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COMMUNICATION

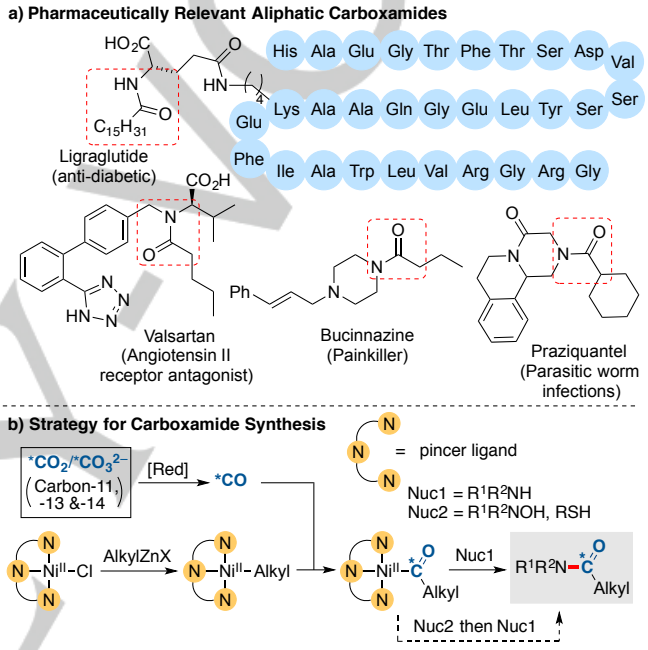
# Synthesis of Aliphatic Carboxamides Mediated by Nickel $NN_2$-Pincer Complexes and Adaptation to Carbon Isotope-Labeling

Karoline T. Neumann,[+] Aske S. Donslund,[+] Thomas L. Andersen, Dennis U. Nielsen and Troels Skrydstrup*

***Abstract:*** *The development of a nickel-mediated aminocarbonylation utilizing $NN_2$-pincer Ni-complexes, alkylzinc reagents, stoichiometric carbon monoxide and amines is described for the first time, which can be adapted to late-stage carbon-isotope labeling. This work expands the scope of the highly established palladium-promoted version of the reaction, by allowing carbon-$sp^3$ fragments to take part in the three-component reaction. Finally, the results obtained show a remarkable effect of the pincer ligand for the reductive elimination step with the amine, which is followed by $^{13}$C-NMR spectroscopy studies.*

Carboxamides represent an important chemical constituent of many pharmaceutically active compounds introduced because of their structural rigidity, high stability, and propensity to participate in strong hydrogen bonding networks.[1] For these reasons, this functional group is also the target for carbon-isotope labeling (carbon-11, carbon-13 and carbon-14), which is an important and mandatory step in pharmaceutical development programs used mainly for distribution and metabolism investigations, as well as environmental fate studies.[2] As such, highly efficient methods for the installation of an amide group is an active research area, which includes the well-studied Pd-catalyzed aminocarbonylation of aryl halides and pseudohalides with an amine and carbon monoxide.[3] Especially the latter reagent is interesting from a radioisotope labeling perspective, as carbon dioxide or carbonate salts represent the starting point for carbon-11 and carbon-14 labeling, and suitable methods for the efficient and low temperature conversion of $CO_2$ to CO in small scale reactions are available.[4]

In order to increase the efficiency of the isotope-labeling step, we have earlier demonstrated the beneficial application of stoichiometric aryl- and methyl-Pd complexes for trapping the labeled CO and incorporation into the amide group of the target compound.[5] Nevertheless, the Pd-mediated aminocarbonylations have their limitations, including restriction to the introduction of a carboxamide functionality onto an $sp^2$-hybridized carbon.[6] As such, this methodology is less suited for carbon isotope labeling of bioactive compounds composed of aliphatic carboxamides, such as the examples in Scheme 1, because of the propensity of the intermediate alkyl-Pd species to undergo competing β-hydride elimination.[7]




***Scheme 1.*** Strategy for Ni-mediated aminocarbonylation with Negishi reagents and adaptation to carbon isotope labeling.

