Ligand-Controlled Regiodivergent Catalytic Amidation of Unactivated Secondary Alkyl Bromides

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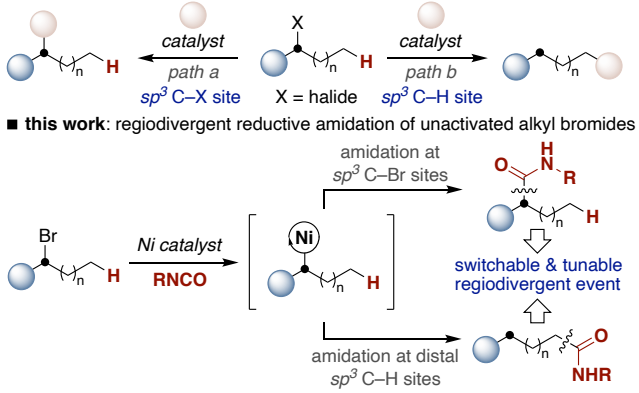
ABSTRACT: A regiodivergent Ni-catalyzed amidation of unactivated secondary alkyl bromides is described. The site-selectivity of the amidation event is dictated by subtle differences on the ligand backbone, allowing to introduce the amide function at either the original sp^3 carbon–halide bond or at distal sp^3 C–H sites within an alkyl side-chain via chain-walking scenarios.

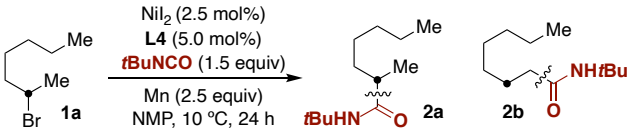
Although cross-coupling reactions of *unactivated* alkyl halides have evolved at a comparatively slower pace than their aryl congeners, these techniques have offered a fertile ground for building up new sp^3 architectures.[1] The latter is particularly important, as an increase of sp^3 character in drug candidates has recently been shown to contribute to clinical success.[2] At present, cross-coupling reactions of *unactivated* alkyl halides rely primarily on bond-formations at prefunctionalized sp^3 sites via functional group interconversion (Scheme 1, *path a*).[1] The recent years have witnessed the design of chain-walking reactions as a new technology to enable functionalization at remote sp^3 C–H sites via formal metal translocation within the alkyl side chain (Scheme 1, *path b*).[3] Despite the advances realized, the ability to rationally, predictably and reliably control the site-selectivity of these reactions by fine tuning the nature of the catalyst still remains an uncharted cartography.

Scheme 1. Cross-Couplings Reactions of Alkyl Halides.

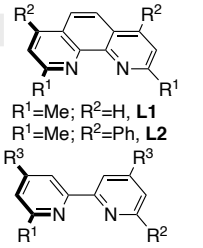


Prompted by the relevance of aliphatic amides in agrochemicals, pharmaceuticals and polymeric materials,[4] we questioned whether it would be possible to dictate the incorporation of an amide function at different sp^3 sites via site-selective Ni-catalyzed amidation of unactivated alkyl halides with isocyanate counterparts. If successful, such a strategy would provide a complementary technique to known catalytic amidations requiring stoichiometric organometallic reagents[5] or hazardous carbon monoxide,[6] among others.[7] At the outset of our investigations, it was unclear whether such strategy could be implemented. Indeed, the high reactivity of isocyanates and their propensity to parasitic di(tri)merization pathways with low-valent metal complexes[8] left a reasonable doubt whether it would be possible to trigger a dynamic translocation of the metal center throughout the alkyl chain. As part of our interest in the field,[9] we report herein the successful development of a catalytic method that provides access to aliphatic amides from unactivated alkyl halides by a subtle modulation of the catalyst of choice (Scheme 1, *bottom*).

