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Suzuki–Miyaura Cross-Coupling of Amides Using Well-Defined, Air- and Moisture-Stable Nickel/NHC (NHC = N-Heterocyclic Carbene) Complexes

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Abstract: In this Special Issue on *N-Heterocyclic Carbenes and Their Complexes in Catalysis*, we report the first example of Suzuki–Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable nickel/NHC (NHC = N-heterocyclic carbene) complexes. The selective amide bond N–C(O) activation is achieved by half-sandwich, cyclopentadienyl [CpNi(NHC)Cl] complexes. The following order of reactivity of NHC ligands has been found: IPr > IMes > IPaul ≈ IPr*. Both the neutral and the cationic complexes are efficient catalysts for the Suzuki-Miyaura cross-coupling of amides. Kinetic studies demonstrate that the reactions are complete in < 1 h at 80 °C. Complete selectivity for the cleavage of exocyclic N-acyl bond has been observed under the experimental conditions. Given the utility of nickel catalysis in activating unreactive bonds, we believe that well-defined and bench-stable [CpNi(NHC)Cl] complexes will find broad application in amide bond and related cross-couplings of bench-stable acyl-electrophiles.

Keywords: N-heterocyclic carbenes; nickel; nickel/NHC; amide bonds; Suzuki–Miyaura; cross-coupling; N–C cleavage; N–C activation; [CpNi(NHC)X]; half-sandwich; cyclopentadienyl

1. Introduction

Nickel catalysis has recently garnered significant attention, enabling cleavage of unreactive bonds by this abundant 3d transition metal [1–3]. Simultaneously, major advances have been made in amide cross-coupling, wherein highly selective oxidative addition of the N–C(O) bond enables to exploit the traditionally unreactive amides as a novel class of acyl and aryl electrophiles [4–10]. This unconventional amide bond disconnection is particularly relevant in the view of common presence of amides in natural products, pharmaceuticals and biopolymers, where the emergence of new catalytic methods has a potentially major impact on the way chemists perceive synthetic routes.

In this context, palladium/NHC (NHC = N-heterocyclic carbene) catalysis using well-defined Pd(II)–NHC precatalysts has been established as the dominant catalytic direction in activating amide N–C(O) bonds for acyl cross-coupling [4, 11–14]. However, to the best of our knowledge, there are no methods for the use of well-defined, air- and moisture-stable nickel/NHC complexes as efficient precatalysts in amide bond activation. In spite of the advances made by *in situ* formed Ni(0) catalysts, the lack of air-stability of $Ni(cod)_2$ severely limits the potential broad applications of the powerful Ni catalysis platform in amide bond activation [15–17].

In this Special Issue on *N-Heterocyclic Carbenes and Their Complexes in Catalysis*, we report the first example of Suzuki–Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable nickel/NHC (NHC = N-heterocyclic carbene) complexes (Figure 1). We were attracted to the recent elegant advances made in the design of half-sandwich, cyclopentadienyl [CpNi(NHC)X] complexes by Chetcuti and co-workers [18–24]. Herein, we demonstrate that these

highly practical [CpNi(NHC)Cl] precatalysts [25–31] are capable of selective activation of amide N–C(O) bonds. The following features of our study are noteworthy: (1) The reaction represents, to best of our knowledge, the first example of acyl-type cross-coupling achieved by half-sandwich [CpNi(NHC)X] complexes. (2) We demonstrate the following order of reactivity of NHC ligands in amide bond cross-coupling: IPr > IMes > IPaul ≈ IPr*. (3) We further establish that both the neutral and the cationic complexes are efficient catalysts for the Suzuki-Miyaura cross-coupling of amides. (4) Kinetic studies demonstrate that the reactions reach full conversion in < 1 h at 80 °C. (5) Furthermore, full selectivity in cleavage of exocyclic N-acyl bond has been observed. Our method opens up the application of a wide variety of [CpNi(NHC)X] and related half-sandwich complexes as well-defined, air- and moisture stable precatalysts for cross-coupling of amide N–C bonds.

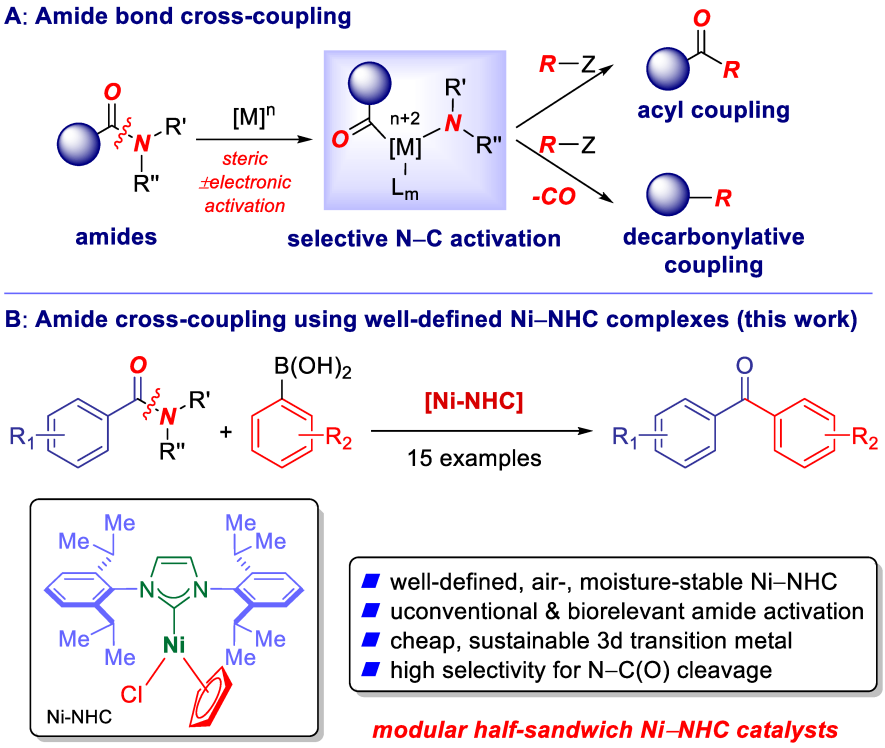


Figure 1. (A) Amide bond cross-coupling. (B) Well-defined, air- and moisture-stable Ni–NHC complexes in selective activation of amide N–C(O) bonds (this work).

