ACS Catalysis

pubs.acs.org/acscatalysis Research Article

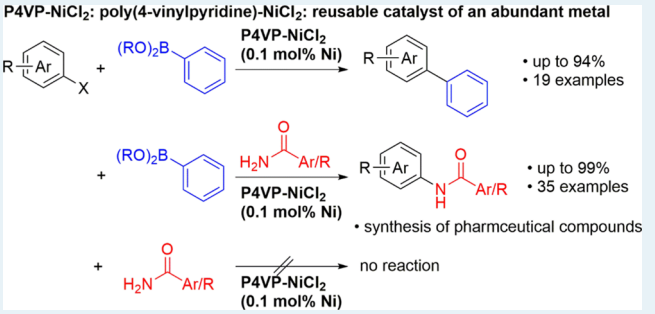
Switching from Biaryl Formation to Amidation with Convoluted Polymeric Nickel Catalysis

Abhijit Sen, Raghu N. Dhital, Takuma Sato, Aya Ohno, and Yoichi M. A. Yamada*

Cite This: *ACS Catal.* 2020, 10, 14410−14418 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A stable, reusable, and insoluble poly(4-vinylpyridine) nickel catalyst (P4VP-$NiCl_2$) was prepared through the molecular convolution of poly(4-vinylpyridine) (P4VP) and nickel chloride. We proposed a coordination structure of the Ni center in the precatalyst based on elemental analysis and Ni K-edge XANES, and we confirmed that it is consistent with Ni K-edge EXAFS. The Suzuki−Miyaura-type coupling of aryl halides and arylboronic esters proceeded using P4VP-$NiCl_2$ (0.1 mol % Ni) to give the corresponding biaryl compounds in up to 94% yield. Surprisingly, when the same reaction of aryl halides and arylboronic acid/ester was carried out in the presence of amides, the amidation proceeded predominantly to give the corresponding arylamides in up to 99% yield. In contrast, the reaction of aryl halides and amides in the absence of arylboronic acid/ester did not proceed. P4VP-$NiCl_2$ successfully catalyzed the lactamization for preparing phenanthridinone. P4VP-$NiCl_2$ was reused five times without significant loss of catalytic activity. Pharmaceuticals, natural products, and biologically active compounds were synthesized efficiently using P4VP-$NiCl_2$ catalysis. Nickel contamination in the prepared pharmaceutical compounds was not detected by ICP-MS analysis. The reaction was scaled to multigrams without any loss of chemical yield. Mechanistic studies for both Suzuki−Miyaura and amidation were performed.



KEYWORDS: *reusable catalyst, nickel catalysis, heterogeneous catalysis, Suzuki−Miyaura coupling, amidation reaction*

INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions are one of the most convenient, versatile, and straightforward methods for C−C or C−N bond construction.[1,2] Despite the widespread application of palladium-catalyzed cross-coupling reactions, such processes are not preferable at industrial scales owing to the high cost of palladium. Compared with palladium, nickel is an inexpensive and earth-abundant metal, which renders nickel-catalyzed cross-coupling reactions a highly economical prospect. However, the relatively high toxicity[3] and the low turnover numbers in catalysis, which requires high catalyst loadings, are the key challenges with its use. Despite several reports on homogeneous nickel-catalyzed C−C[4] and C−N[5] coupling reactions, the development of recoverable and reusable heterogeneous nickel catalysts with high catalytic activity is still in its infancy. While homogeneous catalysis is associated with nickel contamination of the desired products, heterogeneous nickel catalysis, ideally, could provide opportunities for catalyst recovery and reuse without the nickel contamination challenges. Few examples of nickel catalyst immobilization are known;[6] however, their catalytic activity and reusability requires further improvement and is an ongoing challenge. Owing to the higher lability of nickel to ligands, heterogeneous nickel catalysts are unstable and readily decomposed, and therefore, the development of highly active, reusable, and bench-stable heterogeneous nickel catalysts is challenging. We reported a methodology for the preparation of highly active and reusable polymeric palladium and copper catalysts, also known as the molecular convolution methodology.[7] Considering the lack of metal leaching, high activity, and reusability of the nickel catalysts developed with this approach, this methodology was applied to the development of polymeric nickel catalysts.

Amide linkages play crucial roles in pharmaceuticals, natural products, and synthetic intermediates,[8] including paracetamol,[9] acebutolol,[10] and phenanthridinone[11] (Figure 1). The most widely used method for amide synthesis is amidation of carboxylic acid derivatives,[12] and *N*-arylation of amides can be a useful alternative.[13] Unfortunately, there are few reports on nickel-catalyzed amidation of aryl/alkyl amide and aryl halides,[5h] probably because of the poor nucleophilicity of the

Received: September 6, 2020
Revised: November 5, 2020

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

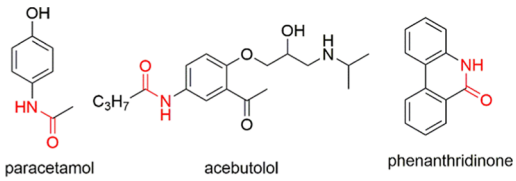
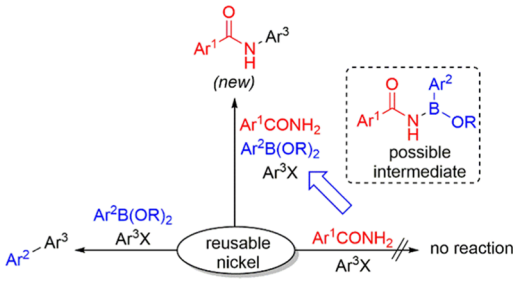


Figure 1. Representative examples of biologically active molecules containing an amide linkage.

amide nitrogen. Recently, we reported phenylboronic acid/ester-assisted Buchwald–Hartwig type amination, wherein the phenylboronic acid/ester acts as an activator for the formation of an ate complex with the amines.[14] In the absence of phenylboronic acid, the amination did not occur. On the basis of this observation, we hypothesized that phenylboronic acid might activate amide substrates via boron–amide complex formation (Scheme 1), and this complex might enable the *N*-

Scheme 1. Hypothesis for Switchable Selectivity from Suzuki–Miyaura Coupling to Amidation



arylation of the amides. On the other hand, phenylboronic acid/ester is itself a good nucleophile in Suzuki–Miyaura-type couplings. The Suzuki–Miyaura carbon–carbon bond formation is widespread with applications in both academia and industry. Despite the several reports on these reactions,[1,4] switchable selectivity[15] between these two reactions has not yet been reported. Therefore, we explored the possibility for switchable selectivity between Suzuki–Miyaura-type coupling and amidation depending on the presence or absence of amides. Herein, we report switchable selectivity from biaryl formation to amidation, promoted by a heterogeneous, bench-stable, reusable, and convoluted polymeric nickel catalyst, poly(4-vinylpyridine)[7] (P4VP)-$NiCl_2$ polymer.

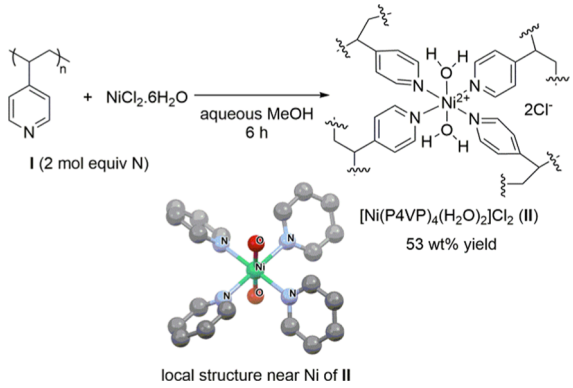
RESULTS AND DISCUSSION

Preparation of Convoluted P4VP-Nickel Catalysts. When a methanol solution of a commercially available linear poly(4-vinylpyridine), P4VP (**I**), was treated with an aqueous solution of $NiCl_2{\cdot}6H_2O$ and stirred for 6 h at room temperature, molecular convolution occurred to yield **II** as a greenish precipitate (Scheme 2).

Catalyst **II** was insoluble in water, methanol, dioxane, chloroform, and hexane. The structure of the catalyst $[Ni(P4VP)_4(H_2O)_2]Cl_2$ (**II**) is shown in Scheme 2 (for more details, see Figures S1–S3 in the Supporting Information).