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



entry	deviation standard conditions	yield/% (**2a**:**2b**)
1	***none***	***72* (4:96)**
2	**L1** instead of **L4**	29 (3:97)
3	**L2** instead of **L4**	35 (8:92)
4	**L3** instead of **L4**	49 (22:78)
5	DMF as solvent	66 (4:96)
6	Zn instead of Mn	42 (7:93)
7	Using $Ni(COD)_2$	5 (50:50)
8	**L5** instead of **L4**	65 (99:1)
9	**L6** instead of **L4**	15 (99:1)
10	**L7** instead of **L4**	62 (99:1)
11	**L8** instead of **L4**	72 (99:1)
12	Using **L8**, DMF, $NiBr_2$ at 3 °C	***93* (99:1)**[b]



[a] Conditions: **1a** (0.50 mmol), *t*BuNCO (0.75 mmol), NiI_2 (2.5 mol%), **L4** (5.0 mol%), Mn (1.25 mmol), NMP (1.0 mL) at 10 °C under N_2, 24h. [b] Conditions: **1a** (0.50 mmol), *t*BuNCO (0.75 mmol), $NiBr_2$ (2.5 mol%), **L8** (5.0 mol%), Mn (0.75 mmol), DMF (0.50 mL) at 3 °C under N_2, 24h. Yields and selectivities were determined by GC analysis using anisole as internal standard.

We began our investigations by studying the reaction of 2-bromoheptane (**1**) with *t*BuNCO (Table 1). The choice of the latter was not arbitrary, as primary amides can be easily accessed by simple deprotection of the *tert*-butyl group.[10] After judicious evaluation of the reaction parameters,[11] we found that a combination of NiI_2 (2.5 mol%), **L4** (5.0 mol %) and Mn as reductant in NMP at 10 °C resulted in amide bond-formation at the sp^3 C–H linkage, delivering **2b** in good yield and excellent selectivity (entry 1). As for other catalytic reductive coupling reactions,[12] 2,2'-bipyridines and 1,10-phenanthroline ligands possessing alkyl substituents adjacent to the nitrogen atom were critical for success (entries 2-4), with 2,2'-bipyridine ligands containing aromatic rings at 4,4'-position being particularly suited for our purposes. While solvents and reductants other than NMP and Mn resulted in lower yields of **2b** (entries 5 and 6), the utilization of $Ni(COD)_2$ as catalyst had a deleterious effect in both reactivity and site-selectivity (entry 7). Interestingly, site-selective amidation at the sp^3 C–Br site was achieved using nitrogen-containing ligands with a single alkyl substituent at C6 of the 2,2'-bipyridine core (**L5**-**L8**). In particular, **2a** could be obtained in an exquisite 99:1 ratio (entries 8-11), and in an excellent 93% yield by employing $NiBr_2$ as precatalyst and **L8** in DMF at 3 °C (entry 12).[9e]