In contrast to palladium, alkyl-Ni complexes generally display greater stability towards β-hydride elimination.[8] Therefore, we contemplated whether such organometallic complexes could serve as suitable reagents for the efficient and late-stage introduction of a carbon isotope into the carbonyl group of pharmaceutical or agrochemical relevant molecules containing aliphatic carboxamides.[9] Our approach to a Ni-mediated aminocarbonylation was also designed to limit the aptitude of nickel to generate multicarbonyl metal species by the use of $Ni^{II}$-pincer complexes, as earlier demonstrated in our work on the carbonylative route to benzyl alkyl ketones.[10] Hence, as illustrated in Scheme 1, transmetalation of a suitable pincer $Ni^{II}$-Cl with an alkylzinc reagent and subsequent CO insertion in the presence of stoichiometric amounts of the gaseous reagent would lead to an acyl-$Ni^{II}$ species. The question was then whether treatment with an appropriate amine could lead directly to the desired carboxamide upon reductive elimination. Such an event could possibly take place by one of two scenarios. Either from the intermediate [($NN_2$-pincer)$Ni^{II}$(C(O)alkyl)($NR_1R_2$)$^-$, or from direct nucleophilic acyl substitution with the acyl-$Ni^{II}$ complex. Alternatively, nucleophiles such

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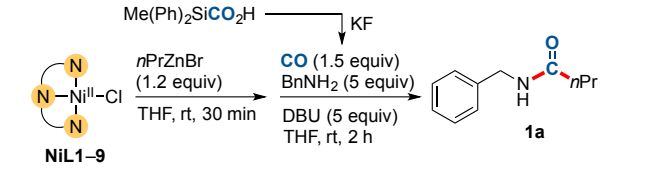
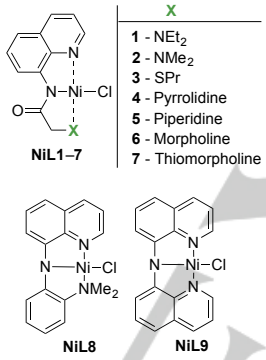
as *N*-hydroxyimides or thiols could potentially be used to generate after reductive elimination an activated ester for an ensuing amide formation.

In this communication, we demonstrate for the first time the viability of applying pincer $Ni^{II}$-complexes for carboxamide synthesis with alkylzinc reagents, as well as the suitability of this approach for the late-stage introduction of a carbon isotope into aliphatic carboxyamides. This is revealed by the use of stoichiometric amounts of $^{13}C$-labeled carbon monoxide applying our two-chamber technology and an isotope labeled CO releasing molecule.[11]

***Table 1.*** Initial results and optimization of aminocarbonylation.[a,b]




| Entry | Nickel Chloride | NMR Yield (Isolated yield)[c] |
|---|---|---|
| 1 | NiL1 | 12 |
| 2 | NiL2 | 19 |
| 3 | NiL3 | 53 |
| 4 | NiL4 | 25 |
| 5 | NiL5 | 80 |
| 6 | NiL6 | 98 (95) |
| 7 | NiL7 | 99 |
| 8 | NiL8 | 14 |
| 9 | NiL9 | 8 |
| 10[d] | NiL2 | 40 |
| 11[e] | NiL6 | 49 |




[a] All reactions were conducted in a two-chamber setup, in which CO was released from a solid precursor in one chamber; see Supporting Information for full detail. [b] Reactions were run using 0.05 mmol of the NiL complex at a concentration of 0.045 M. [c] NMR yield was determined by using dibenzyl ether as internal standard. Isolated yield is shown in brackets, where the reaction was conducted on a 0.2 mmol scale. [d] Reaction was left for 16 h. [e] All reagents were added from the beginning.