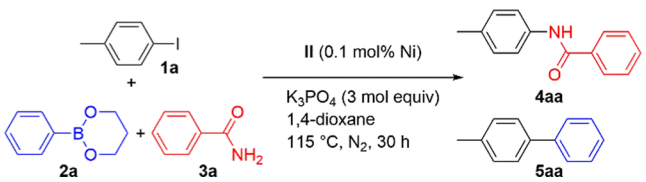
Catalysis. The catalytic activity of **II** was examined for the amidation reaction (for more details, see p S5 in the Supporting Information). When *p*-tolyliodide (**1a**) and benzamide (**3a**) were reacted in the presence of P4VP-Ni (1000 mol ppm (0.1 mol % Ni)), no reaction occurred (Table

Scheme 2. Preparation of a P4VP-Supported Nickel Catalyst



1, entry 1). However, when the reaction was performed in the presence of phenylboronic ester (**2a**) as an activator, we were

Table 1. Switchable Selectivity from C–C to C–N Bond Formation[a]



entry	deviation from standard conditions	yield **4aa** (%)	yield **5aa** (%)
1	without **2a**	0	0
2	none	99	0
3	phenylboronic acid instead of **2a**	98	1
4	without P4VP-Ni	0	0
5	without K_3PO_4	0	0
6	KO*t*Bu instead of K_3PO_4	97	2
7	NaO*t*Bu instead of K_3PO_4	55	33
8	toluene instead of 1,4-dioxane	60	0
9	without **3a**	0	55
10	without **3a** and 5 mol equiv of **2a**	0	91
11	air instead of nitrogen	94	0

[a]Standard reaction conditions: **1a** (1 mol equiv), **2a** (1.5 mol equiv), **3a** (3 mol equiv), **II** (0.1 mol % Ni), K_3PO_4 (3 mol equiv), and 1,4-dioxane (2 mL) at 115 °C for 30 h under N_2.

pleased to find that the desired amidation product **4aa** was obtained in 99% yield with >99% selectivity, in the absence of the typical Suzuki–Miyaura reaction product **5aa** (entry 2).

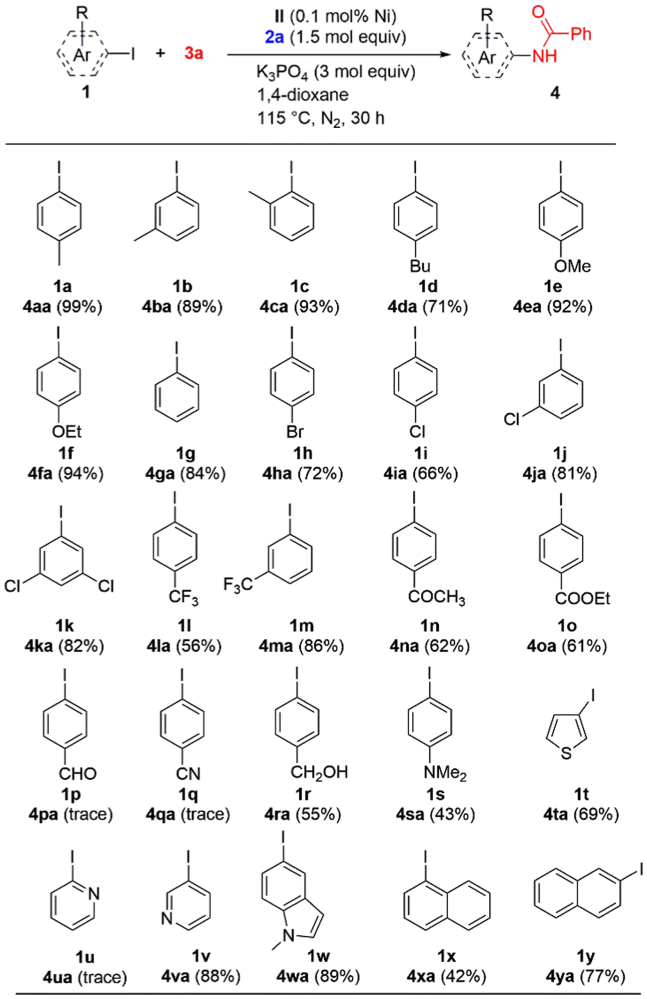
The use of phenylboronic acid instead of phenylboronic ester **2a** had no significant effect on the product outcome (entry 3). In the absence of the nickel complex, no reaction took place, thus proving the role of nickel as a catalyst (entry 4). In addition, when the reaction was performed in the absence of a base, no reaction occurred (entry 5). KO*t*Bu was also an effective base and afforded **4aa** in 97% yield and 97% selectivity (entry 6). On the other hand, NaO*t*Bu provided a mixture of products suggesting that the presence of strong potassium bases is critical for achieving high selectivity (entry 7). Although the use of toluene as a solvent afforded a 60% yield, the amidation proceeded exclusively (entry 8). Importantly, **II** was also useful as a catalyst for Suzuki–Miyaura-type coupling in the absence of **3a** and provided the corresponding biaryl compound **5aa** in up to 91% yield with

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410–14418

>99% selectivity (entries 9 and 10). A use of air instead of N_2 was also successful (entry 11).

With the optimized reaction conditions in hand, the amidation of various aryl iodides with **3a** was investigated (Table 2); it indicated a broad functional group tolerance.

Table 2. Amidation of Various Aryl Iodides[a]

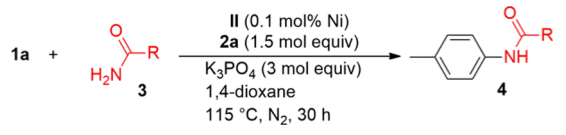


[a]All reactions were performed with **1** (1 mol equiv), **2a** (1.5 mol equiv), **3a** (3 mol equiv), **II** (0.1 mol % Ni), K_3PO_4 (3 mol equiv), and 1,4-dioxane (2 mL) at 115 °C for 30 h under N_2.

Phenylboronic ester **2a** was recoverable in up to 96% yield after the C−N bond-forming amidation. The reaction of 3-methyliodobenzene (**1b**) and 2-methyliodobenzene (**1c**) afforded **4ba** and **4ca** in 89 and 93% yields, respectively. The bulky 4-butyl iodobenzene (**1d**) was converted to **4da** in 71% yield. The electron-rich substrates 4-methoxy- and 4-ethoxy-iodobenzenes (**1e** and **1f**) furnished the desired product in 92 and 94% yields, respectively. Iodobenzene (**1g**) gave **4ga** in 84% yield. Chemoselective reactions were realized when the reaction of 1-bromo-4-iodo-(**1h**) or 1-chloro-4-iodobenzenes (**1i**) was carried out with **3a**. Although a trace amount of *N*-(4-iodophenyl)benzamide was observed in the reaction of **1h**, the aryl chloride did not participate in the reaction. A significant amount of the substrate remained unreactive in both cases (**1h** and **1i**). When 1-chloro-3-iodobenzene (**1j**) and 1,3-dichloro-5-iodobenzene (**1k**) were reacted with **3a**, the corresponding amidation products **4ja** and **4ka** were obtained in 81 and 82% yields, respectively. The electron-deficient 4-trifluoromethyl-, 3-trifluoromethyl-, 4-acetyl-, and 4-ethoxycarbonyl-iodobenzene **1l**−**1o** were readily converted to the corresponding amidation products **4la**−**4oa**. Unfortunately, the aldehyde (**1p**) and nitrile (**1q**) containing substrates were not able to generate the desired product. The reactions of alcohol (**1r**) and amine (**1s**) substrates proceeded with 55% and 43% yields, respectively. Although 2-iodopyridine (**1u**) did not provide the desired reaction but the reaction of 3-iodothiophene (**1t**), 3-iodopyridine (**1v**), and 5-iodo-1-methyl-1*H*-indole (**1w**) afforded **4ta**, **4va**, and **4wa** in 69, 88, and 89% yields, respectively. Notably, bioactive compounds could be synthesized in a single step: *N*-(pyridin-3-yl)benzamide (**4va**) exhibited antiviral[8f] and NAMPT inhibition activities,[8g] and *N*-(thiophen-3-yl)benzamide (**4ta**) is a GK activator.[8h] The naphthalene series substrates, 1-iodonapthalene (**1x**), and 2-iodonapthalene (**1y**) generated the desired products in 42 and 77% yields, respectively. The *N*-(naphthalen-2-yl)benzamide (**4ya**) obtained from 2-iodonapthalene (**1y**) possesses miR−122 inhibition ability.[8c]

