Native amides as Enabling Vehicles for Forging sp^3–sp^3 Architectures via Interrupted Deaminative Ni-catalyzed Chain-Walking

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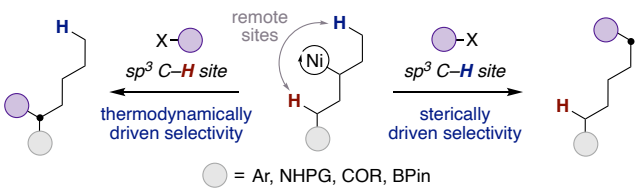
Supporting Information Placeholder

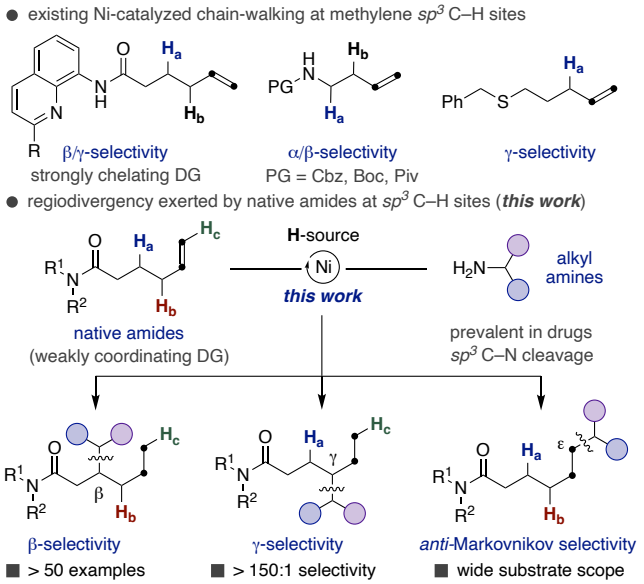
ABSTRACT: Herein, we disclose an interrupted deaminative Ni-catalyzed chain-walking strategy that forges sp^3–sp^3 architectures at remote, yet previously unfunctionalized, methylene sp^3 C–H sites enabled by the presence of native amides. This protocol is characterized by its mild conditions and wide scope, including challenging substrate combinations. Site-selectivity can be dictated by a judicious choice of the ligand, thus offering an opportunity to enable sp^3–sp^3 bond-formations that are otherwise inaccessible in conventional chain-walking events.

The ability to selectively functionalize sp^3 C–H bonds has received considerable attention in medicinal chemistry programs.[1,2] Their popularity arises from the observation that drugs possessing higher content of sp^3 hybridized carbons are oftentimes more selective and deliver higher success in clinical trials.[3] Recently, Ni-catalyzed chain-walking of unactivated olefins has gained momentum as a powerful, yet practical, alternatives to commonly adopted sp^3 C–H functionalization strategies,[1] allowing to promote innovative bond-disconnections for forging sp^3 architectures from simple, yet abundant, precursors.[4] Despite the advances realized, site-selectivity in Ni-catalyzed chain-walking reactions is predominantly dictated by a subtle interplay between electronic and steric effects. Indeed, bond-formation typically takes place adjacent to a stabilizing group on thermodynamic grounds[5] whereas functionalization at distal, primary sp^3 C–H bonds is kinetically preferred (Scheme 1).[6]

Scheme 1. Canonical Ni-catalyzed Chain-Walking Events.