2. Results

We first examined the cross-coupling of N-acyl-glutarimides as model substrates for the cross-coupling with 4-tolylboronic acid using the readily prepared [CpNi(IPr)Cl] under various conditions (Table 1, Figure 2) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). Optimization revealed that the desired cross-coupling proceeds in 85% yield in the presence of [CpNi(NHC)Cl] (10 mol%) as catalyst and K_2CO_3 (3.0 equiv) as base in toluene as solvent at 80 °C using 4-Tol-$B(OH)_2$ (3.0 equiv) (Table 1, entry 1). Interestingly, increasing the reaction temperature to 120 °C had only a minor effect on the cross-coupling (Table 1, entries 2-4). Furthermore, although previous studies suggested the beneficial effect of phosphine ligands on the Suzuki–Miyaura $C(sp^2)$–$C(sp^2)$ cross-coupling catalyzed by Ni–NHC complexes [32], in our case the addition of phosphine had an inhibitory effect on the cross-coupling (Table 1, entries 5-7). Examination of reaction parameters revealed K_2CO_3 as the optimal base and toluene as the preferred solvent (Table 1, entries 8-15). Interestingly, the use of Ni/phosphine catalysts, such as $[Ni(PCy_3)_2Cl_2]$ and $[Ni(PPh_3)_2Cl_2]$ resulted in little or no cross-coupling (Table 1, entries 16-19). Likewise, no reaction was observed with nikelocene (Table 1, entry 20) [33], supporting the key role of the NHC ligand on the cross-coupling. Moreover, the recently studied in cross-coupling of aryl sulfamates [Ni(dppf)(*o*-tol)Cl] [34] was unreactive under our conditions (Table 1, entry 21), while the mixed NHC/phosphine Ni(II)

complex, [Ni(IPr)(PPh_3)Cl_2] [35], appeared as a potentially useful catalyst, but was less reactive than [CpNi(IPr)Cl] (Table 1, entry 22).

Pleasingly, the cationic complex [CpNi(IPr)(NCMe)](PF_6), readily prepared by chloride abstraction with KPF_6 according to the procedure Chetcuti [18] showed promising reactivity (Table 1, entries 23-24), indicating potential application of this class of cationic Ni–NHC catalysts in amide bond cross-coupling in the future.

Further, we were particularly interested in evaluating steric demand of NHC ligands on the performance of [CpNi(NHC)Cl] complexes in amide cross-coupling [36,37]. We found that [CpNi(IMes)Cl] is slightly less reactive than [CpNi(IPr)Cl] (Table 1, entries 25-26). Furthermore, examination of the highly attractive class of bulky but flexible NHC ligands, IPaul [38] and IPr* [39] revealed [CpNi(IPaul)Cl] and [CpNi(IPr*)Cl] as promising catalysts for N–C bond activation. Of note, [CpNi(IPaul)Cl] is commercially-available, which should facilitate the discovery of future cross-couplings of amide bonds mediated by this precatalyst.

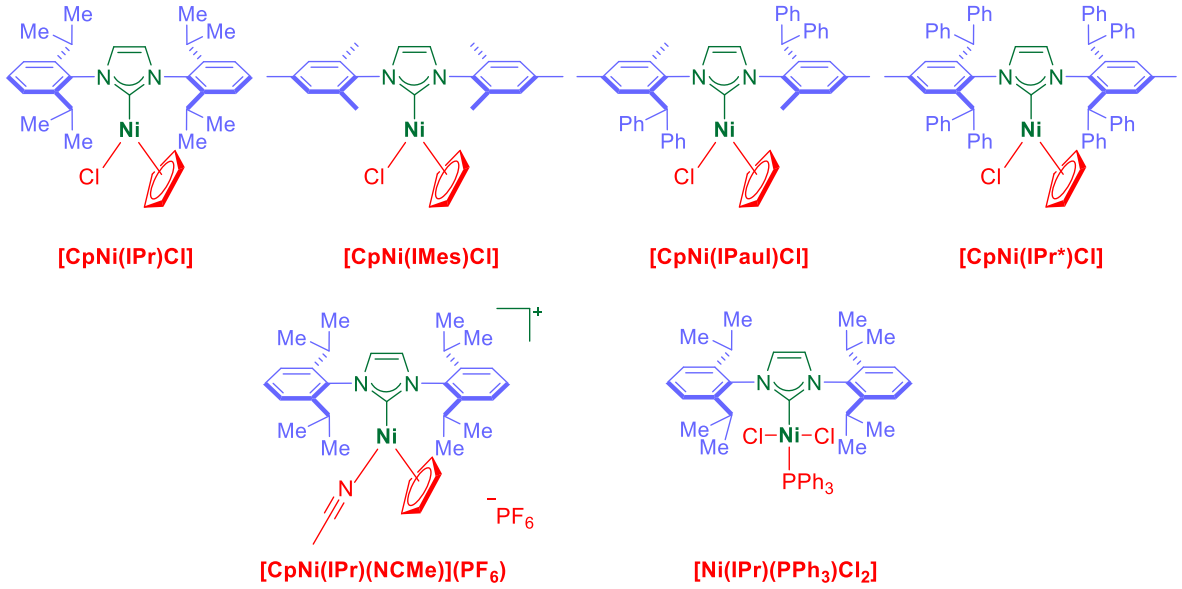
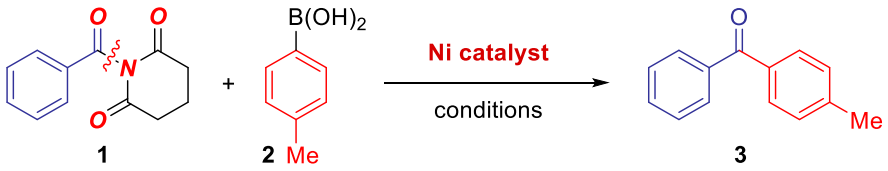


Figure 2. Structures of well-defined, air- and moisture-stable Ni–NHC catalysts.