Next, the amidation of a variety of amide counterparts was investigated (Table 3). The electronic perturbation of aromatic

Table 3. Amidation with Various Amides[a,b]



entry	substrates (**3**)	product yield (**4**)
1	R^1 = H (**3a**)	**4aa** (99%)
2	R^1 = *p*-Me (**3b**)	**4ab** (99%)
3	R^1 = *m*-Me (**3c**)	**4ac** (94%)
4	R^1 = *o*-Me (**3d**)	**4ad** (98%)
5	R^1 = *p*-OMe (**3e**)	**4ae** (99%)
6[b]	R^1 = *p*-NO_2 (**3f**)	**4af** (trace)
7	(**3g**)	**4ag** (68%)
8	n = 0 (**3h**)	**4ah** (82%)
9	n = 2 (**3i**)	**4ai** (98%)
10	n = 4 (**3j**)	**4aj** (84%)
11	(**3k**)	**4ak** (87%)

[a]All reactions were performed with **1a** (1 mol equiv), **2a** (1.5 mol equiv), **3** (3 mol equiv), **II** (0.1 mol % Ni), K_3PO_4 (3 mol equiv), and 1,4-dioxane (2 mL) at 115 °C for 30 h under N_2. [b]Reaction time is 72 h.

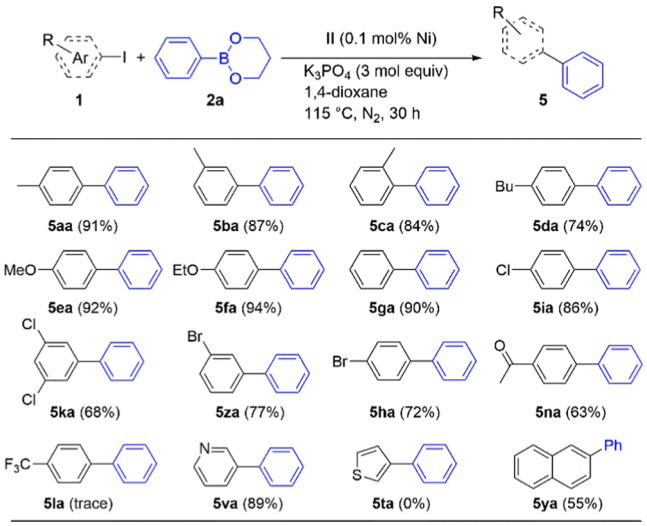
substituents has a crucial effect on product outcomes. However, irrespective of the position of the methyl group on the benzamide (*p*-, *m*-, and *o*-), the amidation proceeded smoothly (entries 2−4). The electron-rich *p*-methoxybenzamide (**3e**) afforded **4ae** in 99% yield (entry 5). Installation of an electron-withdrawing nitro group (**3f**) completely suppressed the reaction by reducing the nucleophilicity of

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

benzamide (entry 6). Interestingly, nicotinamide (**3g**, present in vitamin B3) successfully furnished *N*-(*p*-tolyl)nicotinamide (**4ag**) (entry 7). Aromatic and aliphatic amides are applicable in this amidation. When acetamide (**3h**) was treated under the reaction conditions, *N*-(*p*-tolyl)acetamide (**4ah**) was obtained in 82% yield (entry 8). Similarly, butyramide (**3i**) and hexanamide (**3j**) provided 98 and 84% yields of **4ai** and **4aj**, respectively (entries 9 and 10). In addition, olefin functionalities were tolerated in this reaction. When hex-5-enamide (**3k**) was treated with *p*-tolyliodide (**1a**), the desired amidation product (**4ak**) was obtained in 87% yield (entry 11).

With an extensive exploration of the amidation substrate scope, we turned attention to studying the substrate scope for the C−C bond-forming Suzuki−Miyaura coupling. When the reaction of *p*-tolyliodide (**1a**) was performed with 2-phenyl-1,3,2-dioxaborinane (**2a**) in the presence of 0.1 mol % Ni (**II**) and K_3PO_4 in 1,4-dioxane, 4-methyl biphenyl (**5aa**) was obtained in 91% yield (Table 4). The cross-coupling of 3-

Table 4. Substrate Scope for Aryl Iodides in the Suzuki−Miyaura Reaction[a]

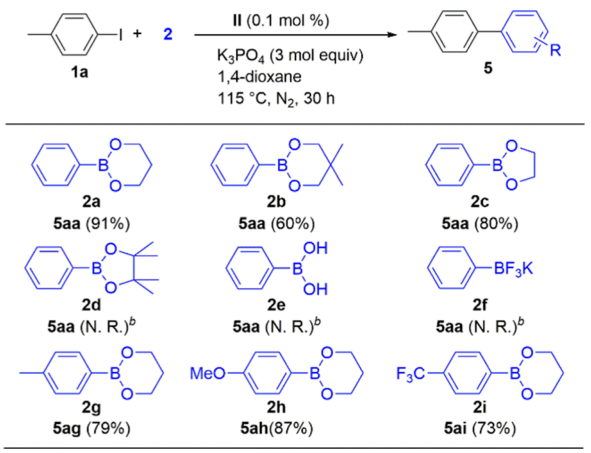


[a]All reactions were performed with **1** (1 mol equiv), **2a** (5 mol equiv), **II** (0.1 mol % Ni), K_3PO_4 (3 mol equiv), and 1,4-dioxane (2 mL) at 115 °C for 30 h under N_2.

methyliodobenzene (**1b**) and 2-methyliodobenzene (**1c**) also afforded coupling products **5ba** and **5ca** in 87 and 84% yields, respectively. The presence of the bulky butyl group at the 4-position of iodobenzene did not have any adverse impact, and the coupling reaction proceeded successfully (**5da**). The reactions of 4-methoxyiodobenzene (**1e**) and 4-ethoxyiodobenzene (**1f**) afforded the corresponding biphenyl derivatives **5ea** and **5fa** in 92 and 94% yields, respectively. In the case of the polyhalide-substituted starting materials, the reaction proceeded with high selectivity. When 1-chloro-4-iodobenzene (**1i**) and 1,3-dichloro-5-iodobenzene (**1k**) were subjected to biphenyl formation conditions, 4-chloro-1,1′-biphenyl (**5ia**) and 3,5-dichloro-1,1′-biphenyl (**5ka**) were obtained in 86 and 68% yields, respectively. Similarly, 1-bromo-3-iodobenzene (**1z**) and 1-bromo-4-iodobenzene (**1h**) also gave the corresponding bromobiphenyls (**5za** and **5ha**) in 77 and 72% yields, respectively, and no iodobiphenyls were observed among the products. The partial electron-withdrawing effect of the halides reduced the reactivity of the aryl iodides; when 1-(4-iodophenyl)ethan-1-one (**1n**) was exposed to the reaction conditions, a 63% yield of the desired product **5na** was obtained, whereas the reaction of the stronger electron-withdrawing *p*-trifluoromethyl substitution (**1l**) hardly proceeded. Although 3-iodopyridine furnished an 89% yield of the coupling product (**5va**), 3-iodothiophene (**1t**) was not able to generate a coupling product (**5ta**). The synthesis of 2-phenylnaphthalene (**5ya**) was successful in 55% yield.

We also examined the effect of different boron sources (Table 5). While 2-phenyl-1,3,2-dioxaborinane **2a** provided

Table 5. Reactivity of Boron Species for Suzuki−Miyaura Coupling[a,b]



[a]All reactions were performed with **1a** (1 mol equiv), **2** (5 mol equiv), **II** (0.1 mol % Ni), K_3PO_4 (3 mol equiv), and 1,4-dioxane (2 mL) at 115 °C for 30 h under N_2. [b]N. R.: No reaction.