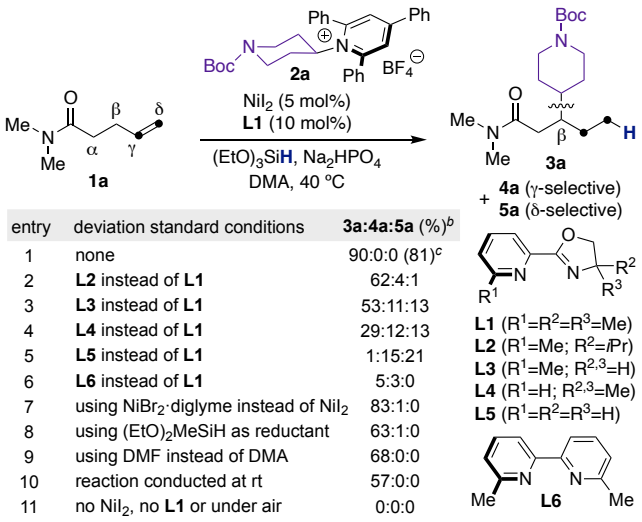
Scheme 2. Interrupted Ni-catalyzed Chain-Walking Events.



Recent elegant disclosures have illustrated the viability for targeting other sp^3 C–H sites within the alkyl side chain with strongly chelating bidentate 8-aminoquinoline,[7] thioethers[8] or protected amines[9] by utilizing alkyl halides or electrophilic nitrogen sources (Scheme 2, *top*). Driven by the prevalence of alkyl amines in a myriad of biologically-relevant molecules and preclinical candidates,[10] we wondered whether we could establish "*a la carte*" site-selective interrupted Ni-catalyzed deaminative[11] chain-walking for forging sp^3–sp^3 linkages at the always elusive methylene sp^3 C–H bonds with predictable and tunable selectivity by using weakly coordinating native amides (Scheme 2, *bottom*).[12] The choice of the latter is not arbitrary as these ubiquitous motifs possess an electron-rich carbonyl fragment suitable for metal chelation without the need for decorating the amide backbone with strongly chelating quinoline or pyridine backbones, hence setting the basis for applying these techniques to

advanced synthetic intermediates.[13] As part of our interest in the field,[14] we report herein the successful realization of this goal. The protocol is distinguished by its mild conditions, broad scope and exquisite site-selectivity, thus offering new opportunities in chain-walking and an unrecognized opportunity to enable formation of unactivated sp^3–sp^3 bonds in deaminative cross-couplings at methylene sp^3 C–H sites.[15] The protocol is inherently modular, allowing to establish regiodivergent scenarios for incorporating sp^3–sp^3 architectures at different methylene sp^3 C–H sites by judicious choice of the ligand backbone.

Table 1. Optimization of the Reaction Conditions.[a]



entry	deviation standard conditions	**3a:4a:5a** (%)[b]
1	none	90:0:0 (81)[c]
2	**L2** instead of **L1**	62:4:1
3	**L3** instead of **L1**	53:11:13
4	**L4** instead of **L1**	29:12:13
5	**L5** instead of **L1**	1:15:21
6	**L6** instead of **L1**	5:3:0
7	using $NiBr_2$·diglyme instead of NiI_2	83:1:0
8	using $(EtO)_2MeSiH$ as reductant	63:1:0
9	using DMF instead of DMA	68:0:0
10	reaction conducted at rt	57:0:0
11	no NiI_2, no **L1** or under air	0:0:0