With the optimized catalyst system in hand, we examined the scope of this Suzuki–Miyaura cross-coupling catalyzed by well-defined Ni(II)–NHC precatalysts (Tables 2 and 3). As shown, the reaction was compatible with electron-donating groups on the boronic acid (**3a-3c**). Steric-hindrance at the ortho-position of the boronic acid was well-tolerated (**3d-3e**). Furthermore, fluorine functionalized boronic acids, such as 3-fluoro and 3-trifluoromethyl (**3f-3g**) could be introduced by this Ni-catalyzed approach. We were further pleased that conjugated arenes, such as naphthalene and biphenyl delivered the desired biaryl ketone products in good yields (**3h-3i**). Only one aliphatic boronic acid was tested, and it was incompatible with the reaction conditions (entry 10). In terms of the amide scope, pleasingly, electron-rich and electron-withdrawing groups were well-tolerated on the amide component (**3a**, **3c**, **3j**), while the electron-deficient amides appeared to be more reactive (*vide infra*). Steric hindrance on the ortho-position of the amide was tolerated, albeit it exerted a more pronounced effect than on the boronic acid, consistent with a decreased amide bond twist by ortho-substitution (**3d**). Furthermore, fluorine-containing amides and heterocyclic amides provided the desired products in good yields (**3k-3l**). It is noteworthy that decarbonylation to give Ar–Ni after loss of CO was not observed [40], consistent with the stability of acyl-Ni(NHC) intermediate.

Next, intermolecular competition experiments were conducted to gain preliminary insight into the reaction (Schemes 1-2). As shown, competitions revealed electron-deficient amides to be significantly more reactive than electron-rich amides (Scheme 1, CF_3:MeO = 93:7). In contrast, a comparable reactivity of electron-rich and electron-deficient boronic acids was observed (Scheme 2, MeO:CF_3, 58:42). These preliminary studies are consistent with oxidative addition of the N–C(O) bond as the rate limiting step of the reaction [41]. Further studies on the mechanism are ongoing.

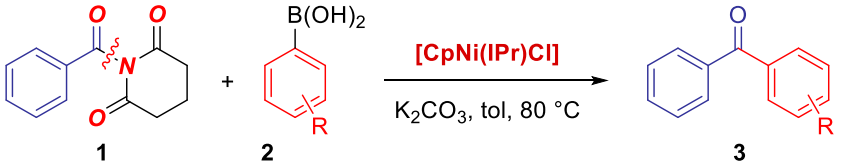
Table 1. Optimization of the Suzuki-Miyaura Cross-Coupling of Amides using Ni–NHCs.[1]



Entry	Catalyst	[Ni] (mol%)	Base	Solvent	*T* (°C)	Yield (%)
1	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	80	85
2	[CpNi(IPr)Cl]	5	K_2CO_3	toluene	80	42
3	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	80
4	[CpNi(IPr)Cl]	5	K_2CO_3	toluene	120	39
5[2]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	40
6[3]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	54
7[3]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	80	27
8	[CpNi(IPr)Cl]	5	K_2CO_3	dioxane	120	34
9	[CpNi(IPr)Cl]	10	K_2CO_3	dioxane	120	48
10	[CpNi(IPr)Cl]	10	K_2CO_3	THF	80	<10
11	[CpNi(IPr)Cl]	10	Na_2CO_3	THF	80	20
12	[CpNi(IPr)Cl]	10	Na_2CO_3	THF	120	<5
13	[CpNi(IPr)Cl]	10	Na_2CO_3	dioxane	80	<5
14	[CpNi(IPr)Cl]	10	Na_2CO_3	dioxane	120	<5
15	[CpNi(IPr)Cl]	10	K_3PO_4	toluene	80	38
16	[Ni(PCy_3)$_2$$Cl_2$]	10	Na_2CO_3	dioxane	80	31
17	[Ni(PCy_3)$_2$$Cl_2$]	10	Na_2CO_3	dioxane	120	16
18	[Ni(PPh_3)$_2$$Cl_2$]	10	K_2CO_3	toluene	120	<5
19	[Ni(PPh_3)$_2$$Cl_2$]	10	Na_2CO_3	dioxane	80	<5
20	[$NiCp_2$]	10	K_2CO_3	toluene	120	<5
21	[Ni(dppf)(*o*-tol)Cl]	10	K_2CO_3	toluene	120	<5
22	[Ni(IPr)(PPh_3)Cl_2]	10	K_2CO_3	toluene	120	64
23	[CpNi(IPr)(NCMe)](PF_6)	10	K_2CO_3	toluene	80	44
24	[CpNi(IPr)(NCMe)](PF_6)	5	K_2CO_3	toluene	80	28
25	[CpNi(IMes)Cl]	10	K_2CO_3	toluene	80	77
26	[CpNi(IMes)Cl]	5	K_2CO_3	toluene	80	40
27	[CpNi(IPaul)Cl]	10	K_2CO_3	toluene	80	68
28	[CpNi(IPaul)Cl]	5	K_2CO_3	toluene	80	39
29	[CpNi(IPr*)Cl]	10	K_2CO_3	toluene	80	63
30	[CpNi(IPr*)Cl]	5	K_2CO_3	toluene	80	42

[1]Conditions: amide (1.0 equiv), 4-Tol-B(OH)$_2$ (3.0 equiv), base (3.0 equiv), [Ni] (5-10 mol%), solvent (0.25 M), *T*, 15 h. [2]PPh_3 (20 mol%). [3]PPh_3 (11 mol%). Yields were determined by ^{1}H NMR.