5aa in 91% yield, phenylboronic acid neopentylglycol ester **2b** could generate a 60% yield of **5aa**. Although phenylboronic acid glycol ester **2c** provided an 80% yield of **5aa**, phenylboronic acid pinacol ester **2d** failed to construct the C−C bond under the catalytic conditions, probably because of the bulky nature of the boron source. Simple phenylboronic acid **2e** was unable to provide a coupling product. Similarly, the trifluoro(phenyl)-λ^4-borane, potassium salt **2f**, was unable to construct the biphenyl derivatives. The electron-donating tolylboronic ester **2g** and (4-methoxyphenyl)boronic ester **2h** furnished the biphenyls in 79 and 87% yields, respectively, whereas the electron-deficient (4-(trifluoromethyl)phenyl)-boronic ester **2i** afforded the coupling product in 73% yield. The results of these experiments reveal that phenylboronic ester derivatives are essential for the P4VP-Ni-catalyzed Suzuki−Miyaura type C−C bond formation.

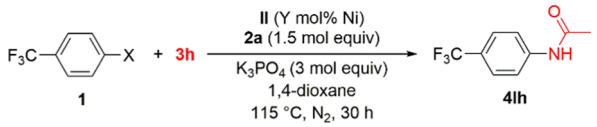
Next, we examined the reactivity of different aryl halides in the amidation reaction. Interestingly, aryl iodides, aryl bromides, and aryl chlorides all furnished amidation reaction products (Table 6).

Having assessed the substrate scope, we investigated the reusability of **II** (0.1 mol %, 0.42 mg in the 1st run) (for more details, see p S37 in the Supporting Information). Unlike the typical nickel catalysts, our catalyst can be reused up to four times without significant loss of reactivity (Table 7).

The recovered catalyst can also be used for the sequential amidation and Suzuki−Miyaura-type cross-coupling sequence (Scheme 3; for more details, see p S37 in the Supporting Information). The Suzuki−Miyaura-type cross-coupling of **1a** and **2a** was carried out with fresh **II** under the standard

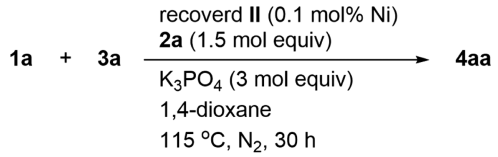
https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

Table 6. Reactivity of Different Aryl Halides



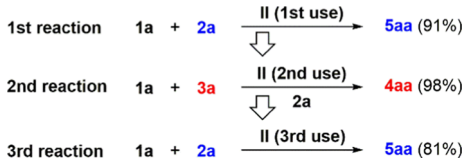
entry	substrate	Y (mol %)	yield (%)
1	**1l**, X = I	0.1	75
2	**1l′**, X = Br	0.5	71
3	**1l″**, X = Cl	0.5	28

Table 7. Catalyst Recovery and Recyclability for the Amidation Reaction



entry	number of runs	yield **4aa** (%)	catalyst recovery yield (%)
1	1st	99	91
2	2nd	93	94
3	3rd	96	85
4	4th	89	89
5	5th	88	82

Scheme 3. Reusability of the Recovered Catalyst in C−C and C−N Bond-Forming Reactions



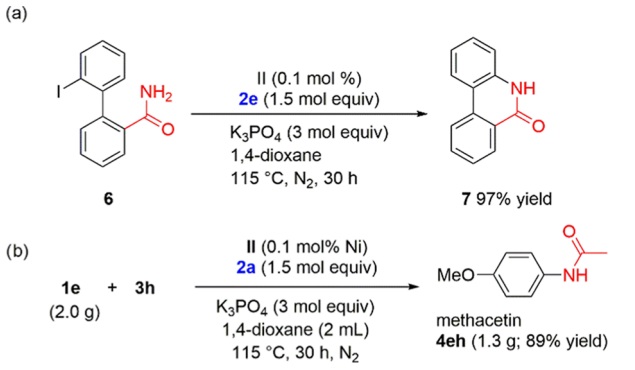
conditions to prepare **5aa** in 91% yield. The catalyst **II** was recovered and reused for the amidation of **1a** and **3a**, and it afforded **4aa** in 98% yield. Catalyst **II** was again recovered and reused for the Suzuki−Miyaura-type cross-coupling and provided **5aa** in 81% yield. These results suggest that the same catalytic species work in both reactions.

When catalyst **II** was applied to the intramolecular amidation reaction (lactam formation) of 2′-iodo-[1,1′-biphenyl]-2-carboxamide **6** in the presence of phenylboronic acid **2e** as an activator, the cyclization proceeded smoothly to afford phenanthridinone (**7**) in 97% yield (Scheme 4a). Further, in the absence of **2e**, cyclization did not proceed. Notably, phenanthridinone is a biologically active compound and is an important synthetic intermediate for the synthesis of several pharmaceutically active molecules.[11e]

We applied this methodology for the 2 g scale reaction (Scheme 4b). The desired amidation product methacetin was observed with 89% yield (1.3 g). We examined the possibility of nickel contamination of the prepared biologically active molecules (for more details, see pp S14 and S38 in the Supporting Information).

The effect of the stoichiometry of **3a** and **2a** in the Suzuki−Miyaura coupling and amidation was examined next. The addition of 10 mol % **3a** in the optimal C−C coupling conditions furnished a 9% yield of the amidation product **4aa** and a 90% yield of **5aa** (Figure 2). A gradual increase of **3a** in the reaction mixture increased the amount of **4aa**. While the

Scheme 4. Intramolecular Reaction for Preparation of Phenanthridinone and the Gram-Scale Reaction



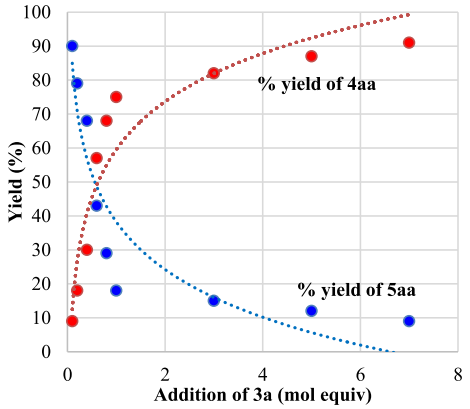


Figure 2. Effect of addition of **3a** in Suzuki−Miyaura coupling.

addition of 1 equiv of **3a** furnished an 82% yield of **4aa**, a one to one ratio of **2a** and **3a** afforded an 87% yield of **4aa**. The use of excess amide generated a 91% yield of **4aa** and afforded **5aa** as a minor product (for more details, see p S30 in the Supporting Information). In contrast, when phenylboronic ester **2a** was added gradually to the optimal amidation reaction conditions, a slow nonlinear increase of the formation of **5aa** with a low yield was seen and a sharp increase in the C−N coupling product was observed (Figure 3). These results indicate that **2a** acts as an activator for the amidation reaction.

Plausible Catalytic Pathway. *Mechanistic Studies.* Since the amidation proceeded smoothly with both phenylboronic

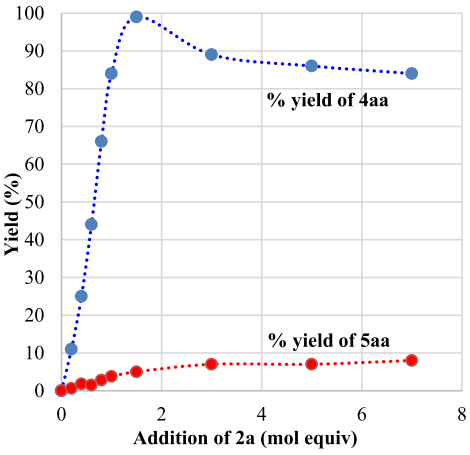
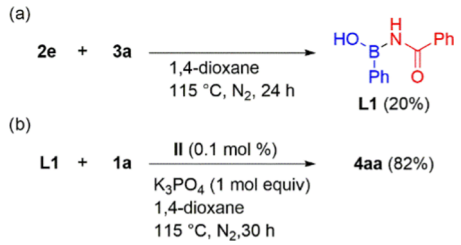


Figure 3. Effect of the addition of **2a** in the amidation.