Our investigations began with the identification of an appropriate pincer $Ni^{II}$-complex that could be adopted for the preparation of aliphatic acyl-$Ni^{II}$ complexes, and subsequent carboxamide synthesis upon amine addition. In initial work, we discovered that the more well-known pincer Ni(II)-compounds, such as Hu's $NN_2$-(nickamine) and Gade's $NP_2$-complexes[12,13] were not suitable for the desired chemistry. In the former case, direct reductive elimination of the acyl complex with the amido nitrogen of the ligand was observed after the CO insertion step, whereas in the latter case, substantial degradation was observed before the amine addition step. In contrast, we have earlier shown that the $NN_2$-Ni-Cl complex **NiL1** provides a stable acyl-Ni complex.[10,14] To our delight, when the corresponding acyl metal complex formed from initial treatment with *n*-propylzinc bromide followed by 1.5 equivalents of CO (from SilaCOgen) was subjected to excess benzylamine in the presence of DBU, a 12% yield of the desired amide **1a** was obtained (Table 1, entry 1). Subsequent exchange of the pincer ligand's *N*,*N*-diethylamino group with alternative substituents as illustrated with **NiL2**–**NiL7** not only led to a substantial increase of the yield of the reductive elimination step to **1a**, but also a remarkable rate enhancement. Thus, introduction of morpholine or thiomorpholine as in **NiL6** and **NiL7** provided an almost quantitative yield of the amide (entries 6 and 7), and in the former case, a 95% isolated yield of amide **1a**. Other pincer ligand modifications as with **NiL8** and **NiL9** proved nonbeneficial (entries 8 and 9). Increasing the reaction time from 2 to 16 h with **NiL2** (dimethylamino) increased the yield by two fold, but still only to 40% yield (entry 10). Adding all reagents to **NiL6** at the same time proved also to be less efficient for the production of carboxamide **1a** (entry 11).

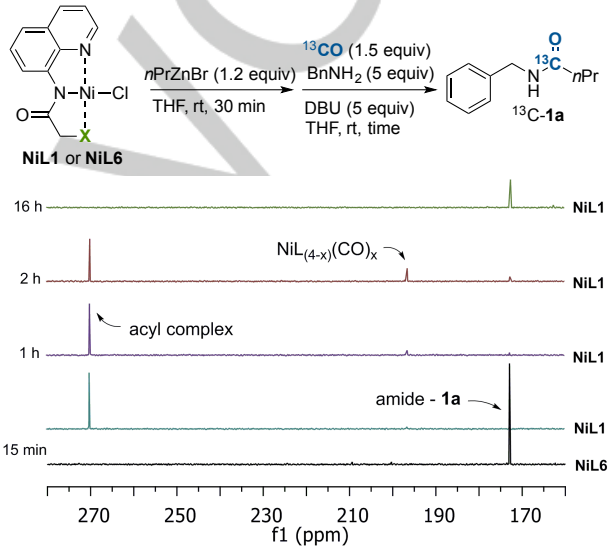



***Figure 1.*** Amide formation studies over time monitored with $^{13}C$-NMR spectroscopy employing nickel(II) pincer complexes **NiL1** and **NiL6**.

The substantial rate increase for these transformations with complexes **NiL6** and **NiL7** was determined by monitoring the progression of the reactions by $^{13}C$-NMR spectroscopy with the use of $^{13}C$-labeled CO prepared from $^{13}C$-SilaCOgen (Figure 1). Little conversion to amide $^{13}C$-**1a** by reductive elimination of the acyl-Ni complex produced from **NiL1** in the presence of the amine was observed after 1 h. Only after a reaction time of 16 h was complete consumption of the acyl-metal complex achieved providing a single peak for the amide carbonyl carbon. On the other hand, for **NiL6**, complete conversion to amide $^{13}C$-**1a** was observed, when the sample was run after 15 min. The exact reasons for this significant rate increase upon introduction of a morpholino group onto the pincer ligand is not fully understood, but the short reaction time does suggest that this strategy may be adapted to carbon-11 labeling ($t_{1/2}$ = 20.1 min).

With the optimized conditions in hand, we then commenced a study on the generality of this transformation (Scheme 2). First, a variety of alkylzinc reagents was examined in their carbonylative coupling with benzylamine, resulting in the formation of carboxamides **1a** to $^{13}C$-**1l** in yields ranging from 35–95%.[15] Functional