Table 2. Scope of the Suzuki-Miyaura Cross-Coupling of Amides using [CpNi(IPr)Cl].[1]

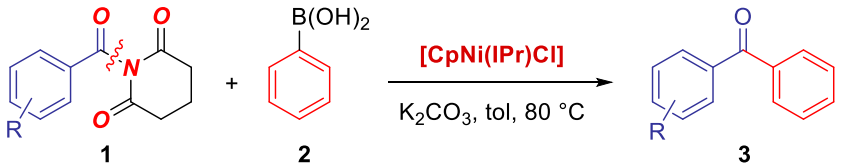


1 2 3

Entry	Amide	Ar-B(OH)$_2$	3	Yield (%)
1	C_6H_5	4-Me-C_6H_4	**3a**	85
2	C_6H_5	4-*t*-Bu-C_6H_4	**3b**	87
3	C_6H_5	4-MeO-C_6H_4	**3c**	79
4	C_6H_5	2-Me-C_6H_4	**3d**	85
5	C_6H_5	2-MeO-C_6H_4	**3e**	58
6	C_6H_5	3-F-C_6H_4	**3f**	48
7	C_6H_5	3-CF_3-C_6H_4	**3g**	56
8	C_6H_5	2-Np	**3h**	71
9	C_6H_5	4-Ph-C_6H_4	**3i**	67
10[2]	C_6H_5	Cyclopentyl	-	<5

[1]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), K_2CO_3 (3.0 equiv), [CpNi(IPr)Cl] (10 mol%), toluene (0.25 M), 80 °C, 15 h. [2]Cyclopentylboronic acid was used.

Table 3. Scope of the Suzuki-Miyaura Cross-Coupling of Amides using [CpNi(IPr)Cl].[1]



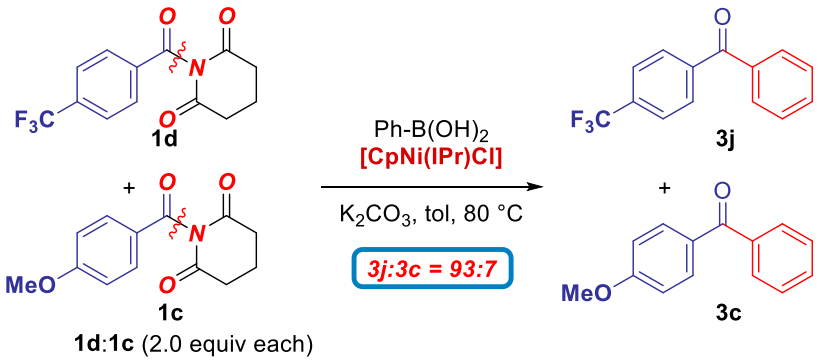
1 2 3

Entry	Amide	Ar-B(OH)$_2$	3	Yield (%)
1	4-Me-C_6H_4	C_6H_5	**3a**	70
2	4-MeO-C_6H_4	C_6H_5	**3c**	67
3	4-CF_3-C_6H_4	C_6H_5	**3j**	96
4	2-Me-C_6H_4	C_6H_5	**3d**	39
5	3,4-F_2-C_6H_3	C_6H_5	**3k**	70
6	2-thienyl	C_6H_5	**3l**	55

[1]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), K_2CO_3 (3.0 equiv), [CpNi(IPr)Cl] (10 mol%), toluene (0.25 M), 80 °C, 15 h.

Kinetic studies were performed to gain insight into the reaction profile (Figure 3). As shown, the reaction reached 75% conversion after 5 min, while 86% and >95% conversion was observed after 30 and 60 min, respectively, consistent with efficient generation of the reactive Ni(0)–NHC catalyst [40,41] under the reaction conditions (TON = 8.5, 10 mol%; TOF = 1.5 min^{-1}). Studies on the mechanism are underway and will be reported in due course.

Finally, we were interested to probe the effect of different acyl leaving groups on the cross-coupling (Scheme 3). N-Acyl-glutarimides have emerged as the go-to amides to develop new cross-coupling methods by N–C activation. Furthermore, the present coupling is compatible with N-sulfonyl activation in acyclic amides, such as N,N-Ph/Ts, and N-acyl-succinimides, albeit the



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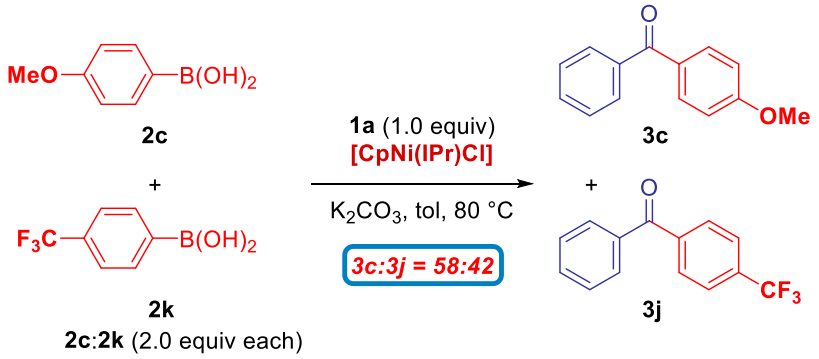
137 **Scheme 1.** Competition experiments – amides.