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

acid (**2e**) and phenylboronic ester (**2a**), we examined the plausible catalytic pathway using phenylboronic acid. The mixture of phenylboronic acid (**2e**) and benzamide (**3a**) provided the reaction intermediate **L1** (Scheme 5a). The

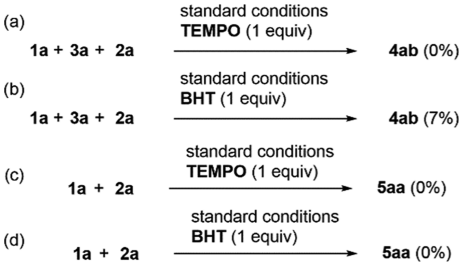
Scheme 5. Identification of Reaction Intermediates



structure of **L1** was proposed based on the ^{1}H NMR, ^{13}C NMR, ESI-MS, and DFT calculations (for more details, see pp S14−S18 in the Supporting Information). The reaction of the isolated intermediate **L1** with **1a** in the presence of catalyst **II** and K_3PO_4 efficiently furnished the desired amidation product **4aa** in 82% yield (Scheme 5b). The use of the intermediate **L1** in the absence of bases did not lead to C−N bond formation (for more details, see p S15 in the Supporting Information).

To examine the catalytic pathway in greater detail, we studied the effect of radical inhibitors on the reaction. The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, TEMPO, or butylated hydroxytoluene(BHT) to both reactions completely suppressed product formation (Scheme 6). These experiments clearly indicate that both reactions involve a radical pathway.[16]

Scheme 6. Effect of the Radical Inhibitor on Reactivity

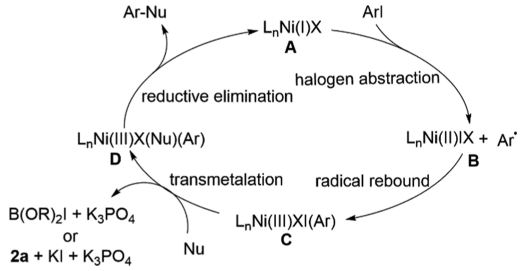


During the analysis of the reaction products from both reactions by GC, we observed biphenyl, which originates from the oxidative coupling of phenylboronic ester **2a**, resulting in a Ni(0) complex, in less than 1% yield. This nickel(0) complex further reacts with the Ni(II) complex to undergo comproportionation and forms the catalytically active Ni(I) complex, **A** (for more details, see p S38 in the Supporting Information). The chemical kinetics for the amidation revealed that the reaction followed zero-order dependence on aryl iodide and the nickel catalyst, first-order dependence on arylboronic ester and amide substrates, and second-order dependence on K_3PO_4 (for more details, see Figures S5−S9 in the Supporting Information). On the other hand, the chemical kinetics for Suzuki−Miyaura-type coupling showed that the reaction followed zero-order dependence on aryl iodide and the nickel catalyst, whereas first-order dependence was observed for arylboronic ester and K_3PO_4 (for more details, see Figures S10−S13 in the Supporting Information). On the basis of these studies, we propose the intermediacy of nucleophile **Nu1** for the C−C coupling reaction and putative nucleophile **Nu2** for the C−N coupling reaction (Scheme 7; for more details, see p S18 in the Supporting Information).

Scheme 7. Proposed Nucleophiles for C−C and C−N Coupling Reactions

Initially, a halogen abstraction reaction between the Ni(I) catalyst and aryl halides generated intermediate **B** and an aryl radical (Scheme 8). After that, a radical rebound step provided

Scheme 8. Plausible Reaction Mechanism



intermediate **C**. Next, **Nu1** or **Nu2** underwent transmetalation to generate intermediate **D**. The generation of the nucleophile was the rate-determining step for both C−C and C−N bond formations. Finally, reductive elimination from intermediate **D** produces either C−C or C−N coupling product based on the nucleophile and regenerates Ni(I) catalyst **A**.

CONCLUSIONS

In summary, a novel polymer-supported nickel complex was developed. The structure of this complex was proposed based on EXAFS, XANES, and DFT analyses. This complex was able to catalyze both Suzuki−Miyaura-type and amidation reactions. Moreover, perfect switchable selectivity from Suzuki−Miyaura coupling to amidation was observed. The construction of several biologically active molecules was successful. The reaction is compatible with large-scale synthesis. Notably, the catalyst is recoverable and recyclable. A more detailed investigation of the reaction mechanism and further application of P4VP-$NiCl_2$ on natural product synthesis is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03888.

Experimental details for C−C and C−N bond formations (optimization, reaction procedure, reaction time-course measurement, and chemical kinetics) and analytical data (elemental analysis and XAFS) for the nickel catalyst; ^{1}H NMR, ^{13}C NMR, HRMS, and DFT for reaction intermediate **L1**; and ^{1}H NMR, ^{13}C NMR, melting point, and ^{19}F NMR for all C−C and C−N coupling products (PDFs)

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

AUTHOR INFORMATION

Corresponding Author

Yoichi M. A. Yamada − *RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan;* orcid.org/0000-0002-3901-5926; Email: ymayamada@riken.jp

Authors

Abhijit Sen − *RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan*

Raghu N. Dhital − *RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan*

Takuma Sato − *RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan*

Aya Ohno − *RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c03888

Author Contributions

The manuscript was written through the contributions of all the authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Tetsuo Honma (JASRI, SPring-8) for assistance with the XAFS studies (SPring-8, BL14B2). We would like to thank RIKEN for assistance with elemental analysis (materials characterization support team, CEMS, RIKEN) and ESI-MS (molecular structure characterization unit, CSRS, RIKEN) measurements. We gratefully acknowledge financial support from AMED (#19ak0101115h) and RIKEN.

REFERENCES

(1) (a) Miura, M.; Nomura, M. *Cross-Coupling Reactions*, 1st ed.; Springer-Verlag: Berlin, Heidelberg, 2002; p 211. (b) Miyaura, N.; Buchwald, S. L.; Fugami, K.; Hiyama, T.; Kosugi, M.; Miura, M.; Miyaura, N.; Muci, A. R.; Nomura, M.; Shirakawa, E. *Cross-Coupling Reactions: A Practical Guide*; Springer: Berlin, Heidelberg, 2003; p 131. (c) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: 2004; p 699. (d) Djakovitch, L.; Köhler, K.; de Vries, J. G. The Role of Palladium Nanoparticles as Catalysts for Carbon-Carbon Coupling Reactions. In *Nanoparticles and Catalysis*, Astruc, D., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 10, p 303. (e) Lamblin, M.; Nassar-Hardy, L.; Hierso, J.-C.; Fouquet, E.; Felpin, F.-X. Recyclable heterogeneous palladium catalysts in pure water: sustainable developments in Suzuki, Heck, Sonogashira and Tsuji-Trost reactions. *Adv. Synth. Catal.* **2010**, *352*, 33. (f) Balanta, A.; Godard, C.; Claver, C. Pd nanoparticles for C-C coupling reactions. *Chem. Soc. Rev.* **2011**, *40*, 4973. (g) Fihri, A.; Bouhrara, M.; Nekoueishahraki, B.; Basset, J.-M.; Polshettiwar, V. Nanocatalysts for Suzuki cross-coupling reactions. *Chem. Soc. Rev.* **2011**, *40*, 5181. (h) Suzuki, A. Cross-coupling reactions of organoboranes: an easy way to construct C-C bonds (Nobel lecture). *Angew. Chem., Int. Ed.* **2011**, *50*, 6722. (i) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062. (j) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. Development of preformed Pd catalysts for cross-coupling reactions, beyond the 2010 Nobel prize. *ACS Catal.* **2012**, *2*, 1147. (k) *Science of Synthesis Series*, Molander, G. A.; Molander, G. A.; Larhed, M.; Wolfe, J., Eds.; Thieme Chemistry: Stuttgart, 2013; p 601. (l) *Applied Cross-Coupling Reactions*; Springer-Verlag: Berlin, Heidelberg, 2013; p 17. (m) *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*, Molnár, Á., Ed.; Wiley-VCH: Weinheim, 2013; p 287. (n) de Meijere, A.; Bräse, S.; Oestreich, M. *Metal Catalyzed Cross Coupling Reactions and More*, Wiley, 2013; Vol. 3, p 995. (o) *Metal Catalyzed Cross-coupling Reactions and More, 3 Vol. Set*, De Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley-VCH: Weinheim, 2014; p 13001. (p) Paul, S.; Islam, M. M.; Islam, S. M. Suzuki-Miyaura reaction by heterogeneously supported Pd in water: recent studies. *RSC Adv.* **2015**, *5*, 42193. (q) Gildner, P. G.; Colacot, T. J. Reactions of the 21st century: two decades of innovative catalyst design for palladium-catalyzed cross-couplings. *Organometallics* **2015**, *34*, 5497. (r) Biffis, A.; Centomo, P.; Zotto, A. D.; Zecca, M. Pd metal catalysts for cross-couplings and related reactions in the 21st century: A critical review. *Chem. Rev.* **2018**, *118*, 2249. (s) Korch, K. M.; Watson, D. A. Cross-coupling of heteroatomic electrophiles. *Chem. Rev.* **2019**, *119*, 8192.

