Decarbonylation

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Nickel-Catalyzed Decarbonylative Borylation of Amides: Evidence for Acyl C–N Bond Activation

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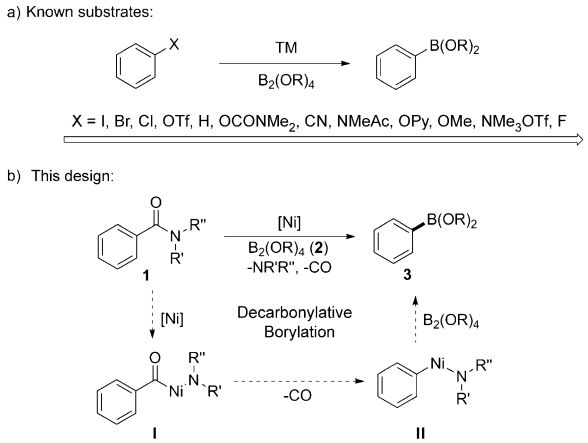
Abstract: *A nickel/N-heterocyclic carbene catalytic system has been established for decarbonylative borylation of amides with B_2nep_2 by C–N bond activation. This transformation shows good functional-group compatibility and can serve as a powerful synthetic tool for late-stage borylation of amide groups in complex compounds. More importantly, as a key intermediate, the structure of an acyl nickel complex was first confirmed by X-ray analysis. Furthermore, the decarbonylative process was also observed. These findings confirm the key mechanistic features of the acyl C–N bond activation process.*

Arylboronic acids or arylboronates are versatile synthetic intermediates in modern organic synthesis.[1] These compounds are usually prepared by either alkyl and aryl lithium compounds or Grignard reagents, processes which are not compatible with numerous functional groups.[2] In recent years, the development of transition-metal-catalyzed Miyaura borylation reactions has allowed the synthesis of aryl boronate esters under mild reaction conditions (Scheme 1 a). Numerous palladium-catalyzed methods have emerged for the conversion of aryl iodides, bromides, chlorides, and triflates into either the corresponding pinacol or catechol boronate esters.[3] Remarkably, borylation of unreactive bonds has shown promise because it confers synthetic versatility of such inert functional groups.[4] Among them, nickel-catalyzed[5] cleavage of C–O and C–N bonds have led to the cross-coupling of unconventional phenol- and aniline-based electrophiles, such as aryl carbamates,[6] ethers,[7] N-aryl amides,[8] ammonium triflates,[9] and cleavage of C–F bonds have allowed the cross-coupling of various fluoroarenes.[10] Since Yamamoto et al. demonstrated the stoichiometric nickel(0)-mediated decarbonylation of aryl carboxylates via an acylmetal species in 1980,[11] catalytic decarbonylative coupling reactions of aroyl derivatives, including acyl chlorides,[12] ketones,[13] carboxylic anhydrides,[14] carboxylates,[15] phthalimides,[16] aldehydes,[17] isatins,[18] and distorted cyclic imides,[19] have been reported in succession.[20] Despite the reported advances, the decarbonylative Miyaura borylation process has been virtually unexplored.

Amides are abundant in naturally occurring and artificial chemicals, and are poor electrophiles because of the resonance stability of the amide bond. In 2015, Garg and Houk et al.[21] reported an important breakthrough for the conversion of amides into esters by nickel-catalyzed activation of the amide C–N bond. DFT calculations support a catalytic cycle which involves a rate-determining oxidative addition step, followed by ligand exchange and reductive elimination. With the aim of developing borylation of amides using nickel salts, we hypothesized that the acyl nickel(II) intermediate **I**, formed after nickel(0) insertion into the inert C(acyl)–N bond, might undergo decarbonylation to give the aryl nickel intermediate **II**, thereby providing access to Miyaura borylation reactions (Scheme 1 b). To achieve this goal, several difficulties need to be considered: 1) this transformation is to cleave a stable C–N bond while forming an easily transformable C–B bond; 2) the C–N bond scission[22] has a high activation energy and its selective cleavage in the presence of C–H, C–O, and C–F bonds is challenging; 3) the arylboronate products have a tendency to undergo Suzuki–Miyaura coupling with unconsumed amides.[23] Herein we report our results on the utilization of N-Boc-activated secondary amides as the electrophilic component in a nickel-catalyzed decarbonylative borylation reaction.



Scheme 1. Miyaura borylation reactions. Tf = trifluoromethanesulfonyl, TM = transition metal.