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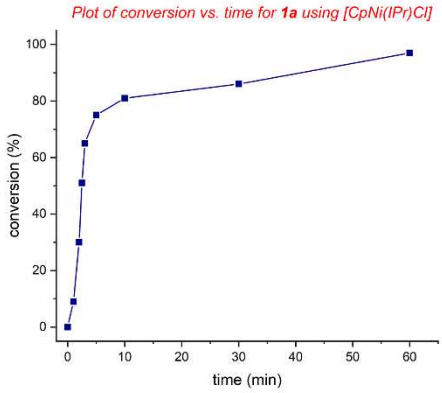
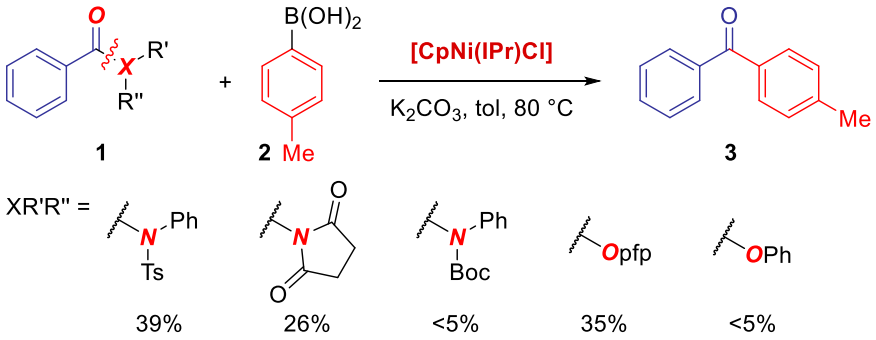
139 **Scheme 2.** Competition experiments – boronic acids.



140

141 **Figure 3.** Kinetic profile of **1a**. Conditions: **1a**, 4-Tol-B(OH)$_2$ (3.0 equiv), [CpNi(IPr)Cl] (10 mol%),
142 K_2CO_3 (3.0 equiv), toluene (0.25 M), 80 °C, 1-60 min.



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144 **Scheme 3.** Suzuki-Miyaura Cross-Coupling of Different Amides and Esters using [CpNi(IPr)Cl].

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cross-coupling product was obtained in lower yield under the present conditions. In contrast, N-Boc-carbamates, were recovered unchanged from the reaction conditions, indicating a potential for chemoselective coupling. Typically, N-Ts amides and N-acyl-succinimides are consumed under the reaction conditions, while other electrophiles were recovered unchanged. Moreover, the C–O cross-coupling is also feasible under the present conditions as demonstrated by the cross-coupling of Opfp ester (pfp = pentafluorophenyl) [42,43]. In contrast, the unactivated phenolic ester was recovered unchanged, consistent with a considerable potential of [CpNi(NHC)Cl] catalysts in chemoselective activation of C(acyl)–O electrophiles.

3. Discussion

In summary, we have reported the first example of Suzuki–Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable nickel/NHC complexes. The reaction delivers biaryl ketones in good yields using inexpensive nickel catalyst with excellent N–C(O) cleavage selectivity cf. endocylic amide bond and acyl vs. decarbonylative coupling. In a broad sense, this report establishes the capacity of highly attractive half-sandwich [CpNi(NHC)Cl] complexes as catalysts for activation of amide N–C(O) bonds. Furthermore, we have established the order of reactivity of NHC ligands in [CpNi(NHC)Cl] complexes as IPr > IMes > IPaul ≈ IPr*, and showed that both neutral and cationic complexes serve as efficient catalysts for amide bond cross-coupling. Reaction profile studies demonstrated that these reactions are complete in < 1 h at 80 °C. In a broader context, the present method should be evaluated in comparison with other known approaches to biaryl ketones from amides [3-10] and acyl electrophiles [15]. The use of Ni catalysis [1-3] and the beneficial performance of Ni–NHC complexes [25-29] may accelerate the development of new approaches to activating amide bonds. Considering the utility of nickel catalysis in activation of unreactive bonds, we anticipate that [CpNi(NHC)Cl] complexes will be of interest in activation of bench-stable acyl electrophiles. Further mechanistic studies as well as efforts to expand the scope of electrophiles in cross-coupling catalyzed by well-defined Ni–NHC complexes are ongoing.

4. Materials and Methods

General Information. General methods have been published.[11]

General Procedure for [CpNi(IPr)Cl] Catalyzed Cross-Coupling of Amides. In a typical cross-coupling procedure, an oven-dried vial was charged with an amide substrate (neat, 1.0 equiv), boronic acid (typically, 3.0 equiv), potassium carbonate (typically, 3.0 equiv), [CpNi(NHC)Cl] (typically, 10 mol%), placed under a positive pressure of argon or nitrogen, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (to reach 0.25 M concentration) was added at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C, and stirred at 80 °C. After the indicated time, the reaction was cooled down, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Unless stated otherwise, all compounds have been previously reported. All compounds have been quantified by ^1H NMR spectroscopy using nitromethane as internal standard (500 MHz, CD_3Cl). All reactions have been carried out in microwave vials with heavy-wall, Type I, Class A borosilicate. These vials are designed to withstand pressures up to 300 PSI (20 bars) and are equivalent to Fisher-Porter tube.

Representative Procedure for [CpNi(IPr)Cl] Catalyzed Cross-Coupling of Amides. An oven-dried vial was charged with 1-benzoylpiperidine-2,6-dione (neat, 108.6 mg, 0.5 mmol), 4-tolylboronic acid (204.0 mg, 1.5 mmol, 3.0 equiv), K_2CO_3 (207.3 mg, 1.5 mmol, 1.5 equiv), [CpNi(IPr)Cl] (10 mol%, 27.4 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.25 M, 2.0 mL) was added at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C, and stirred for 15 h at 80 °C. After the indicated time, the reaction was cooled down, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain

conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product. Yield 81% (79.5 mg). White solid. Characterization data are included in the section below.

Characterization Data for Products 3a-3l (Tables 2-3).

Phenyl(*p*-tolyl)methanone (3a). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82-7.80 (d, *J* = 8.1 Hz, 2 H), 7.76-7.74 (d, *J* = 8.0 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.32-7.28 (d, *J* = 7.9 Hz, 2 H), 2.47 (s, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

(4-(*tert*-Butyl)phenyl)(phenyl)methanone (3b). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84-7.82 (d, *J* = 7.7 Hz, 2 H), 7.80-7.78 (d, *J* = 8.3 Hz, 2 H), 7.61-7.58 (t, *J* = 7.3 Hz, 1 H), 7.53-7.48 (m, 4 H), 1.39 (s, 9 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.45, 156.19, 137.97, 134.85, 132.17, 130.15, 129.98, 128.22, 125.26, 35.13, 31.17.