(2) (a) Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Rational development of practical catalysts for aromatic carbon-nitrogen bond formation. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Surry, D. S.; Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) Bariwal, J.; der Eycken, E. V. C-N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2013**, *42*, 9283. (e) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C-N cross-coupling reactions. *Chem. Rev.* **2016**, *116*, 12564. (f) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig reaction: an overview. *J. Organomet. Chem.* **2018**, *861*, 17. (g) Luo, J.; Wei, W.-T. Recent advances in the construction of C-N bonds through coupling reactions between carbon radicals and nitrogen radicals. *Adv. Synth. Catal.* **2018**, *360*, 2076. (h) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl monophosphine ligands in palladium-catalyzed C−N coupling: an updated user's guide. *Tetrahedron* **2019**, *75*, 4199.

(3) Egorova, K. S.; Ananikov, V. P. Which metals are green for catalysis? Comparison of the toxicities of Ni, Cu, Fe, Pd, Pt, Rh, and Au Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 12150.

(4) (a) Tsou, T. T.; Kochi, J. K. Mechanism of oxidative addition. Reaction of nickel(0) complexes with aromatic halides. *J. Am. Chem. Soc.* **1979**, *101*, 6319. (b) Montgomery, J. Nickel-catalyzed reductive cyclizations and couplings. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (c) *Modern Organonickel Chemistry*, Tamaru, Y., Ed.; Wiley-VCH: 2005; p 41. (d) Saito, B.; Fu, G. C. Alkyl−alkyl Suzuki cross-couplings of unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (e) Saito, B.; Fu, G. C. Enantioselective alkyl-alkyl Suzuki cross-couplings of unactivated homobenzylic halides. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (f) Son, S.; Fu, G. C. Nickel-catalyzed asymmetric Negishi cross-couplings of secondary allylic chlorides with alkylzincs. *J. Am. Chem. Soc.* **2008**, *130*, 2756. (g) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. Nickel-catalyzed Suzuki-Miyaura reaction of aryl fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 19505. (h) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. Nickel-catalyzed cross-couplings involving carbon-oxygen bonds. *Chem. Rev* **2011**, *111*, 1346. (i) Ge, S.; Hartwig, J. F. Highly reactive, single-component nickel catalyst precursor for Suzuki-Miyuara cross-coupling of heteroaryl boronic acids with heteroaryl halides. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837. (j) Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. Nickel-catalyzed Suzuki-Miyaura couplings in green solvents. *Org. Lett.* **2013**, *15*, 3950. (k) Cornella, J.; Gómez-Bengoa, E.; Martin, R. Combined experimental and theoretical study on the reductive cleavage of inert C-O bonds with silanes: ruling out a classical Ni(0)/Ni(II) catalytic couple and evidence for Ni(I) intermediates. *J. Am. Chem. Soc.* **2013**, *135*, 1997. (l) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299. (m) Weix, D. J. Methods and mechanisms for cross-electrophile coupling of C_{sp^2} halides with alkyl electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767. (n) Choi, J.; Fu, G. C. Transition metal-catalyzed alkyl-alkyl

