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Letter

# Ligand-Controlled Regiodivergent Catalytic Amidation of Unactivated Secondary Alkyl Bromides

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A lthough 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<sup>3</sup> architectures.<sup>1</sup> The latter is particularly important, as an increase of sp<sup>3</sup> character in drug candidates has recently been shown to contribute to clinical success.<sup>2</sup> At present, cross-coupling reactions of *unactivated* alkyl halides rely primarily on bond-formations at prefunction-alized sp<sup>3</sup> sites via functional group interconversion (Scheme 1,



path a).<sup>1</sup> The recent years have witnessed the design of chainwalking reactions as a new technology to enable functionalization at remote sp<sup>3</sup> C–H sites via formal metal translocation within the alkyl side chain (Scheme 1, path b).<sup>3</sup> Despite the advances realized, the ability to rationally, predictably, and reliably control the site-selectivity of these reactions by finetuning the nature of the catalyst still remains an uncharted cartography.

Prompted by the relevance of aliphatic amides in agrochemicals, pharmaceuticals, and polymeric materials,<sup>4</sup> we questioned whether it would be possible to dictate the incorporation of an amide function at different sp<sup>3</sup> 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<sup>5</sup> or hazardous carbon monoxide,<sup>6</sup> among others.<sup>7</sup> 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<sup>8</sup> 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,<sup>9</sup> 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).

We began our investigations by studying the reaction of 2bromoheptane (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.<sup>10</sup> After judicious evaluation of the reaction parameters,<sup>11</sup> we found that a combination of NiI<sub>2</sub> (2.5 mol%), L4 (5.0 mol%), and Mn as reductant in NMP at 10 °C resulted in amide bondformation at the sp<sup>3</sup> C–H linkage, delivering **2b** in good yield

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<sup>a</sup>Conditions: **1a** (0.50 mmol), *t*BuNCO (0.75 mmol), NiI<sub>2</sub>(2.5 mol %), **L4** (5.0 mol %), Mn (1.25 mmol), NMP (1.0 mL) at 10 °C under N<sub>2</sub>, 24 h. <sup>b</sup>Conditions: **1a** (0.50 mmol), *t*BuNCO (0.75 mmol), NiBr<sub>2</sub> (2.5 mol %), **L8** (5.0 mol %), Mn (0.75 mmol), DMF (0.50 mL) at 3 °C under N<sub>2</sub>, 24 h. Yields and selectivities were determined by GC analysis using anisole as an internal standard.

and excellent selectivity (entry 1). As for other catalytic reductive coupling reactions,<sup>12</sup> 2,2'-bipyridines and 1,10phenanthroline 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 the 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<sup>3</sup> C-Br site was achieved using nitrogencontaining 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<sub>2</sub> as precatalyst and L8 in DMF at 3 °C (entry 12).9

With 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  $\alpha$ -branched amides in good yields and excellent site-selectivities. In contrast with traditional catalytic amidation techniques,<sup>5–7</sup> 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  $\alpha$ -methyl



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<sub>2</sub> (5.0 mol %), L4 (10 mol %).

substituted alkyl halides, as 2b could be within reach from 3bromo 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<sup>3</sup> 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.<sup>13</sup> As evidently 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 the weak benzylic sp<sup>3</sup> C-H bonds was not found en route to 7b and 15b.<sup>14</sup> 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 Nicatalyzed chain-walking scenarios.<sup>15</sup> Remarkably, 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  $\beta$ -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.

#### Scheme 2. Synthetic Applicability

■ regioconvergent catalytic amidation of unactivated saturated hydrocarbons

![](_page_2_Figure_6.jpeg)

synthesis of primary, secondary & tertiary aliphatic amides

![](_page_2_Figure_8.jpeg)

As shown, 17 was exclusively obtained from *n*-hexanes via a sequence consisting of an unselective sp<sup>3</sup> bromination followed by an amidation at the primary sp<sup>3</sup> 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 treatment with MeI. Furthermore, primary aliphatic amides such as 21 could easily be prepared by simple deprotection of the *tert*-butyl group with Sc(OTf)<sub>3</sub>.<sup>16</sup> More importantly, 22 could easily be prepared from 19 by tandem methylation/deprotection, thus showcas-

ing the opportunity of accessing secondary aliphatic amides that would otherwise be derived from flammable and toxic MeNCO. $^{17}$ 

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)L<sub>2</sub> species within the catalytic cycle. Initial attempts to synthesize  $(L4)_2Ni$  and  $(L8)_2Ni$  from Ni(COD)<sub>2</sub> 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 LNiX<sub>2</sub> with either TMSCH<sub>2</sub>MgCl or EtMgBr.<sup>11</sup> The structure of these complexes in the solid state is depicted in Scheme 3. A closer inspection

#### Scheme 3. Mechanistic Experiments

![](_page_2_Figure_13.jpeg)

![](_page_2_Figure_14.jpeg)

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  $(81^{\circ} \text{ vs } 65^{\circ})$  was found for (L8)<sub>2</sub>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,  $(L8)_2Ni$  and  $(L4)_2Ni$  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  $\beta$ -hydride elimination.<sup>18</sup> 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  $\beta$ -hydride elimination being formed predominantly in the crude mixtures.<sup>19</sup> Taken together, these results strongly suggest 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  $\beta$ -hydride elimination/migratory insertion events.

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 bondformation at either the initial C-halide bond or at remote sp<sup>3</sup> 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.

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02913.

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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## **Author Contributions**

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#### Notes

The authors declare no competing financial interest.

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(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.