(4-Methoxyphenyl)(phenyl)methanone (3c). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.87-7.85 (d, *J* = 8.7 Hz, 2 H), 7.79-7.77 (d, *J* = 8.2 Hz, 2 H), 7.61-7.58 (t, *J* = 6.8 Hz, 1 H), 7.51-7.48 (t, *J* = 7.6 Hz, 2 H), 7.00-6.98 (d, *J* = 8.7 Hz, 2 H), 3.92 (s, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

Phenyl(*o*-tolyl)methanone (3d). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84-7.82 (d, *J* = 8.3 Hz, 2 H), 7.62-7.59 (t, *J* = 7.5 Hz, 1H), 7.50-7.47 (t, *J* = 7.9 Hz, 2 H), 7.43-7.40 (t, *J* = 7.5 Hz, 1 H), 7.35-7.31 (t, *J* = 7.8 Hz, 2 H), 7.29-7.26 (t, *J* = 7.5 Hz, 1 H), 2.36 (s, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

(2-Methoxyphenyl)(phenyl)methanone (3e). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85-7.83 (d, *J* = 7.7 Hz, 2 H), 7.59-7.56 (t, *J* = 7.5 Hz, 1 H), 7.51-7.48 (t, *J* = 7.4 Hz, 1 H), 7.47-7.44 (t, *J* = 7.2 Hz, 2 H), 7.39-7.38 (d, *J* = 7.7 Hz, 1 H), 7.08-7.05 (t, *J* = 7.2 Hz, 1 H), 7.03-7.01 (d, *J* = 7.7 Hz, 1 H), 3.75 (s, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.48, 157.37, 137.83, 132.93, 131.88, 129.85, 129.61, 128.88, 128.22, 120.50, 111.46, 55.62.

(3-Fluorophenyl)(phenyl)methanone (3f). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.83-7.82 (d, *J* = 7.5 Hz, 2 H), 7.65-7.59 (m, 2 H), 7.54-7.47 (m, 4 H), 7.33-7.30 (t, *J* = 8.3 Hz, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 164.59, 162.51 (d, J^F = 246.78 Hz), 137.05, 132.79, 130.03, 130.01, 129.95, 128.44, 125.83 (d, J^F = 2.9 Hz), 119.44 (d, J^F = 21.4 Hz), 116.77 (d, J^F = 22.3 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -111.99.

Phenyl(3-(trifluoromethyl)phenyl)methanone (3g). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.09 (s, 1 H), 8.01-7.99 (d, *J* = 7.7 Hz, 1 H), 7.88-7.86 (d, *J* = 7.8 Hz, 1 H), 7.83-7.81 (d, *J* = 7.1 Hz, 2 H), 7.67-7.64 (t, *J* = 7.6 Hz, 2 H), 7.55-7.52 (t, *J* = 7.8 Hz, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.24, 138.29, 136.76, 133.14, 133.03, 131.01 (q, J^2 = 32.7 Hz), 130.04, 128.97, 128.86 (q, J^F = 3.5 Hz), 128.58, 126.72 (q, J^F = 3.8 Hz), 123.71 (q, J^F = 270.8 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -62.74.

Naphthalen-2-yl(phenyl)methanone (3h). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.30 (s, 1 H), 7.98 (s, 2 H), 7.96-7.94 (d, *J* = 8.0 Hz, 2 H), 7.90-7.89 (d, *J* = 7.4 Hz, 2 H), 7.65 (s, 2 H), 7.60-7.53 (m, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.78, 137.93, 135.29, 134.85, 132.40, 132.28, 131.89, 130.12, 129.44, 128.36, 128.34, 128.32, 127.84, 126.82, 125.81.

[1,1'-Biphenyl]-4-yl(phenyl)methanone (3i). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.94-7.92 (d, *J* = 7.2 Hz, 2 H), 7.88-7.86 (d, *J* = 7.5 Hz, 2 H), 7.75-7.73 (d, *J* = 7.3 Hz, 2 H), 7.69-7.68 (d, *J* = 7.7 Hz, 2 H),

7.65-7.62 (t, *J* = 7.1 Hz, 1 H), 7.55-7.50 (m, 4 H), 7.45-7.42 (t, *J* = 6.7 Hz, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.38, 145.26, 140.01, 137.79, 136.26, 132.40, 130.75, 130.02, 128.99, 128.33, 128.21, 127.33, 126.99.

Phenyl(4-(trifluoromethyl)phenyl)methanone (3j). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.93-7.91 (d, *J* = 8.0 Hz, 2 H), 7.84-7.82 (d, *J* = 8.2 Hz, 2 H), 7.79-7.77 (d, *J* = 8.1 Hz, 2 H), 7.67-7.64 (t, *J* = 7.6 Hz, 1 H), 7.55-7.52 (t, *J* = 7.7 Hz, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.55, 140.74, 136.75, 133.74 (q, J^2 = 32.5 Hz), 133.11, 130.15, 130.12, 128.55, 125.37 (q, J^3 = 3.7 Hz), 123.69 (q, J^1 = 270.9 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -63.00.

(3,4-Difluorophenyl)(phenyl)methanone (3k). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.7 Hz, 2 H), 7.68 (t, *J* = 9.0 Hz, 1 H), 7.60 (t, *J* = 13.0 Hz, 2 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.27 (q, *J* = 8.3 Hz, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 194.22, 154.42 (dd, J^F = 255.0, 12.5 Hz), 150.33 (dd, J^F = 255.0, 12.5 Hz), 137.01, 134.58 (t, J^F = 3.8 Hz), 132.94, 129.98, 128.63, 127.23 (q, J^F = 3.8 Hz), 119.46 (dd, J^F =17.5, 1.2 Hz), 117.41 (d, J^F = 17.5 Hz). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -130.59 (d, *J* = 21.4 Hz), -136.17 (d, *J* = 21.4 Hz).