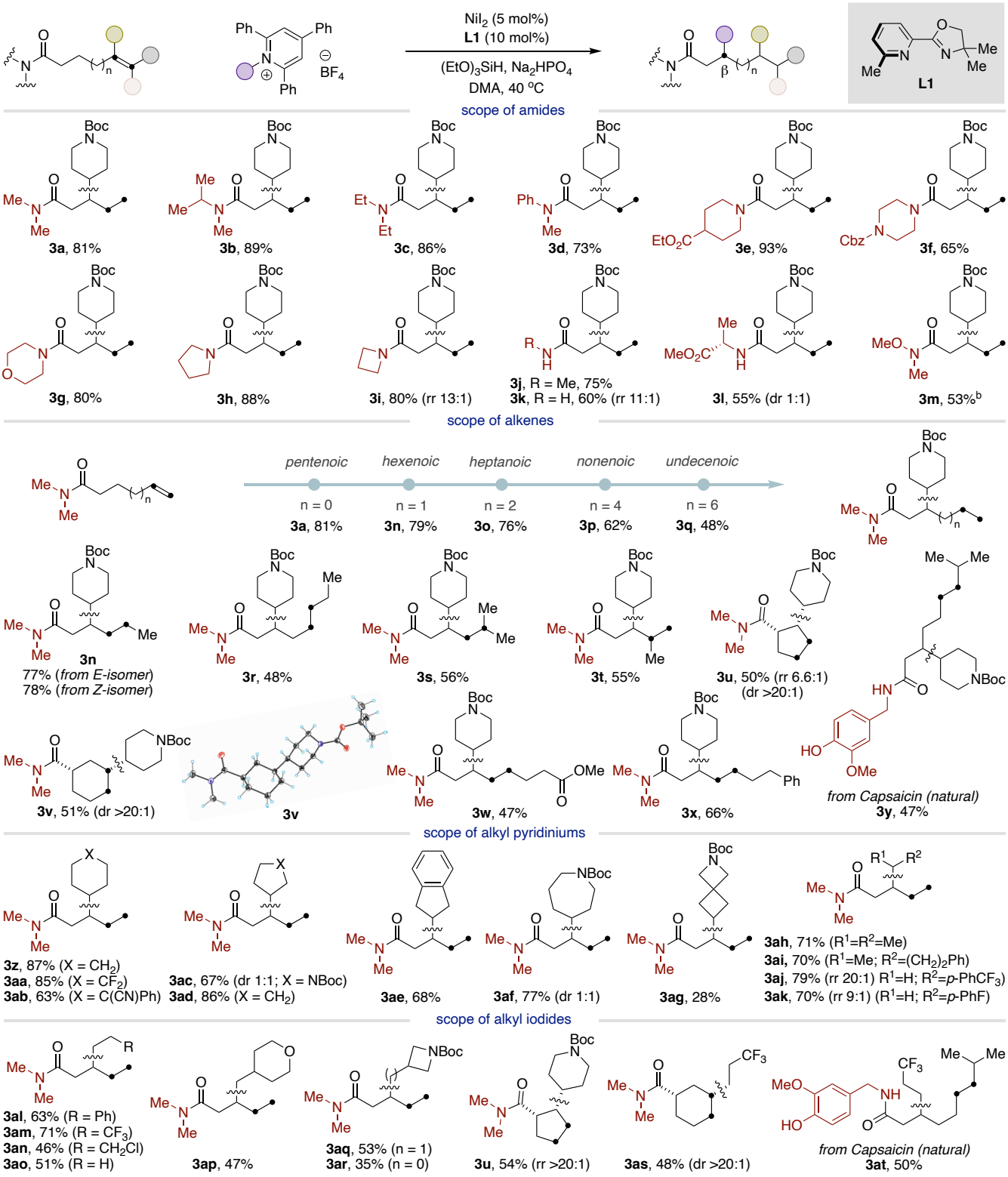
[a] Conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), NiI_2 (5 mol%), **L1** (10 mol%), $(EtO)_3SiH$ (0.20 mmol), Na_2HPO_4 (0.20 mmol), DMA (0.10 M) at 40 ºC for 15h. [b] GC yields using dodecane as internal standard. [c] Isolated yield.