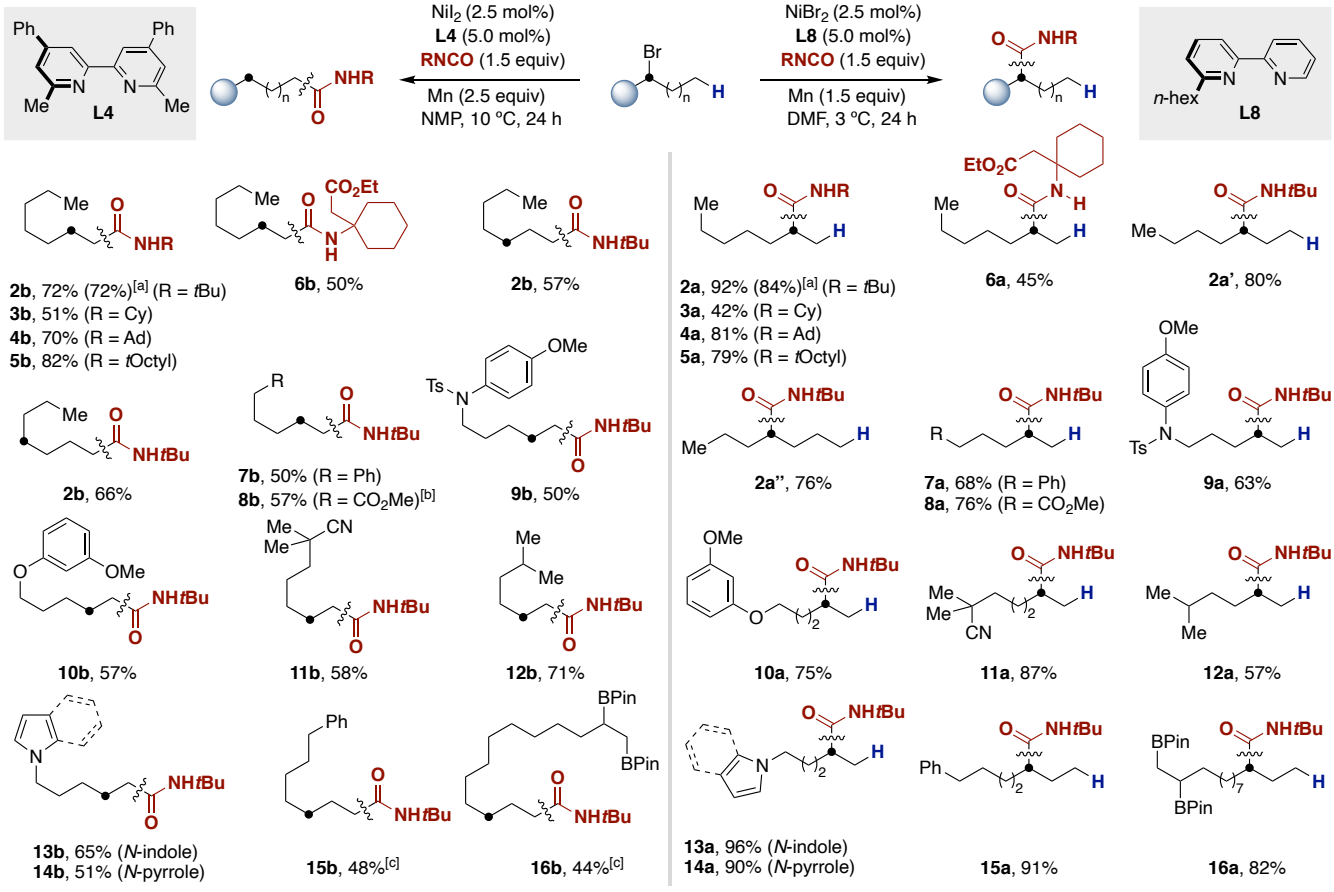
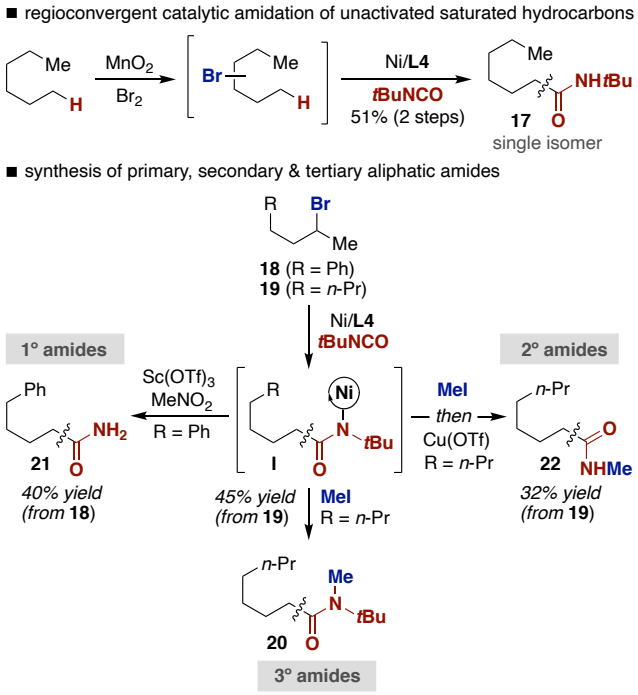


Figure 1. Regiodivergent Amidation of Unactivated Secondary Alkyl Bromides. Isolated yields, average of at least two independent runs. Conditions Ni/**L4**: As for Table 1, entry 1; Conditions Ni/**L8**: As for Table 1, entry 12. [a] 1 mmol scale. [b] Obtained as 92:8 ratio of **8b** and the corresponding amidation event adjacent to the ester motif. [c] NiI_2 (5.0 mol%), **L4** (10 mol%).