bond formation: another dimension in cross-coupling chemistry. *Science* **2017**, *356*, No. eaaf7230.
(5) (a) Wolfe, J. P.; Buchwald, S. L. Nickel-catalyzed amination of aryl chlorides. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (b) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, X.; Garg, N. K. Nickel-catalyzed amination of aryl carbamates and sequential site-selective cross-couplings. *Chem. Sci.* **2011**, *2*, 1766. (c) Ge, S.; Green, R. A.; Hartwig, J. F. Controlling first-row catalysts: amination of aryl and heteroaryl chlorides and bromides with primary aliphatic amines catalyzed by a BINAP-ligated single-component Ni(0) complex. *J. Am. Chem. Soc.* **2014**, *136*, 1617. (d) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. Development of an air-stable nickel precatalyst for the amination of aryl chlorides, sulfamates, mesylates, and triflates. *Org. Lett.* **2014**, *16*, 220. (e) Green, R. A.; Hartwig, J. F. Nickel-catalyzed amination of aryl chlorides with ammonia or ammonium salts. *Angew. Chem., Int. Ed.* **2015**, *54*, 3768. (f) Camasso, N. M.; Sanford, M. S. Design, synthesis, and carbon-heteroatom coupling reactions of organometallic nickel(IV) complexes. *Science* **2015**, *347*, 1218. (g) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. Challenging nickel-catalysed amine arylations enabled by tailored ancillary ligand design. *Nat. Commun.* **2016**, *7*, No. 11073. (h) Lavoie, C. M.; MacQueen, P. M.; Stradiotto, M. Nickel-catalyzed *N*-arylation of primary amides and lactams with activated (hetero)aryl electrophiles. *Chem. Eur. J.* **2016**, *22*, 18752. (i) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Aryl amination using ligand-free Ni(II) salts and photoredox catalysis. *Science* **2016**, *353*, 279. (j) Marín, M.; Rama, R. J.; Nicasio, M. C. Ni-Catalyzed Amination Reactions: an Overview. *Chem. Rec.* **2016**, *16*, 1819. (k) Inatomi, T.; Fukahori, Y.; Yamada, Y.; Ishikawa, R.; Kanegawa, S.; Koga, Y.; Matsubara, K. Ni(I)−Ni(III) cycle in Buchwald−Hartwig amination of aryl bromide mediated by NHC-ligated Ni(I) complexes. *Catal. Sci. Technol.* **2019**, *9*, 1784. (l) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, N. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019**, *141*, 6392.
(6) (a) Jin, G.; Zhang, D. Micron-granula polyolefin with self-immobilized nickel and iron diimine catalysts bearing one or two allyl groups. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 1018. (b) Chen, X.; Wang, L.; Liu, J. Kumada cross-coupling of aryl Grignard reagents with aryl halides catalyzed by an immobilized nickel catalyst. *Synthesis* **2009**, *14*, 2408. (c) Yoon, H.-J.; Choi, J.-W.; Kang, H.; Kang, T.; Lee, S.-M.; Jun, B.-H.; Lee, Y.-S. Recyclable NHC-Ni complex immobilized on magnetite/silica nanoparticles for C-S cross-coupling of aryl halides with thiols. *Synlett* **2010**, *16*, 2518. (d) Zhang, L. Y.; Hu, W. C.; Li, Z.; Hua, LiP.; Li, Z. X.; Lei, W. Immobilized nickel(II) on organic-inorganic hybrid materials: the effective and reusable catalysts for Biginelli reaction. *Sci. China Chem.* **2011**, *54*, 74. (e) Kalbasi, R. J.; Mazaheri, O. Synthesis and characterization of hierarchical ZSM-5 zeolite containing Ni nanoparticles for one-pot reductive amination of aldehydes with nitroarenes. *Catal. Commun.* **2015**, *69*, 86. (f) Nikoorazm, M.; Arash, G.-C.; Khanmoradi, M. Synthesis and characterization of Ni(ii)-vanillin-Schiff base-MCM-41 composite as an efficient and reusable nanocatalyst for multi-component reactions. *RSC Adv.* **2016**, *6*, 56549. (g) Kalbasi, R. J.; Parishani, P.; Mazaheri, O. Encapsulation of nickel nanoparticles and homopoly(vinylsulfonic acid) in mesoporous carbon CMK-3 as an acid-metal bifunctional catalyst for tandem reductive amination. *J. Cluster Sci.* **2018**, *29*, 561. (h) Elumalai, P.; Mamlouk, H.; Yiming, W.; Feng, L.; Yuan, S.; Zhou, H.-C.; Madrahimov, H. T. Recyclable and reusable heteroleptic nickel catalyst immobilized on metal-organic framework for Suzuki-Miyaura coupling. *ACS Appl. Mater. Interfaces* **2018**, *10*, 41431. (i) Ghosh, D.; Febriansyah, B.; Gupta, D.; Leonard, K.-S. N.; Xi, S.; Du, Y.; Baikie, T.; Dong, Z.; Soo, H. S. Hybrid nanomaterials with single-site catalysts by spatially controllable immobilization of nickel complexes via photoclick chemistry for alkene epoxidation. *ACS Nano* **2018**, *12*, 5903. (j) Hahn, G.; Kunnas, P.; Jonge, N. D.; Kempe, R. General synthesis of primary amines via reductive amination employing a reusable nickel catalyst. *Nat. Catal.* **2019**, *2*, 71. (k) Murugesan, K.; Beller, M.; Jagadeesh, R. V. Reusable nickel nanoparticles-catalyzed reductive amination for selective synthesis of primary amines. *Angew. Chem., Int. Ed.* **2019**, *58*, 5064.
(7) (a) Sarkar, S. M.; Uozumi, Y.; Yamada, Y. M. A. A highly active and reusable self-assembled poly(imidazole /palladium) catalyst: allylic arylation/alkenylation. *Angew. Chem., Int. Ed.* **2011**, *50*, 9437. (b) Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. Amphiphilic self-assembled polymeric copper catalyst to parts per million levels: Click chemistry. *J. Am. Chem. Soc.* **2012**, *134*, 9285. (c) Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. Self-assembled poly(imidazole-palladium): highly active, reusable catalyst at parts per million to parts per billion levels. *J. Am. Chem. Soc* **2012**, *134*, 3190. (d) Hudson, R.; Zhang, H. R.; LoTemplio, A.; Bennedetto, G.; Hamasaka, G.; Yamada, Y. M. A.; Katz, J. L.; Uozumi, Y. Poly(meta-phenylene oxides) for the design of a tunable, efficient, and reusable catalytic platform. *Chem. Commun* **2018**, *54*, 2878. (e) Hu, H.; Ohno, A.; Sato, T.; Mase, T.; Uozumi, Y.; Yamada, Y. M. A. Self-assembled polymeric pyridine copper catalysts for Huisgen cycloaddition with alkynes and acetylene gas: Application in synthesis of Tazobactam. *Org. Process Res. Dev.* **2019**, *23*, 493. (f) Ohno, A.; Sato, T.; Mase, T.; Uozumi, Y.; Yamada, Y. M. A. A convoluted polyvinylpyridine-palladium catalyst for Suzuki-Miyaura coupling and C-H arylation. *Adv. Synth. Catal.* **2020**, *362*, 4687−4698.
(8) (a) Tan, L. T. Bioactive natural products from marine cyanobacteria for drug discovery. *Phytochemistry* **2007**, *68*, 954. (b) Yu, S.; Haight, A.; Kotecki, B.; Wang, L.; Lukin, k.; Hill, D. R. Synthesis of a TRPV1 Receptor Antagonist. *J. Org. Chem.* **2009**, *74*, 9539. (c) Young, D. D.; Connelly, C. M.; Grohmann, C.; Deiters, A. Small molecule modifiers of microRNA miR-122 function for the treatment of hepatitis C virus infection and hepatocellular carcinoma. *J. Am. Chem. Soc.* **2010**, *132*, 7976. (d) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. One-pot formation of C-C and C-N bonds through palladium-catalyzed dual C-H activation: synthesis of phenanthridinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380. (e) Roy, S.; Roy, S.; Gribble, G. W. Metal-catalyzed amidation. *Tetrahedron* **2012**, *68*, 9867. (f) Ponraj, K.; Prabhakar, M.; Rathore, R. S.; Bommakanti, A.; Kondapi, A. K. HIV-1 associated Topoisomerase IIβ kinase: a potential pharmacological target for viral replication. *Curr. Pharm. Des.* **2013**, *19*, 4776. (g) Dragovich, P. S.; Zhao, G.; Baumeister, T.; Bravo, B.; Giannetti, A. M.; Ho, Y.-C.; Hua, R.; Li, G.; Liang, X.; Ma, X.; O'Brien, T.; Oh, A.; Skelton, N. J.; Wang, C.; Wang, W.; Wang, Y.; Xiao, Y.; Yuen, P.-W.; Zak, M.; Zhao, Q.; Zheng, X. Fragment-based design of 3-aminopyridine-derived amides as potent inhibitors of human nicotinamide phosphoribosyltransferase (NAMPT). *Bioorg. Med. Chem. Lett.* **2014**, *24*, 954. (h) Taha, M. O.; Habash, M.; Khanfar, M. A. The use of docking-based comparative intermolecular contacts analysis to identify optimal docking conditions within glucokinase and to discover of new GK activators. *J. Comput. Aided Mol. Des.* **2014**, *28*, 509. (i) Zhang, L.; Hu, X. Room temperature C(sp^2)-H oxidative chlorination via photoredox catalysis. *Chem. Sci.* **2017**, *8*, 7009. (j) Reber, K. P.; Burdge, H. E. Total synthesis of pyrophen and campyrones A−C. *J. Nat. Prod.* **2018**, *81*, 292. (k) Borra, S.; Lapinskaite, R.; Kempthorne, C.; Liscombe, D.; McNulty, J.; Hudlicky, T. Isolation, synthesis, and semisynthesis of amaryllidaceae constituents from narcissus and galanthus sp.: De novo total synthesis of 2-epi-narciclasine. *J. Nat. Prod.* **2018**, *81*, 1451.
(9) (a) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: New York, 1989; Experiment 6.109, p 985. (b) Hinson, J. A.; Roberts, D. W.; James, L. P. *Handbook of Experimental Pharmacology, Adverse Drug Reactions*; Springer: Berlin, 2010; Chapter 12, p 369. (c) *Martindale, The Complete Drug Reference*, 37th ed.; Sweetman, S. C., Ed.; Pharmaceutical Press: London, 2011; Vol. *A*, p 112. (d) Moffat, A. C.; Osselton, M. D.; Widdop, B. *Clarke's Analysis of Drugs and Poisons*, 4th ed.; Pharmaceutical Press: London, 2011; Vol. *2*, p 1856.

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418

(10) (a) Li, Y.; Jung, N.-Y.; Yoo, J. C.; Kim, Y.; Yi, G.-S. Acebutolol, a cardioselective beta blocker, promotes glucose uptake in diabetic model cells by inhibiting JNK-JIP1 interaction. *Biomol. Ther.* **2018**, *26*, 458. (b) Zilker, M.; Sörgel, F.; Holzgrabe, U. A long-time stability study of 50 drug substances representing common drug classes of pharmaceutical use. *Drug Test Anal.* **2019**, *11*, 1065.

(11) (a) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. One-pot formation of C-C and C-N bonds through palladium-catalyzed dual C-H activation: synthesis of phenanthridinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380. (b) Karthikeyan, J.; Cheng, C. H. Synthesis of phenanthridinones from *N*-methoxybenzamides and arenes by multiple palladium-catalyzed C-H activation steps at room temperature. *Angew. Chem., Int. Ed.* **2011**, *50*, 9880. (c) Pimparkar, S.; Jeganmohan, M. Palladium-catalyzed cyclization of benzamides with arynes: application to the synthesis of phenaglydon and *N*-methylcrinasiadine. *Chem. Commun.* **2014**, *50*, 12116. (d) Zhang, Z.; Liao, L. L.; Yan, S. S.; Wang, L.; He, Y. Q.; Ye, J. H.; Li, J.; Zhi, Y. G.; Yu, D. G. Lactamization of sp^2 C-H bonds with CO_2: transition metal-free and redox-neutral. *Angew. Chem., Int. Ed.* **2016**, *55*, 7068. (e) Thorat, V. H.; Upadhyay, N. S.; Murakami, M.; Cheng, C. H. Nickel-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4-(3*H*)-ones with benzynes for construction of phenanthridinone scaffolds. *Adv. Synth. Catal.* **2018**, *360*, 284. (f) Subhedar, D. D.; Mishra, A. A.; Bhanage, B. M. *N*-Methoxybenzamide: a versatile directing group for palladium-, rhodium- and ruthenium- catalyzed C-H bond activations. *Adv. Synth. Catal.* **2019**, *361*, 4149.