We began our studies by evaluating the Ni-catalyzed interrupted deaminative chain-walking reaction of **1a** with **2a**, readily accessible in large amounts from the corresponding *tert*-butyl 4-aminopiperidine-1-carboxylate in a single step (Table 1). After judicious screening of the reaction parameters,[16] we found that a combination of NiI_2 (5 mol%), **L1** (10 mol%), $(EtO)_3SiH$, Na_2HPO_4 in DMA at 40 ºC afforded the best results, giving rise to **3a** in 81% isolated yield with exquisite β-selectivity (>150:1). As anticipated, the nature of the ligand was critical for success, with pyrox ligands providing better results than 2,2'-bipyridine congeners (entry 1 vs entry 6). Low β-selectivity was obtained with **L3** and **L4** lacking substituents adjacent to the nitrogen atom at either pyridine or oxazoline motif (entries 3 and 4), whereas a selectivity switch was observed when utilizing non-substituted analogues, thus showing the subtleties of our reaction. In addition, nickel sources, silanes or solvents other than NiI_2, $(EtO)_3SiH$ or DMA led to lower yields of **3a** (entries 7-9). Similarly, conducting the reaction at room temperature led to significantly lower reactivity (entry 10). As expected, control experiments indicated that all of the reaction parameters were critical for success (entry 11).

As shown in Table 2, our interrupted chain-walking sp^3–sp^3 bond-formation turned out to be widely applicable regardless of the substitution pattern at the amide backbone. Indeed, excellent yields and exclusive β-selectivities were observed for a series of amides derived from acyclic amines (**3a**–**3c**), anilines (**3d**), piperidine (**3e**), piperazine (**3f**), morpholine (**3g**), and pyrrolidine (**3h**). Even secondary amides exhibiting acidic N–H bonds delivered **3j** and **3l** in good yields and exquisite β-selectivity. Notably, excellent regiocontrol was obtained with Weinreb amides with just 1 mol% NiI_2 (**3m**) thus leaving ample room for further manipulation by using the amide backbone as a masked carbonyl fragment.[17] These results contribute to the perception that our protocol does not operate under substrate control and that **L1** dictates the β-selectivity pattern. Note, however, that azetidine **3i** and primary amides (**3k**) led to slightly lower regioselectivities, probably due to a poor orbital overlap in the former and an ineffective coordination mode in the latter. Next, we turned our attention to study the influence of the olefin on both reactivity and selectivity. Importantly, our interrupted β-selective deaminative chain-walking event could be applied across a wide number of substrates with exclusive β-selectivity. It is worth noting that long-range chain-walking events are within reach with exclusive β-selectivity, albeit in slightly lower yields (**3a** *vs* **3n-q**). More importantly was the observation that both *E*- or *Z*-internal olefins could participate equally well in our β-selective sp^3–sp^3 bond-forming reaction (**3n-3x**), even by utilizing advanced reaction intermediates (**3y**). Notably, 1,1-disubstituted olefins or even trisubstituted olefins could be employed as substrates with similar ease (**3s, 3t**). Equally interesting was the ability to extend this technique to cyclic amines such as 3-cyclopentenamide, obtaining the targeted β-alkylated **3u** as the major isomer. Interestingly, 3-cyclohexenamide only delivered γ–selective **3v** – unambiguously characterized by X-ray diffraction – in 51% yield. At present, we tentatively ascribe these results with an enhanced chelation of the nickel catalyst to the amide backbone through *syn*-pentane interactions.[18] Although one might argue that the presence of a pending, coordinating ester or an arene on the alkyl side chain might compromise site-selectivity,[5a,6b] this was not the case and **3w** and **3x** were both obtained in good yields, thus highlighting the strong chelation exerted by the native amide backbone.[12] The successful preparation of **3z-3ak** with pyridinium salts arising from aliphatic or cyclic secondary amines showcases the generality of our β-alkylation beyond **2a**. While the utilization of pyridinium salts derived from benzyl amines led to the targeted products **3aj** and **3ak**, the coupling of the corresponding primary alkyl congeners was better suited with alkyl iodides, delivering **3al-3ar** in good yields as exclusive β-isomers, even when utilizing Capsaicin as substrate (**3at**). As expected, **3u** and **3as** were both obtained with exquisite regioselectivity en route to the corresponding β- or γ-alkylated products, thus

illustrating the intriguing site-selectivity observed depending on the size of the pre-existing ring.