Initial studies involved the evaluation of the selective borylation of the imide derivative **1a** with $B_2(nep)_2$ (Table 1). In the presence of 10 mol% $[Ni(COD)_2]$, 15 mol% PCy_3, and 3.0 equivalents K_3PO_4, at 150 °C under an Ar atmosphere in toluene. We indeed observed, by GC-MS, the desired product **3aa** in trace amounts after 24 hours (entry 1). Among various NHC ligands (**L1**–**L5**), a dramatic effect of ICy·HCl (**L3**) was observed with 46% yield of **3aa** (entry 3). Under these reaction conditions, K_2CO_3 was not as effective as K_3PO_4 (Table 1, entry 4), and nearly the same yield was observed by

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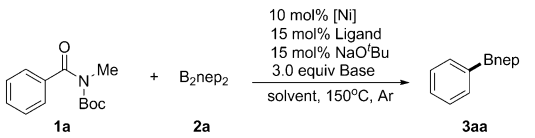
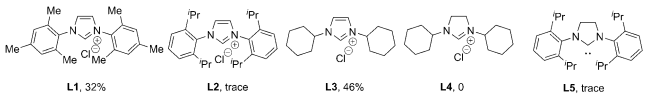
Table 1: Reaction development.[a]



1a 2a 3aa

Entry	[*M*]	L	Base	Solvent	Yield [%][b]
1	$[Ni(COD)_2]$	PCy_3	K_3PO_4	toluene	trace
2	$[Ni(COD)_2]$	**L1**	K_3PO_4	toluene	32
3	$[Ni(COD)_2]$	**L3**	K_3PO_4	toluene	46
4	$[Ni(COD)_2]$	**L3**	K_2CO_3	toluene	25
5	$[Ni(COD)_2]$	**L3**	KOAc	toluene	44
6	$[Ni(COD)_2]$	**L3**	K_3PO_4	*c*Hexane	58
7	$[Ni(COD)_2]$	**L3**	K_3PO_4	toluene/*c*Hexane	65
8	$[Ni(COD)_2]$	ICy	K_3PO_4	toluene/*c*Hexane	66
9	$Ni(OAc)_2{\cdot}4H_2O$	**L3**	K_3PO_4	toluene/*c*Hexane	82 (72)[c]
10	$Ni(OAc)_2$	**L3**	K_3PO_4	toluene/*c*Hexane	75
11	$Ni(OTf)_2$	**L3**	K_3PO_4	toluene/*c*Hexane	60
12[d]	$Ni(OAc)_2{\cdot}4H_2O$	**L3**	K_3PO_4	toluene/*c*Hexane	75
13[e]	$Ni(OAc)_2{\cdot}4H_2O$	**L3**	K_3PO_4	toluene/*c*Hexane	70
14	–	**L3**	K_3PO_4	toluene/*c*Hexane	0

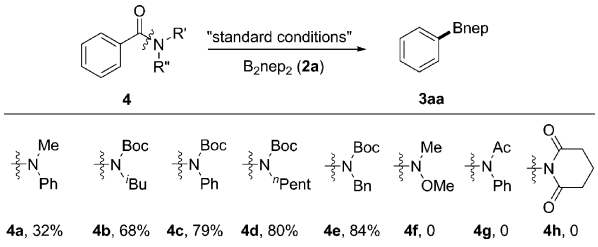
[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.60 mmol) in solvent (3.0 mL), 24 h, under Ar. [b] Determined by GC analysis. [c] Yield of isolated product. [d] At 120°C. [e] Using 5 mol% catalyst. Boc = *tert*-butoxycarbonyl, COD = 1,5-cyclooctadiene, nep = neopentyl glycolato.



L1, 32% **L2**, trace **L3**, 46% **L4**, 0 **L5**, trace

employing AcOK as the base (entry 5). Changing the solvent to cyclohexane provided 58% yield of **3aa** (entry 6). Using a binary solvent system, toluene and cyclohexane (v/v = 1:2), resulted in much higher yield (entry 7). Removing HCl in **L3** did not affect the reactivity (entry 8). To our delight, the more stable and less expensive nickel salt $Ni(OAc)_2{\cdot}4H_2O$ functioned as a pre-catalyst and exhibited higher reactivity and afforded the product **3aa** in 82% yield (entry 9). Other nickel sources such as anhydrous $Ni(OAc)_2$ and $Ni(OTf)_2$ were also proven successful in this coupling reaction with a high reactivity (entries 10 and 11). Temperature effect was also examined, and 150°C was found to be optimal (entry 12). Notably, decreasing the $Ni(OAc)_2{\cdot}4H_2O$ loading to 5 mol% still resulted in a good yield (entry 13), and no product was observed in the absence of the nickel catalyst (entry 14)