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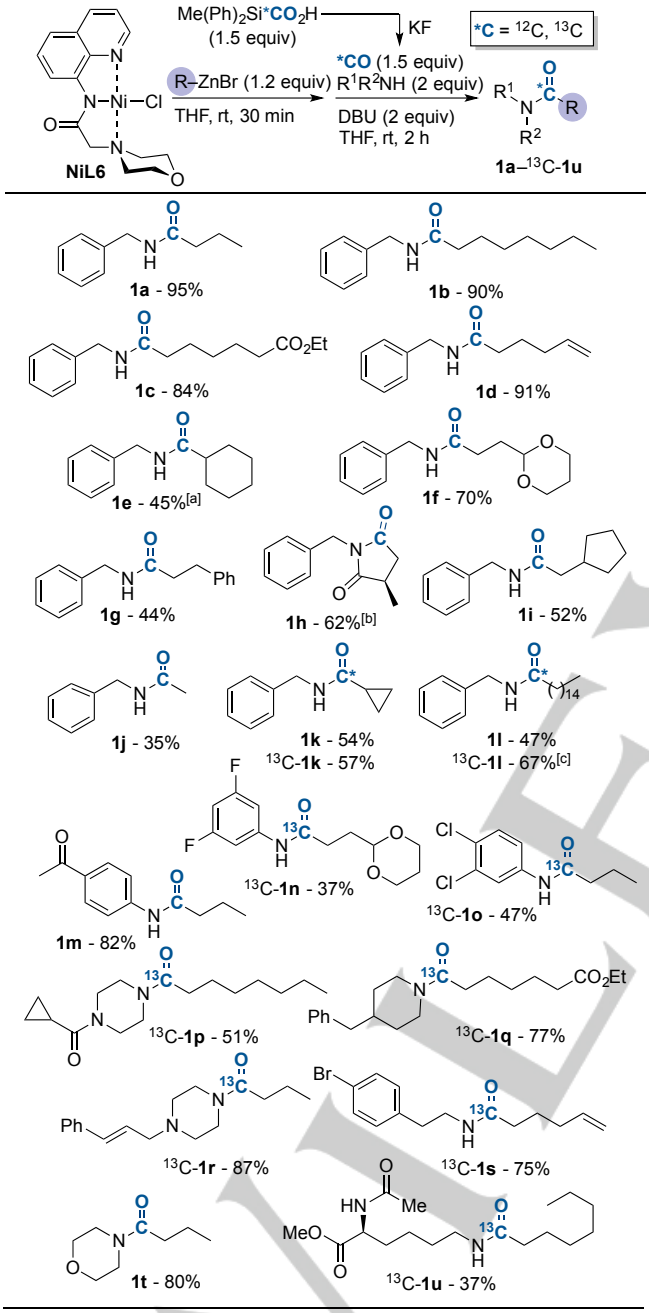
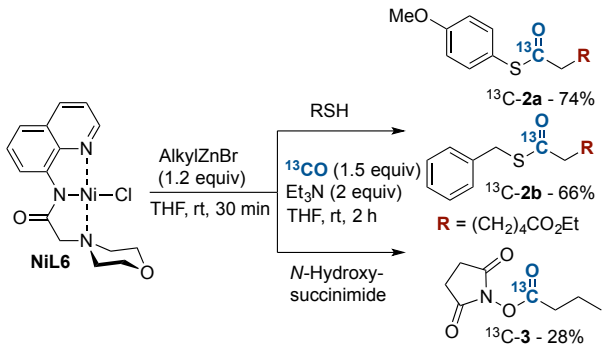
groups such as a carboxylate, alkene and acetal were well tolerated under the reaction conditions, affording the products in good overall yields as exemplified with compounds **1c**, **1d** and **1f**. In the case of the zinc reagent, 3-methoxy-2-methyl-3-oxopropylzinc-bromide, the aminocarbonylation was followed up by an intramolecular cyclization to generate the imide **1h**. A modest yield for compound **1j** was obtained using methylzinc chloride with acetone observed as the major side product.[16] On the other hand, the use of cyclohexylzinc bromide, representing a secondary alkyl Negishi reagent, turned out to be challenging. While the conditions above were initially studied, no product was observed, and the reaction immediately turned black upon addition of the alkyzinc reagent. Gratifyingly, it was found that the product **1e** could be obtained in a 45% yield, when the transmetalation step was performed in the presence of carbon monoxide for 1 h, before the addition of benzylamine and DBU. $^{13}$C-Labeled carboxamides could be achieved with $^{13}$C-silaCOgen as the $^{13}$C-CO source, which was illustrated with the products $^{13}$C-**1k** and $^{13}$C-**1l**. It should be mentioned that we did examine other nickel pincer complexes for one of the moderate yielding reactions (e.g. compound **1g**) in an attempt to improve this yield. As such, the next best complexes **NiL3** and **NiL5** were tested for this reaction, although in both cases, the aminocarbonylation proved less efficient providing **1g** with isolated yields of 9% and 38%, respectively.