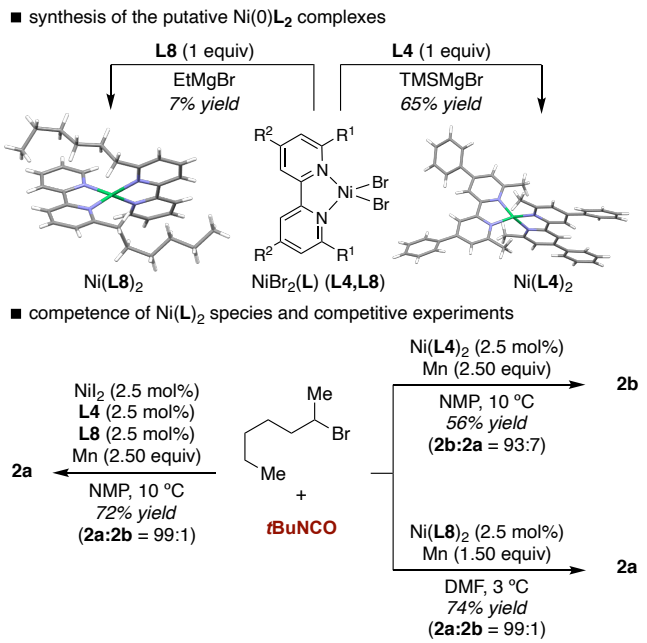
With a reliable access to both **2a** and **2b** in hand, we turned our attention to evaluating the generality of our regiodivergent Ni-catalyzed amidation based on a Ni/**L4** or Ni/**L8** regime (Figure 1). As shown, a series of unactivated secondary alkyl bromides could be utilized with similar ease, resulting in the corresponding linear or α-branched amides in good yields and excellent site-selectivities. In contrast with traditional catalytic amidation techniques,[5-7] we found that our protocol was particularly suited for accessing bulky amides by employing a range of differently substituted isocyanates (**2-6**). Notably, remote amidation could be extended beyond α-methyl substituted alkyl halides, as **2b** could be within reach from 3-bromo or 4-bromoheptane in 57% and 66% yield, respectively. Similarly, **15b** and **16b** could also be obtained by incorporating the amide function at distal sp^3 C–H bonds with substrates containing aromatic or boron fragments within the alkyl side chain. The latter is particularly interesting, thus leaving ample room for further derivatization via conventional cross-coupling reactions.[13] As evident illustrated in Figure 1, amines (**9**), nitriles (**11**), esters (**6, 8**) or nitrogen-containing heterocycles (**13**, **14**) did not interfere with productive C–C bond-forming reaction. Interestingly, a competitive chain-walking amidation at weak benzylic sp^3 C–H bonds was not found en route to **7b** and **15b**.[14] Notably, amide bond-formation adjacent to an ester motif was observed as a minor byproduct (**8b**), thus complementing related C–C bond-forming reactions via Ni-catalyzed chain-walking scenarios.[15] Notably, branched substituents do not compete with the efficacy of C–C bond-formation, with the targeted amidation occurring exclusively at the less-sterically hindered primary sp^3 C–H site (**12b**). In line with the results of entry 12 (Table 1), the utilization of **L8** suppressed β-hydride elimination and chain-walking, forging the targeted amide bond at the initial C–Br site in excellent yields for all substrates employed (**2a-16a**). The synthetic applicability of our method is further illustrated in Scheme 2. As shown, **17** was exclusively obtained from *n*-hexanes via a sequence consisting of an unselective sp^3 bromination followed by an amidation at the primary sp^3 C–H bond based on the Ni/**L4** couple. Aiming at extending the generality of our reaction, we anticipated that tertiary aliphatic amides might be within reach by intercepting **I** with an appropriate electrophile. Indeed, this turned out to be the case and **20** could be obtained in good overall yield from **19** by exposure with MeI. Furthermore, primary aliphatic amides such as **21** could easily be prepared by simple deprotection of the *tert*-butyl group with $Sc(OTf)_3$.[16] More importantly, **22** could easily be prepared from **19** by tandem methylation/deprotection, thus showcasing the opportunity of accessing secondary aliphatic amides that would otherwise be derived from flammable and toxic MeNCO.[17]

Scheme 2. Synthetic Applicability.