Phenyl(thiophen-2-yl)methanone (3l). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.90-7.89 (d, *J* = 8.2 Hz, 2 H), 7.76-7.75 (d, *J* = 4.9 Hz, 1 H), 7.68-7.67 (d, *J* = 3.7 Hz, 1 H), 7.64-7.61 (t, *J* = 7.5 Hz, 1 H), 7.54-7.51 (t, *J* = 7.7 Hz, 2 H), 7.20-7.19 (t, *J* = 4.8 Hz, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

Supplementary Materials: Experimental procedures and characterization data are available online at www.mdpi.com/xxx/s1.

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References

1. Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299-309.
2. Ananikov, V. P. Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 1964-1971.
3. Diccianni, J. B.; Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem.* **2019**, *1*, 830-844.
4. Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC (NHC = N-Heterocyclic Carbene) Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective Acyl CO–X (X = N, O) Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589-2599.
5. Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide Activation: an Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899-7925.
6. Meng, G.; Szostak, M. *N*-Acyl-Glutarimides: Privileged Scaffolds in Amide N–C Bond Cross-Coupling. *Eur. J. Org. Chem.* **2018**, *20-21*, 2352-2365.
7. Liu, C.; Szostak, M. Decarbonylative Cross-Coupling of Amides. *Org. Biomol. Chem.* **2018**, *16*, 7998-8010.
8. Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc. Rev.* **2017**, *46*, 5864-5888.
9. Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413-1423.
10. Liu, C.; Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N–C Amide Bond Activation. *Chem. Eur. J.* **2017**, *23*, 7157-7173.

11. For [(NHC)Pd(allyl)Cl] complexes, see: Lei, P.; Meng, G.; Szostak, M. General Method for the Suzuki-Miyaura Cross-Coupling of Amides Using Commercially Available, Air- and Moisture-Stable Palladium/NHC (NHC = N-Heterocyclic Carbene) Complexes. *ACS Catal.* **2017**, *7*, 1960-1965.
12. For [Pd-PEPPSI] complexes, see: Lei, P.; Meng, G.; Ling, Y.; An, J.; Szostak, M. Pd-PEPPSI: Pd-NHC Precatalyst for Suzuki-Miyaura Cross-Coupling Reactions of Amides. *J. Org. Chem.* **2017**, *82*, 6638-6646.
13. For [(NHC)Pd(acac)Cl] complexes, see: Zhou, T.; Li, G.; Nolan, S. P.; Szostak, M. [Pd(NHC)(acac)Cl]: Well-Defined, Air-Stable, and Readily Available Precatalysts for Suzuki and Buchwald-Hartwig Cross-coupling (Transamidation) of Amides and Esters by N-C/O-C Activation. *Org. Lett.* **2019**, *21*, 3304-3309.
14. For an instructive example of Pd(II)–NHC optimization for amide cross-coupling, see: Wang, T.; Guo, J.; Wang, H.; Guo, H.; Jia, D.; Zhang, W.; Liu, L. N-heterocyclic carbene palladium(II)-catalyzed Suzuki-Miyaura cross coupling of N-acylsuccinimides by C-N cleavage. *J. Organomet. Chem*. **2018**, 877, 80-84.
15. For a review on acyl cross-couplings, see: Buchspies; J.; Szostak, M. Recent Advances in Acyl Suzuki Cross-Coupling. *Catalysts* **2019**, *9*, 53.
16. Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-catalysed Suzuki–Miyaura coupling of Amides. *Nature Chem.* **2016**, *8*, 76-80.
17. For the application of $Ni(cod)_2$ paraffin capsules, see: Dander, J. E.; Weires, N. A.; Garg, N. K. Benchtop Delivery of $Ni(cod)_2$ using Paraffin Capsules. *Org. Lett.* **2016**, *18*, 3934-3936.
18. Ritleng, V.; Oertel, A. M.; Chetcuti, M. J. Half-sandwich NHC-nickel(II) complexes as pre-catalysts for the fast Suzuki coupling of aryl halides: a comparative study. *Dalton Trans.* **2010**, *39*, 8153-8160.
19. Oertel, A. M.; Ritleng, V.; Burr, L.; Chetcuti, M. J. Synthesis and structural characterization of half-sandwich nickel complexes bearing two different N-heterocyclic carbene ligands. *Organometallics* **2011**, *30*, 6685-6691.
20. Oertel, A. M.; Ritleng, V.; Chetcuti, M. J. Synthesis and Catalytic Activity in Suzuki Coupling of Nickel Complexes Bearing n-Butyl- and Triethoxysilylpropyl-Substituted NHC Ligands: Toward the Heterogenization of Molecular Catalysts. *Organometallics* **2012**, *31*, 2829-2840.
21. Henrion, M.; Chetcuti, M. J.; Ritleng, V. From acetone metalation to the catalytic α-arylation of acyclic ketones with NHC–nickel(ii) complexes. *Chem. Commun.* **2014**, *50*, 4624-4627.
22. Bheeter, L. P.; Henrion, M.; Brelot, L.; Darcel, C.; Chetcuti, M. J.; Sortais, J. B.; Ritleng, V. Hydrosilylation of Aldehydes and Ketones Catalyzed by an N-Heterocyclic Carbene-Nickel Hydride Complex under Mild Conditions. *Adv. Synth. Catal.* **2012**, *354*, 2619-2624.
23. Bheeter, L. P.; Henrion, M.; Chetcuti, M. J.; Darcel, C.; Ritleng, V.; Sortais, J. B. Cyclopentadienyl N-heterocyclic carbene–nickel complexes as efficient pre-catalysts for the hydrosilylation of imines. *Catal. Sci. Technol.* **2013**, *3*, 3111-3116.
24. Oertel, A. M.; Freudenreich, J.; Gein, J.; Ritleng, V.; Veiros, L. F.; Chetcuti, M. J. Intramolecular Nitrile C–H Bond Activation in Nickel NHC Complexes: A Route to New Nickelacycles. *Organometallics* **2011**, *30*, 3400-3411.
25. For a comprehensive review on Ni–NHC complexes, see: Danopoulos, A. A.; Simler, T.; Braunstein, P. N-Heterocyclic Carbene Complexes of Copper, Nickel, and Cobalt. *Chem. Rev.* **2019**, *119*, 3730-3961.
26. For excellent review on Ni–NHCs in C–C bond forming reactions, see: Henrion, M.; Ritleng, V.; Chetcuti, M. J. Nickel N-Heterocyclic Carbene-Catalyzed C–C Bond Formation: Reactions and Mechanistic Aspects. *ACS Catal.* **2015**, *5*, 1283-1302.
27. For excellent review on Ni–NHCs in C–X bond forming reactions, see: Ritleng, V.; Henrion, M.; Chetcuti, M. J. Nickel N-Heterocyclic Carbene-Catalyzed C–Heteroatom Bond Formation, Reduction, and Oxidation: Reactions and Mechanistic Aspects. *ACS Catal.* **2016**, *6*, 890-906.
28. For excellent review on [CpNi(NHC)X] complexes, see: Banach, L.; Guńka, P.A.; Zachara, J.; Buchowicz, W. Half-sandwich Ni(II) complexes [Ni(Cp)(X)(NHC)]: From an underestimated discovery to a new chapter in organonickel chemistry. *Coord. Chem. Rev.* **2019**, *389*, 19-58.
29. For a comprehensive review of Ni–NHC complexes in C–H activation reactions, see: Zhao, Q.; Meng, G.; Nolan, S. P.; Szostak, M. N-Heterocyclic Carbene Complexes in C–H Activation Reactions. *Chem. Rev.* **2020**, *120*, 1981-2048.