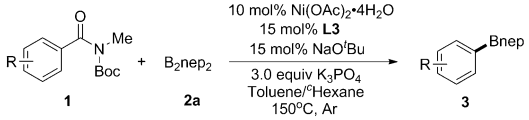
Under the optimized reaction conditions, a range of electronically and sterically varies amides were tested (Scheme 2). The use of the anilide **4a** only led to 32% yield (GC) of the desired product. The N-Boc-substituted imides **4b–e** generated the borylation products in moderate to good yields (68–84%) and coupling of the Weinreb amide **4f**, *N*-acetyl-*N*-phenylbenzamide (**4g**), and the distorted cyclic imide **4h** were completely unsuccessful. These results show a unique behavior of the N-Boc-activated imide group in this transformation.



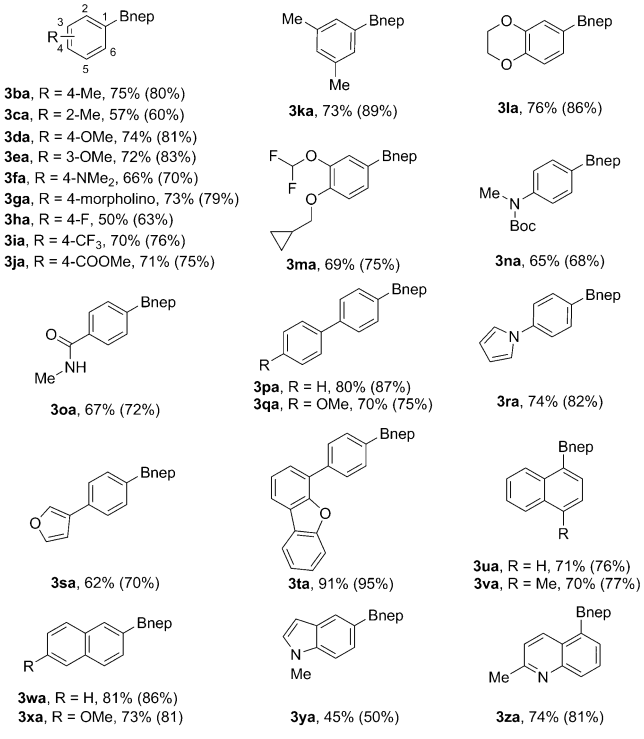
4a, 32% **4b**, 68% **4c**, 79% **4d**, 80% **4e**, 84% **4f**, 0 **4g**, 0 **4h**, 0

Scheme 2. Evaluating different amide groups.

Table 2: Nickel-catalyzed borylation of acyl C–N bonds.[a]



1 2a 3

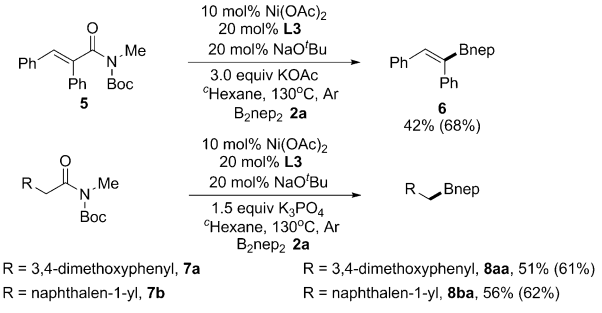


[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), 10 mol% of $Ni(OAc)_2{\cdot}4H_2O$, 15 mol% of **L3**, 15 mol% of NaO*t*Bu, 3.0 equiv of K_3PO_4 in 3.0 mL toluene/*c*Hexane (v/v = 1:2) at 150°C, 24 h, under Ar. Yield is that of isolated product. Yields given within parentheses were determined by ^{1}H NMR analysis of crude reaction mixture.

To evaluate the utility of this decarbonylative borylation reaction, a series of N-Me-N-Boc imides were tested (Table 2). As shown, a wide range of imides which incorporate electron-neutral, electron-donating, and electron-withdrawing substituents at the *ortho*, *meta*, and *para* positions were readily tolerated (**3ba–oa**). The chemoselectivity profile of this method was nicely illustrated by the fact that ethers (**3da**,**3ea**, **3la**,**ma**), amines (**3fa**,**ga**), fluoro-containing substrates (**3ha**,**ia**), and esters (**3ja**) could all be equally accommodated. The unique selectivity toward N-Me-N-Boc imides was corroborated by the presence of other types of amide C–N bonds such as BocNMe (**3na**) and CONHMe (**3oa**). Moreover, a wide variety of π-extended systems participated in the reaction to afford the borylation products **3pa–ta** in moderate to high yields. Importantly, the presence of substituted nitrogen- and oxygen-containing heterocycles (**3ra–ta**) did not interfere with productive C–B bond for-