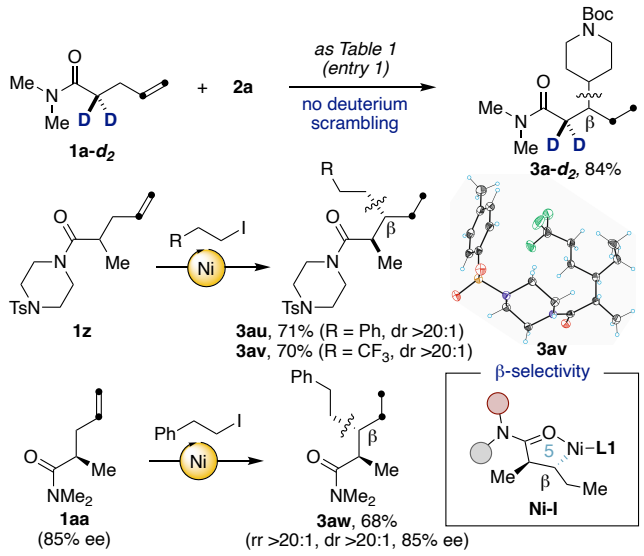
Table 2. Scope of the Ni-catalyzed Deaminative Interrupted Chain-Walking β-Alkylation of Native Amides.[a]



[a]As for Table 1, entry 1 (0.30 mmol scale). [b] NiI_2 (1 mol%), **L1** (2 mol%).

Taking into consideration the exclusive β-selectivity observed in Table 2, we wondered whether our interrupted chain-walking deamination proceeded via five-membered nickelacycles or acrylamides formed upon olefin isomerization prior to sp^3–sp^3 bond-formation. To this end, the reaction of **1a** and **2a** was monitored by both ^{1}H NMR spectroscopy and GC analysis.[16] Under the limits of detection, not even traces of acrylamide were detected in the crude mixtures. In addition, no deuterium incorporation was observed at the β-position when utilizing **1a-*d*$_2$** as substrate, thus arguing against acrylamides as reaction intermediates (Scheme 3). However, it was not particularly straightforward to rigorously distinguish whether sp^3–sp^3 bond-formation occurred via nickelacycles of type **Ni-I** or open-shell intermediates. High diastereoselectivity for the reaction of **1z** was anticipated in the former; on the contrary, statistical mixtures of diastereoisomers in **3au-3av** would indicate a radical-type pathway. As shown in Scheme 3, high yields and dr >20:1 were obtained for both products, with an *anti*-stereochemistry unequivocally confirmed by X-ray diffraction of **3av**. In line with this observation, the reaction of enantioenriched **1aa** resulted in **3aw** with an excellent selectivity profile and more importantly, with preservation of the chiral integrity at the α-position. Taken together, these findings advocate the notion that the formation of **Ni-I** precedes sp^3–sp^3 bond-formation.

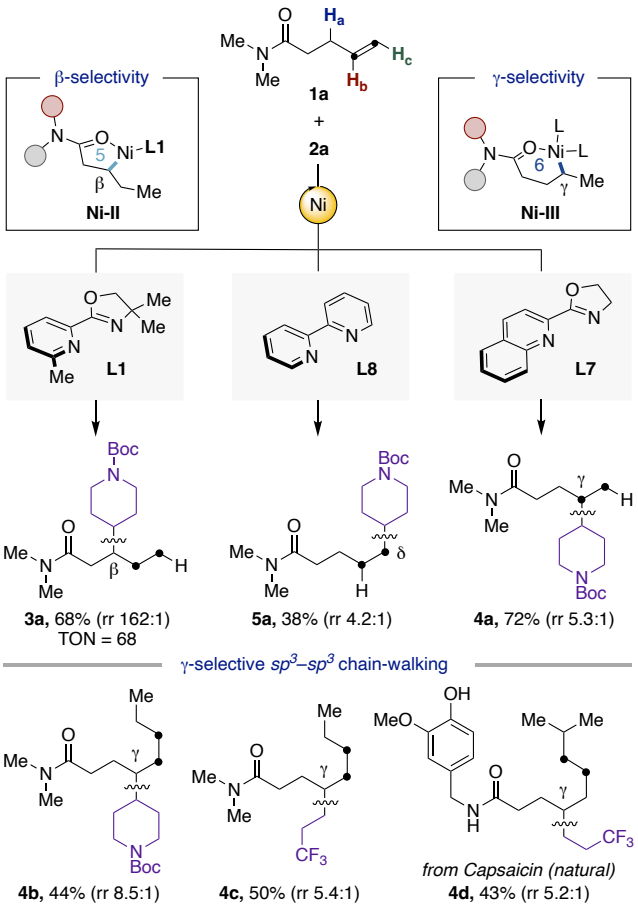
Scheme 3. Preliminary Mechanistic Experiments.[a]