To gain further information about the mechanism of the reaction, we turned our attention to study the reactivity of the putative, low-valent Ni(0)$\mathbf{L}_2$ species within the catalytic cycle. Initial attempts to synthesize (**L4**)$_2$Ni and (**L8**)$_2$Ni from Ni(COD)$_2$ were met with failure, probably due to the difficulty of displacing COD with both **L4** and **L8**. However, these complexes could be prepared in analytically pure form by an alternative route consisting of reduction of **L**NiX_2 with either TMSMgBr or EtMgBr.[11] The structure of these complexes in the solid state is depicted in Scheme 3. A closer inspection into the crystal structures reveals a significant difference in the coordination geometry. While (**L4**)$_2$Ni shows a traditional tetrahedral backbone, a significant deviation from tetrahedral and square planar geometry (81° vs 65°) was found for (**L8**)$_2$Ni, thus showing the intriguing impact that subtle modifications on the 2,2'-bipyridine backbone might have on the putative Ni intermediates within the catalytic cycle. As expected, (**L8**)$_2$Ni and (**L4**)$_2$Ni were found to be catalytically competent, delivering **2a** and **2b** in 74% and 56% yield, respectively. Interestingly, a competitive experiment with both **L4** and **L8** showed that **2a** was exclusively formed (99:1 ratio) in 72% yield, tacitly suggesting a stronger binding of **L8** to the nickel center and the ability of the in situ generated alkyl-Ni(**L8**) to prevent β-hydride elimination.[18] Note, however, that stoichiometric experiments with Ni/**L8** or Ni/**L4** in the absence of Mn revealed traces of **2a** or **2b**, with alkenes arising from β-hydride elimination being formed predominantly in the crude mixtures.[19] Taken together, these results strongly suggests a mechanistic pathway consisting of the intermediacy of alkyl-Ni(I) species generated via single electron transfer of Mn to the putative alkyl-Ni(II) intermediates prior to RNCO insertion. At present, we hypothesize that the striking differences of **L8** and **L4** are tentatively attributed to a more congested environment in alkyl-Ni(II)(**L4**)Br, thus facilitating halide dissociation en route to cationic intermediates that might favor a chain-walking scenario via iterative sequences of β-hydride elimination/migratory insertion events.

Scheme 3. Mechanistic Experiments.



In conclusion, a nickel-catalyzed regiodivergent amidation of secondary alkyl bromides has been described. This protocol tacitly shows the subtle differences that the ligand backbone might have on the site-selectivity pattern, favoring amide bond-formation at either the initial C–halide bond or at remote sp^3 C–H sites within the alkyl side chain. The reaction is distinguished by its mild conditions, wide substrate scope and exquisite site-selectivity profile while minimizing unproductive isocyanate dimerization or trimerization events. Further extensions to related regiodivergent events are currently underway.

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Author Contributions

All authors have given approval to the final version of the manuscript, ‡These authors contributed equally.

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Supporting Information.

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

Crystallographic data for **Ni(L4)$_2$** (.cif)
Crystallographic data for **Ni(L8)$_2$** (.cif)

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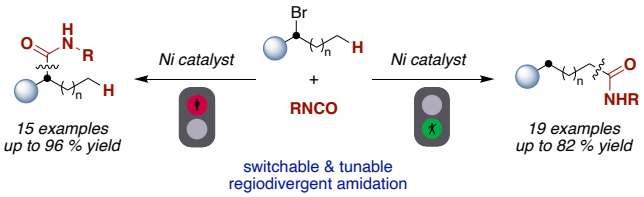
(18) The comparison of the C_{py}–C_{py} bond of Ni(**L4**)$_2$ and Ni(**L8**)$_2$ is highly illustrative. Interestingly, an elongation of the C_{py}–C_{py} linkage was observed in the former, indirectly suggesting less back-donation than in the analogous Ni(**L8**)$_2$ (1.453(8) vs 1.437(2) Å).

(19) Although tentative, these results suggest that the putative alkyl-Ni(II) species generated upon oxidative addition might be incapable of undergoing insertion of RNCO into the C–Ni(II) bond and that single-electron reduction en route to alkyl-Ni(I) might be required to drive the reaction forward. See ref. 11 for additional experiments along these lines.


Br
H
n
Ni catalyst
+
RNCO
Ni catalyst
O
NHR
15 examples
up to 96 % yield
19 examples
up to 82 % yield
switchable & tunable
regiodivergent amidation