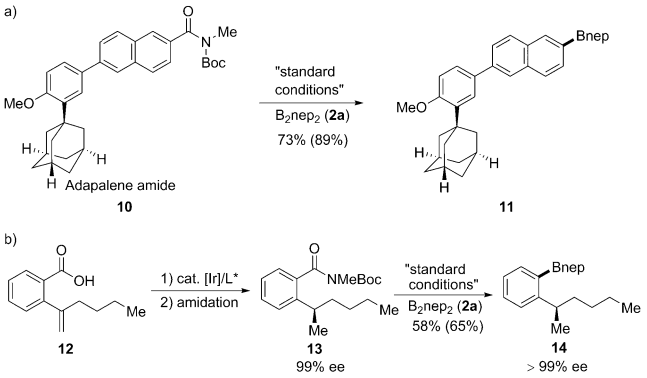
mation. Polyaromatic substrates, including naphthalenes (**3ua–xa**), indoles (**3ya**), and quinolones (**3za**) were also shown to exhibit high levels of reactivity.

As shown in Scheme 3, this approach also allowed the breakdown of α,β-unsaturated imides such as **5**, thus providing a method of synthesizing alkenyl boronic acid derivatives. In addition, when 2-(3,4-dimethoxyphenyl) and 1-(naphthalen-1-yl)amide (**7a**,**b**) were treated with **2a** under the standard reaction conditions, the corresponding decarbonylative borylation products **8a**,**b** were produced in moderate yields by sp^3 C–B bond formation.



Scheme 3. Further investigations. **L3** = ICy·HCl.

This nickel-catalyzed borylation reaction was also viable with complex molecular precursors. For example, Adapalene (**9**),[24] a second-generation topical retinoid primarily used in the treatment of mild to moderate acne, could be subjected, after imidation, to decarbonylative borylation with **2a** to produce the arylboronate **11** in 73% yield upon isolation (Scheme 4a). An iridium-catalyzed carboxy-directed asymmetric hydrogenation of the olefin **12** can provide the carboxylic acid product with a chiral benzylmethyl center.[25] The corresponding amidation substrate underwent borylation to give the desired product **14** in moderate yield, thus retaining the stereochemistry (Scheme 4b).



Scheme 4. Synthetic applications.

The events for nickel-catalyzed acyl C–O[15f,26] and C–N[20] bond cleavage were supported by DFT calculations. As a key intermediate, the transient acylnickel(II) species has never been structurally characterized. To our surprise, the treatment of the imide **1v** with [Ni(COD)$_2$] and **L3** in toluene/cyclohexane at 35 °C resulted in the formation of the acylnickel species **1v-1**, which was isolated in 59% yield (Figure 1). The molecular structure of **1v-1** was confirmed by NMR spectroscopy and X-ray analysis, and notably, this complex was stable in DCM/*n*-hexane solution at room temperature under air for at least two weeks. The structure displays the expected square-planar geometry, stabilized by two carbene ligands *trans* to each other. However, by just elevating reaction temperature to 50 °C, **1v-1** undergoes decarbonylation to produce the aryl nickel intermediate **1v-2** with full conversion. This complex was obtained in pure form after column chromatography, and was also confirmed by NMR spectroscopy and X-ray analysis.[27] These experiments suggested that the barrier to CO deinsertion/decarbonylation probably has a large entropic term and may not be rate limiting at 50 °C. Upon treatment with B_2nep_2, **1v-2** was converted into the corresponding arylboronate **3av** at 60 °C in 82% yield with the help of K_3PO_4. Furthermore, product **3av** was formed in 75% yield using **1v-1** as the catalyst at 150 °C