30. For an earlier example on the synthesis and reactivity of [CpNi(NHC)X], see: Kelly, R. A.; Scott, N. M.; Díez-González, S.; Stevens, E. D.; Nolan, S. P. Simple Synthesis of CpNi(NHC)Cl Complexes (Cp = Cyclopentadienyl; NHC = N-Heterocyclic Carbene). *Organometallics* **2005**, *24*, 3442-3447.
31. For a leading example of the reactivity of [(NHC)Ni(allyl)Cl] complexes, see: Iglesias, M. J.; Prieto, A.; Nicasio, M. C. Kumada–Tamao–Corriu Coupling of Heteroaromatic Chlorides and Aryl Ethers Catalyzed by (IPr)Ni(allyl)Cl. *Org. Lett.* **2012**, *14*, 4318-4321.
32. Lee, C. C.; Ke, W. C.; Chan, K. T.; Lai, C. L.; Hu, C. H.; Lee, H. M. Nickel(II) Complexes of Bidentate N-Heterocyclic Carbene/Phosphine Ligands: Efficient Catalysts for Suzuki Coupling of Aryl Chlorides. *Chem. Eur. J.* **2007**, *13*, 582-591.
33. Leadbeater, N. E. Bis-cyclopentadienyl nickel (nickelocene): a convenient starting material for reactions catalyzed by Ni(0) phosphine complexes. *J. Org. Chem.* **2001**, *66*, 7539-7541.
34. Beromi, M. M.; Nova, A.; Balcells, D.; Brasacchio, A. M.; Brudvig, G. W.; Guard, L. M.; Hazari, N.; Vinyard, D. J. Mechanistic Study of an Improved Ni Precatalyst for Suzuki–Miyaura Reactions of Aryl Sulfamates: Understanding the Role of Ni(I) Species. *J. Am. Chem. Soc.* **2017**, *139*, 922-936.
35. Matsubara, K.; Ueno, K.; Shibata, Y. Synthesis and Structures of Nickel Halide Complexes Bearing Mono- and Bis-coordinated N-Heterocyclic Carbene Ligands, Catalyzing Grignard Cross-Coupling Reactions. *Organometallics* **2006**, *25*, 3422-3427.
36. Izquierdo, F.; Manzini, S.; Nolan, S. P. The use of the sterically demanding IPr* and related ligands in catalysis. *Chem. Commun.* **2014**, *50*, 14926-14937.
37. Gómez-Suárez, A.; Nelson, D. J.; Nolan, S. P. Quantifying and understanding the steric properties of N-heterocyclic carbenes. *Chem. Commun.* **2017**, *53*, 2650-2660.
38. Shaw, P.; Kennedy, A. R.; Nelson, D. J. Synthesis and characterisation of an N-heterocyclic carbene with spatially-defined steric impact. *Dalton Trans.* **2016**, *45*, 11772-11780.
39. Martin, A. R.; Makida, Y.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. Enhanced Activity of [Ni(NHC)CpCl] Complexes in Arylamination Catalysis. *Organometallics* **2013**, *32*, 6265-6270.
40. Shi, S.; Meng, G.; Szostak, M. Synthesis of Biaryls via Nickel Catalyzed Suzuki–Miyaura Coupling of Amides by Carbon–Nitrogen Cleavage. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959-6963.
41. For an excellent mechanistic review on Ni-catalysis in amide bond cross-coupling, see: Wang, H.; Zhang, S. Q.; Hong, X. Computational studies on Ni-catalyzed amide C–N bond activation. *Chem. Commun.* **2019**, *55*, 11330-11341.
42. Buchspies, J.; Pyle, D. J.; He, H.; Szostak, M. Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of Pentafluorophenyl Esters. *Molecules* **2018**, 23, 3134-2144.
43. Lei, P.; Meng, G.; Shi, S..; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Suzuki–Miyaura cross-coupling of amides and esters at room temperature: correlation with barriers to rotation around C–N and C–O bonds. *Chem. Sci*. **2017**, *8*, 6525-6530.