[a] Conditions for **1z** and **1aa**: amide (0.30 mmol), alkyl iodide (0.45 mmol), NiI_2 (10 mol%), **L1** (20 mol%), $(EtO)_3SiH$ (0.60 mmol), Na_2HPO_4 (0.60 mmol), DMA (0.10 M) at 50 ºC for 15h.

Encouraged by the results of Table 2, we wondered whether the nature of the ligand might dictate the site-selectivity of our interrupted Ni-catalyzed deaminative chain-walking event. As shown in Scheme 4, regiodivergency could be accomplished in the reaction of **1a** and **2a** by a judicious choice of the ligand. Specifically, a Ni/**L1** regime delivered **3a** with exclusive β-selectivity (>99:1) and high TON (68). Notably, the utilization of **L7** or **L8** gave rise to **4a** and **5a** with γ- and δ-selectivity, respectively.[19] These results should be interpreted against the challenge that is addressed, offering a gateway to develop *"a la carte"* site-selective deaminative sp^3–sp^3 bond-formations by controlling the motion at which Ni catalysts promote chain-walking reactions. Gratifyingly, our chain-walking scenario based on the Ni/**L7** couple be extended to internal olefins with either primary or secondary alkyl electrophiles (**4b, 4c**). In addition, the successful preparation of **4d** from Capsaicin stands as a testament to the impact that this technique might have in the context of late-stage diversification of advanced intermediates.

Scheme 4. Regiodivergent β/γ/δ sp^3–sp^3 Bond-Formations.



[a] Conditions for **4a-d**: amide (0.36 mmol), pyridinium salt or alkyl iodide (0.36 mmol), $NiBr_2$·diglyme (5 mol%), **L7** (10 mol%), $(EtO)_3SiH$ (0.72 mmol), Na_2HPO_4 (0.72 mmol), DMA (0.10 M) at rt for 15h.

In summary, we report the successful utilization of native amides for forging sp^3–sp^3 architectures via interrupted site-selective deaminative nickel chain-walking catalysis at methylene sp^3 C–H sites. This method is characterized by its mild conditions, excellent site-selectivity and wide scope, including challenging substrate combinations and advanced intermediates. A judicious choice of the ligand backbone allows the effective discrimination among different methylene sp^3 C–H sites, offering an opportunity to promote regiodivergent strategies when forging sp^3

architectures. Further studies into the mechanism and extension to related transformations are currently ongoing.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral and crystallographic data (PDF)

Data for **3v** (CCDC-2223418) (CIF)
Data for **3av** (CCDC-2223419) (CIF)

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19. We hypothesize that the less sterically encumbered ligand **L7** provides more degrees of freedom and ample room for amide chelation, hence stabilizing nickelacycle **Ni-III** en route to γ-alkylation. The reactivity of a Ni/**L8** might be interpreted on the basis of a classical *anti*-Markovnikov hydrometallation of a nickel hydride across the terminal olefin prior to sp^3–sp^3 bond-formation.