE) measurements: inverse secondary H/D isotope effects indicate sp^2-to-sp^3 rehybridization in the turnover-limiting transition state, while significant natural-abundance ^{13}C KIEs at both the α and β carbons are consistent with an asynchronous amidonickelation event as the key C–N bond-forming step.

3.3. Mechanistic Divergence in TMH-Catalyzed Hydroamidation of Vinylarenes

A defining consequence of transposed NiH catalysis is its ability to override the intrinsic benzylic selectivity of vinylarenes. Whereas CuH- and NiH-catalyzed hydroamidation reactions, as developed by Buchwald[22] and Zhu,[39,41] respectively, uniformly deliver benzylic amides through hydrometalation-generated benzylmetal intermediates, nitrenoid-first generation enables regioreversed homobenzylic C–N bond formation by shifting the selectivity-determining step from alkene insertion to C–N bond construction (Scheme 17).[4]

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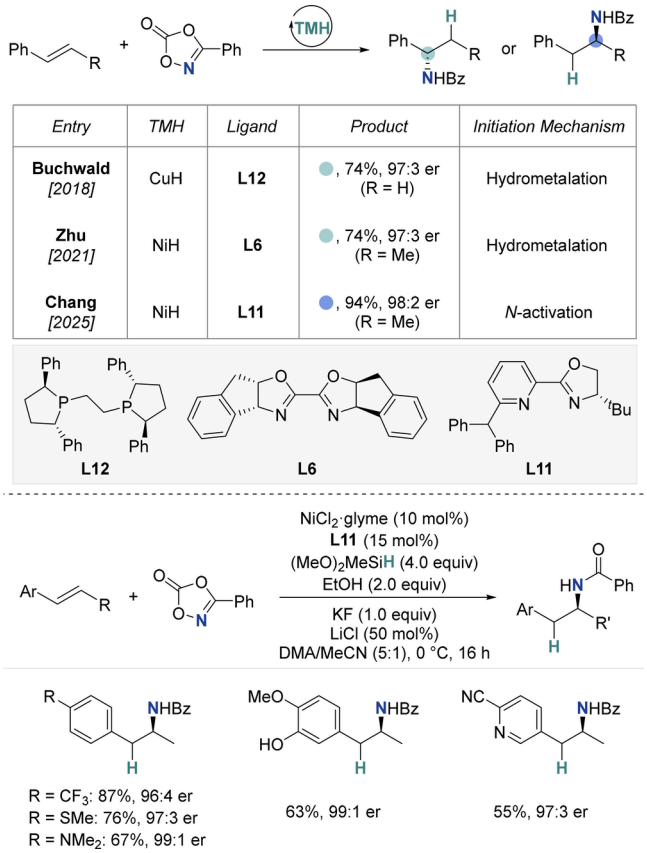
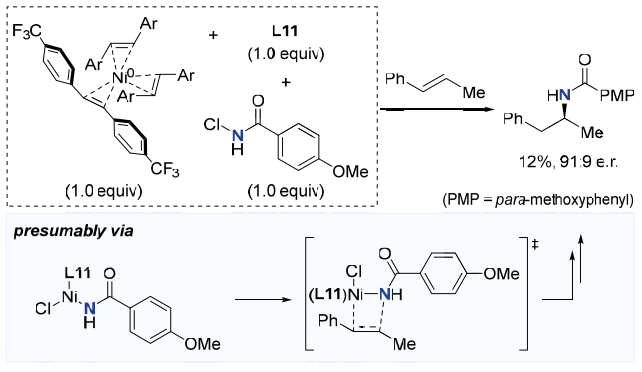
Scheme 17. Regioreversed Homobenzylic Hydroamidation of Vinylarenes



Entry	TMH	Ligand	Product	Initiation Mechanism
Buchwald *[2018]*	CuH	**L12**	, 74%, 97:3 er (R = H)	Hydrometalation
Zhu *[2021]*	NiH	**L6**	, 74%, 97:3 er (R = Me)	Hydrometalation
Chang *[2025]*	NiH	**L11**	, 94%, 98:2 er (R = Me)	*N*-activation