***Scheme 2.*** Scope of aminocarbonylation. All reactions were conducted using Method A in a two-chamber setup, in which CO was released from a solid precursor in one chamber; see Supporting Information for full details. Yields are isolated. [a] Conducted using Method B (see Supporting Information for full details). [b] Starting from (*S*)-3-methoxy-2-methyl-3-oxopropylzinc bromide. [c] Run with 5 equiv. of benzylamine.

The reactivity of various amines in combination with different alkylzinc reagents was also explored, some with stochiometric $^{13}$C-CO as well. Different anilines were tolerated in the reaction, providing the corresponding carboxamides **1m**, $^{13}$C-**1n** and $^{13}$C-**1o** in yields ranging from 37–82%. It was also possible to employ secondary amines in the transformation, providing amides $^{13}$C-**1p**–$^{13}$C-**1r** and **1t** in good overall yields (51–87%). It is worth highlighting that compound $^{13}$C-**1r** represents the $^{13}$C-labeled version of the analgesic drug, bucinnazine. Furthermore, an amine containing an aryl bromide could be coupled in a good 75% yield as shown for compound **1s**, allowing a handle for further manipulations. Finally, a partially protected lysine underwent acylation with $^{13}$C-CO to generate the corresponding carboxyamide $^{13}$C-**1u**. Although the yield is modest and will require further optimization, thus demonstrating the option of using this method for labeling lysine residues with aliphatic acyl groups.




***Scheme 3.*** Conversion of Negishi reagents to thioesters and an ester of *N*-hydroxysuccinimide. All reactions were conducted in a two-chamber setup, in which CO was released from a solid precursor in one chamber; see Supporting Information for full detail. Yields are isolated.

In a final demonstration, we investigated the possibility of synthesizing carbon isotope-labeled activated esters as shown in Scheme 3. Starting from the Ni$^{II}$-complex **NiL6** and substituting

the amine nucleophile with thiols, provided the $^{13}$C-labeled thioesters $^{13}$C-**2a** and $^{13}$C-**2b** in satisfactory yields. Furthermore, when *N*-hydroxysuccinimide (NHS) was used, the corresponding NHS-ester $^{13}$C-**3** could be produced in an unoptimized yield.

In summary, a novel protocol has been developed for the acylation of amines applying a new class of Ni$^{II}$-pincer complexes, carbon monoxide and alkylzinc reagents. Particularly noteworthy with this method is its adaptability to carbon-isotope labeling by the use of isotope labeled CO. We believe this method will find suitable applications for carbon-14 labeling of pharmaceutically relevant molecules, and considering the fast reaction times as illustrated in one of the examples, it could also find uses for isotope-labeling with the short-lived carbon-11.

**Acknowledgments**

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**Keywords:** • aminocarbonylation • nickel • pincer complexes • alkylzinc reagents • isotope-labeling

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[16] The formation of acetone could originate either from the anionic Ni$^{II}$-species, [(NN$_2$-pincer)Ni$^{II}$(C(O)CH$_3$)(CH$_3$)$^-$, generated from the reaction of [(NN$_2$-pincer)Ni$^{II}$(C(O)CH$_3$) with methylzinc chloride, or from the direct acyl substitution of the acyl-Ni$^{II}$ complex with the methylzinc reagent.

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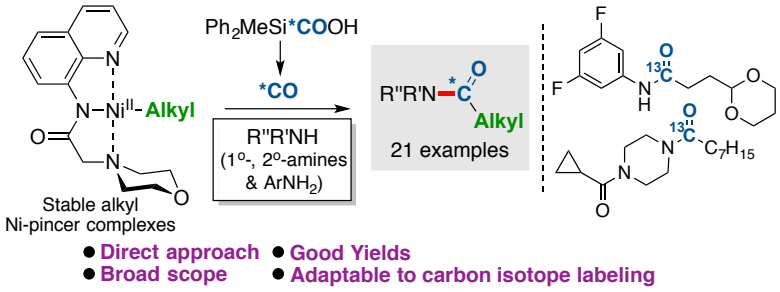


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**Synthesis of Aliphatic Carboxamides Mediated by Nickel $NN_2$-Pincer Complexes and Adaptation to Carbon Isotope-Labeling**

**Nickel is best:** Specific alkyl nickel $NN_2$-pincer complexes could easily be converted to the corresponding acyl-Ni(II) derivatives in the presence of stoichiometric CO. Subsequent reaction with an amine leads to aliphatic carboxamides, providing a new method for the carbon isotope-labeling of this important functional group.