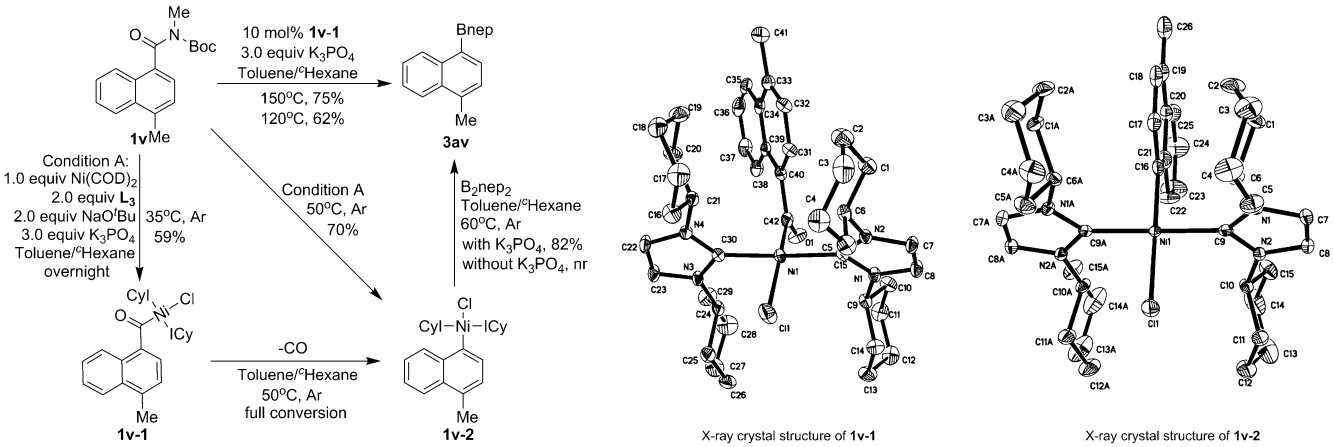
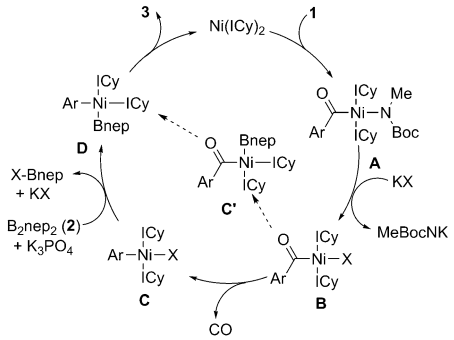


Figure 1. Stoichiometric reaction of the amide **1v** with [Ni(COD)$_2$] and catalytic process using intermediate **1v-1** as the catatyst. ORTEP representation[29] of **1v-1** and **1v-2** with thermal ellipsoids at a 30% probability level. H atoms are omitted for clarity. Selected bond lengths of **1v-1** (Å): O1-C42 1.269(8), C15-Ni1 1.927(6), C30-Ni1 1.923(6), C42-Ni1 1.845(7), Cl1-Ni1 2.288(2). Selected bond lengths of **1v-2** (Å): C9-Ni 1.908(4), C16-Ni 1.889(6), Cl1-Ni1 2.2455(15), C9A-Ni1 1.908(4). nr = no reaction.

(62% at 120°C), and was confirmed as a viable intermediate in the catalytic cycle. Compared with each steps in stoichiometric reaction, the catalytic process obviously needs a much higher reaction temperature.

Because of the first separation and characterization of these key organonickel(II) intermediates in acyl C–N bond activation, we were encouraged to investigate the mechanism for this new reaction (Scheme 5). This reaction is triggered by



Scheme 5. Proposed catalytic cycle.

oxidative addition of the nickel(0) catalyst to the imide C–N bond to generate the *trans* acylnickel(II) intermediate **A**. This complex can easily undergo ligand exchange with Cl^-, thus generating the *trans* acyl nickel species **B**, followed by decarbonylation to the aryl nickel species **C**. Considering that Cl^- is not a critical factor for this transformation (as shown in Table 1, entry 8), we believe that other anionic reagents in the system such as AcO^-, $tBuO^-$, or PO_4^{3-} can play the same role. Decarbonylation of **B** to *trans* aryl nickel species **C**, followed by boryl transfer assisted by the base[28] and subsequent *cis* reductive elimination delivers the targeted product **3** and regenerates the $[Ni(ICy)_2]$ species. Based on our experimental investigations, an alternative process involving boryl transfer of **B** ahead of decarbonylation can be excluded at this point.

In summary, we have developed an efficient nickel-catalyzed system which is capable of activating amide C–N bonds for decarbonylative borylation to produce various organoboronates. In view of the widespread occurrence of the amide group and the precursor carboxylic acid group in chemicals, this method offers a meaningful tool to enable their use as valuable building blocks. Moreover, the elucidation of key mechanistic features of this newly developed reaction led to the identification of two well-characterized nickel intermediates. Studies to determine further mechanistic details of this borylation process, as well as to expand the scope of this transformation are underway in our laboratory.

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Keywords: amides · boron · decarbonylation · nickel · structure elucidation

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[29] CCDC 1481576 (**1v-1**) and 1481577 (**1v-2**)contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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