Across a broad range of vinyl(hetero)arenes, this strategy furnishes chiral β-arylethylamides with high levels of enantioselectivity. The operative amidonickelation pathway was substantiated by stoichiometric experiments involving independently generated Ni-amido species (Scheme 18). In

Scheme 18. Mechanistic Validation of Amidonickelation with Vinylarenes

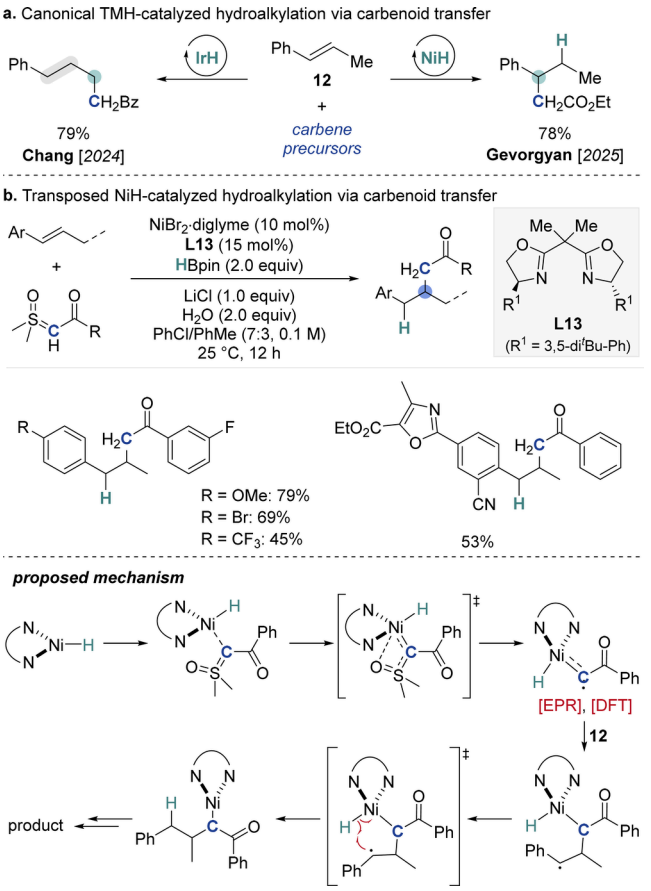


particular, reaction of Cornella's Ni(0) complex[64,65] with an *N*-chlorobenzamide is proposed to generate a amido-Ni(II)Cl intermediate in situ, which successfully delivered the homobenzylic amide product with high enantioselectivity (91:9 e.r.). These findings further validate the competence of Ni-amido intermediates in homobenzylic C−N bond formation and underscore how transposed NiH catalysis enables regioselectivity patterns inaccessible under conventional hydrometalation-first manifolds.

3.4. Extension to Carbene Radicals: Transposed NiH Catalysis beyond Nitrenoids

Given the conceptual parallels between metal-nitrenoid and metal-carbenoid reactivity, we envisioned that the transposed NiH framework could be extended beyond nitrenoid transfer to carbenoid-based processes. In conventional TMH−carbenoid systems, hydrometalation typically precedes carbenoid precursor engagement, leading to benzylic[66] or terminal-selective[67] C−C bond formation dictated by alkene insertion (Scheme 19a). To invert this sequence, we evaluated a range of

Scheme 19. Extension of Transposed NiH Catalysis to Carbenoid Transfer



carbenoid precursors and identified sulfoxonium ylides as uniquely competent partners (Scheme 19b).[68] In this system, chelation-assisted activation of sulfoxonium ylides enables NiH to initiate carbene formation prior to alkene engagement, thereby establishing a transposed NiH−carbenoid manifold.