(12) (a) Bon, E.; Bigg, D. C. H.; Bertrand, G. Aluminum chloride-promoted transamidation reactions. *J. Org. Chem.* **1994**, *59*, 4035. (b) Dineen, T. A.; Zajac, M. A.; Myers, A. G. Efficient transamidation of primary carboxamides by in situ activation with *N*,*N*-dialkylformamide dimethyl acetals. *J. Am. Chem. Soc.* **2006**, *128*, 16406. (c) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. Discovery and mechanistic study of Al^{III}-catalyzed transamidation of tertiary amides. *J. Am. Chem. Soc.* **2008**, *130*, 647. (d) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. Catalytic transamidation reactions compatible with tertiary amide metathesis under ambient conditions. *J. Am. Chem. Soc.* **2009**, *131*, 10003. (e) Zhang, M.; Imm, S.; Bahn, S.; Neubert, L.; Neumann, H.; Beller, M. Efficient copper (II)-catalyzed transamidation of non-activated primary carboxamides and ureas with amines. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905. (f) Tamura, M.; Tonomura, T.; Shimizu, K.-I.; Satsuma, A. Transamidation of amides with amines under solvent-free conditions using a CeO_2 catalyst. *Green Chem.* **2012**, *14*, 717. (g) Lee, S. I.; Son, S. U.; Chung, Y. K. Catalytic one-pot synthesis of *N*-phenyl alkyl amides from alkene and aniline in the presence of cobalt on charcoal under carbon monoxide. *Chem. Commun.* **2002**, *12*, 1310. (h) Hosoi, K.; Nozaki, K.; Hiyama, T. Carbon monoxide free aminocarbonylation of aryl and alkenyl iodides using DMF as an amide source. *Org. Lett.* **2002**, *4*, 2849. (i) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. Palladium-catalyzed aminocarbonylation of aryl chlorides at atmospheric pressure: the dual role of sodium phenoxide. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460. (j) Liu, W.; Li, J.; Querard, P.; Li, C.-J. Transition-Metal-Free C−C, C-O, and C-N cross-couplings enabled by light. *J. Am. Chem. Soc.* **2019**, *141*, 6755. (k) Yuan, S.-W.; Han, H.; Li, Y.-L.; Wu, X.; Bao, X.; Gu, Z.-Y.; Xia, J.-B. Intermolecular C-H amidation of (hetero)arenes to produce amides through rhodium-catalyzed carbonylation of nitrene intermediates. *Angew. Chem., Int. Ed.* **2019**, *58*, 8887. (l) Álvarez-Pérez, A.; Esteruelas, M. A.; Izquierdo, S.; Varela, J. A.; Saa′, C. Ruthenium-catalyzed oxidative amidation of alkynes to amides. *Org. Lett.* **2019**, *21*, 5346.

(13) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. A general and eficient copper catalyst for the amidation of aryl halides and the *N*-arylation of nitrogen heterocycles. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.; Buchwald, S. L. A general and efficient copper catalyst for the amidation of aryl halides. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (c) Gao, G.-Y.; Chen, Y.; Zhang, X. P. General synthesis of meso-amidoporphyrins via palladium-catalyzed amidation. *Org. Lett.* **2004**, *6*, 1837. (d) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. Amino acid-mediated Goldberg reactions between amides and aryl iodides. *Tetrahedron Lett.* **2004**, *45*, 2311. (e) van den Hoogenband, A. V. D.; Lange, J. H. M.; den Hartog, J. A. J.; Henzen, R.; Terpstra, J. W. An efficient synthesis of 4-bromo-*N*-substituted oxindoles by an intramolecular copper-catalyzed amidation reaction. *Tetrahedron Lett.* **2007**, *48*, 4461. (f) Ma, F.; Xie, X.; Zhang, L.; Peng, Z.; Ding, L.; Fu, L.; Zhang, Z. Palladium-catalyzed amidation of aryl halides using 2-dialkylphosphino-2′-alkoxyl-1,1′-binaphthyl as ligands. *J. Org. Chem.* **2012**, *77*, 5279. (g) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. Bippyphos: a single ligand with unprecedented scope in the Buchwald-Hartwig amination of (hetero)aryl chlorides. *Chem. Eur. J.* **2013**, *19*, 16760. (h) Heshmatpour, F.; Abazari, R. Formation of dispersed palladium-nickel bimetallic nanoparticles in microemulsions: synthesis, characterization, and their use as efficient heterogeneous recyclable catalysts for the amination reactions of aryl chlorides under mild conditions. *RSC Adv.* **2014**, *4*, 55815. (i) Sambiagio, C.; Munday, R. H.; John, B.; Marsden, S. P.; McGowan, P. C. Green alternative solvents for the copper-catalysed arylation of phenols and amides. *RSC Adv.* **2016**, *6*, 70025. (j) De, S.; Yin, J.; Ma, D. Copper-catalyzed coupling reaction of (hetero)aryl chlorides and amides. *Org. Lett.* **2017**, *19*, 4864.

(14) Dhital, R. N.; Sen, A.; Sato, T.; Hu, H.; Ishii, R.; Hashizume, D.; Takaya, H.; Uozumi, Y.; Yamada, Y. M. A. Activator-promoted aryl halide-dependent chemoselective Buchwald-Hartwig and Suzuki-Miyaura type cross-coupling reactions. *Org. Lett.* **2020**, *22*, 4797.

(15) For recent work on switchable selectivity, see: (a) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. Switchable selectivity in an NHC-catalysed dearomatizing annulation reaction. *Nat. Chem.* **2015**, *7*, 842. (b) Jiang, Y.-Y.; Yan, L.; Yu, H.-Z.; Zhang, Q.; Fu, Y. Mechanism of vanadium-catalyzed selective C-O and C-C cleavage of lignin model compound. *ACS Catal.* **2016**, *6*, 4399. (c) Bhojgude, S. S.; Roy, T.; Gonnade, R. G.; Biju, A. T. Substrate-controlled selectivity switch in the three-component coupling involving arynes, aromatic tertiary amines, and CO_2. *Org. Lett.* **2016**, *18*, 5424. (d) Ray, R.; Chandra, S.; Yadav, V.; Mondal, P.; Maiti, D.; Lahiri, G. K. Ligand controlled switchable selectivity in ruthenium catalyzed aerobic oxidation of primary amines. *Chem. Commun.* **2017**, *53*, 4006. (e) Bhatt, D.; Patel, N.; Chowdhury, H.; Bharatam, P. V.; Goswami, A. Additive-controlled switchable selectivity from cyanobenzenes to 2-alkynylpyridines: ruthenium(II)-catalyzed [2+2+2] cycloadditions of diynes and alkynylnitriles. *Adv. Synth. Catal.* **2018**, *360*, 1876. (f) Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. Switchable selectivity in the Pd-catalyzed alkylative cross-coupling of esters. *Org. Lett.* **2018**, *20*, 4094. (g) Roy, T.; Gaykar, R. N.; Bhattacharjee, S.; Biju, A. T. The aryne Sommelet-Hauser rearrangement. *Chem. Commun.* **2019**, *55*, 3004. (h) Zhao, M.; Shan, C.-C.; Wang, J.-L.; Yang, C.; Fu, Y.; Xu, Y.-H. Ligand-dependent-controlled copper-catalyzed regio- and stereoselective silaboration of alkynes. *Org. Lett.* **2019**, *21*, 6016.

(16) (a) Dudnik, A. S.; Fu, G. C. Nickel-catalyzed coupling reactions of alkyl electrophiles, including unactivated tertiary halides, to generate carbon−boron bonds. *J. Am. Chem. Soc.* **2012**, *134*, 10693. (b) Zultanski, S. L.; Fu, G. C. Nickel-catalyzed carbon−carbon bond-forming reactions of unactivated tertiary alkyl halides: Suzuki arylations. *J. Am. Chem. Soc.* **2013**, *135*, 624.

https://dx.doi.org/10.1021/acscatal.0c03888
ACS Catal. 2020, 10, 14410−14418