The resulting nickel-carbenoid intermediate undergoes regioselective addition to aryl alkenes, followed by NiH-mediated hydride transfer to furnish homobenzylic hydroalkylation products with pronounced β-selectivity. The requirement for a coordinating carbenoid precursor highlights the importance of chelation assistance in lowering the barrier for carbenoid generation and suppressing premature hydrometalation. Multiple lines of evidence support the intermediacy of a carbene radical species. EPR experiments detected spin-trapped carbenoid-derived radicals, and the reaction was strongly inhibited in the presence of TEMPO. Consistent

https://doi.org/10.1021/acs.accounts.6c00040
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with these observations, DFT calculations revealed substantial spin density localized at the carbenoid carbon. Further support for a radical addition pathway was obtained from radical clock experiments, in which a cyclopropyl-substituted alkene underwent ring opening upon carbenoid insertion.

Deuterium-labeling studies using DBpin showed exclusive deuterium incorporation at the benzylic position of the product, indicating that hydride transfer occurs after C−C bond formation and ruling out a hydrometalation-initiated pathway. Collectively, these findings demonstrate that inversion of the catalytic sequence, from alkene-first activation to carbenoid-first generation, suppresses competing pathways such as cyclopropanation and direct carbenoid reduction.

4. CONCLUSION AND OUTLOOK

In this Account, we have articulated how the merger of TMH catalysis with nitrenoid transfer defines a cohesive strategy for programmable C−N bond construction. In canonical manifolds, regioselectivity is set by hydrometalation preferences, with TMH catalysts guiding the formation of well-defined organometallic intermediates that engage electrophilic nitrenoid precursors. In contrast, *transposed hydroamidation* inverts this sequence: initial activation of the nitrenoid precursor generates a metal-amido species that dictates the site of C−N bond formation prior to hydride insertion. This inversion of step order enables β-selective amidation, regioreversed homobenzylic functionalization, and related transformations that are inaccessible under conventional TMH logic. These advances illustrate a broader design principle in which the selectivity-determining step, hydride insertion versus heteroatom activation, can be programmed to achieve orthogonal outcomes from the same classes of unsaturated substrates.

Looking forward, a key challenge is the precise characterization and quantification of reactive intermediates, including TMH, metal-amido, and related species, to unambiguously define their electronic structures and roles. Such mechanistic clarity will enable rational expansion of TMH−nitrenoid strategies to new nitrogen precursors, remote C−N bond formations, and coupling manifolds involving other heteroatoms. As these conceptual foundations mature, we anticipate that the TMH−nitrenoid synergy will evolve from a collection of distinct transformations into a predictive platform for selective, programmable C−N bond synthesis.

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Author Contributions

[§]X.L. and H.C. contributed equally.

Notes

The authors declare no competing financial interest.

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Xiang Lyu received his Ph.D. degree from the University of Southampton in 2018 under Professor Richard Brown, focused on natural product total synthesis. He then joined the group of Prof. Sukbok Chang at the Institute for Basic Science (IBS) and the Korea Advanced Institute of Science and Technology (KAIST), where he has served as a postdoctoral researcher and is currently a senior researcher. His research interests focus on nickel-catalyzed nitrene transformations.

Hoonchul Choi received his Ph.D degree in Chemistry at KAIST under the supervision of Professor Sukbok Chang in 2025. He is currently a postdoctoral research fellow in the same research group at IBS. His research interests are the mechanism-guided development of transition-metal catalysts for selective C−N bond formation.

Sukbok Chang is a Director at IBS and a Professor at KAIST. In 1996, he earned his Ph.D. degree in organic chemistry at Harvard University under the supervision of Professor Eric N. Jacobsen. After postdoctoral experience with Professor Robert H. Grubbs at Caltech, he joined Ewha Womans University in Seoul, Korea, as an Assistant Professor in 1998 and then moved to KAIST in 2002. Since 2012 he has been the Director of the Center for Catalytic Hydrocarbon Functionalizations at IBS. His research interests are on the development, understanding, and synthetic applications of transition-metal catalysis.

ACKNOWLEDGMENTS

This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea.

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https://doi.org/10.1021/acs.accounts.6c00040
Acc. Chem. Res. 2026, 59, 1215−1226