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A Highly Practical and Reliable Nickel Catalyst for Suzuki–Miyaura Coupling of Aryl Halides

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Abstract: We disclose that [1,3-bis(diphenylphosphino)methane]nickel(II) chloride [$NiCl_2$(dppp)] is a highly active, universally applicable, cheap, and stable catalyst for Suzuki–Miyaura cross-coupling reactions of aryl halides with a catalyst loading of lower than 1 mol%, and more notably, in the absence of extra supporting ligands. Under the optimized reaction conditions, a broad range of aryl bromides as well as the notoriously unreactive aryl chlorides, including activated, non-activated, deactivated, and heteroaromatic and sterically hindered substrates can be coupled smoothly with various boronic acids (47 examples, 48–98% yields). In addition, the transformation is tolerant of various functional groups such as ether, ester, ketone, aldehyde, cyano, and unprotected amino and hydroxy groups. Finally, the potential utilization of the methodology was further demonstrated by the gram-scale synthesis of several core structures of commercialized antihypertensive drugs and fungicides. Thus, the combination of high activity, broad applicability, cheapness, and high stability of $NiCl_2$(dppp) presented in this work constitutes one of the few prominent catalysts which allow for practical and reliable construction of biaryls and heterobiaryls with structural diversity from readily available aryl halides and boronic acids.

Keywords: aryl bromides; aryl chlorides; biaryl formation; nickel catalysts; Suzuki coupling

Introduction

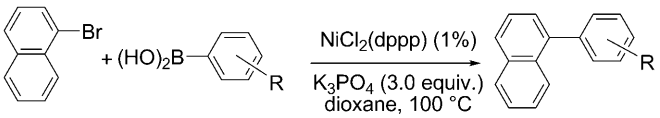
The transition metal-catalyzed cross-coupling reaction is an exceedingly powerful tool for the sp^2-sp^2 C–C bond formation. This has been well recognized with the 2010 Nobel Prize for Chemistry awarded to Profs. R. Heck, E. Negishi, and A. Suzuki.[1] Among the reported pathways, the Suzuki–Miyaura reaction represents arguably the most important and widely used one.[2] The Pd-catalyzed couplings have been extensively studied over the past decades,[2,3] they allow one to conduct the reaction of various aryl halides (or pseudohalides) even at room temperature,[4] and to handle sterically hindered substrates.[5] Also notably, a very recent contribution from Buchwald's group[4d] has expanded remarkably the scope of boronic acids, the second coupling partner, from the common phenyl-based structures to the unstable polyfluorophenyl and 2-heterocyclic analogues.

On the other hand, since the first report on the $NiCl_2$(dppf)-catalyzed Suzuki–Miyaura coupling of aryl sulfonates in the presence of a zinc reductant,[6] numerous efforts have been devoted to the development of inexpensive Ni-based catalysts, with $NiCl_2(PCy_3)_2$, $Ni(cod)_2$, $NiCl_2(PPh_3)_2$, $NiCl_2$(dppf), and nickel/N-heterocyclic carbene (NHC) systems being frequently studied. Great success has been achieved recently for the coupling of various phenol derivatives such as aryl sulfonates,[7] ethers,[8] esters,[9] carbamates,[10] carbonates,[10a] sulfamates,[10a] phosphates,[11] phosphoramides,[12] and phosphonium salts.[13] In addition, the coupling of aryl halides has also been reported.[7c,g,14] However, despite these great efforts, a limited substrate scope or a high loading of the nickel complex (typically 3–10 mol%) paired with the extra

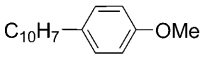
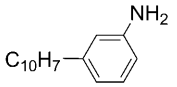
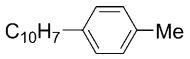
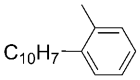
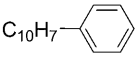
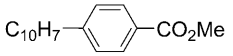
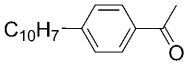
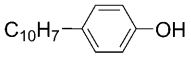
addition of a large excess of supporting ligands (1–5 equiv.) have restricted their general use. For instance, the expense of a large excess of ligands diminished the advantages of using nickel catalysts since many ligands are much more expensive even than the precious metals such as palladium. In addition, the separation of products from ligands is an important concern. Consequently, these issues go against the philosphy of modern synthesis referred to as efficient, clean and atom-economic.[15]

Thus, there is great interest in developing a highly active nickel catalyst that enables the general and practical coupling of aryl halides, especially aryl chlorides, because these substrates are commercially bulk chemicals and have been widely used for the preparation of organic building blocks, pharmaceuticals, and agrochemicals in industry *via* the transition metal-catalyzed coupling protocols.[16] We have recently demonstrated that a combination of $NiCl_2$ and dppp could be an effective precatalyst for the Suzuki–Miyaura coupling of a broad range of phenol derivatives such as aryl sulfonates,[7h] phosphoramides,[12] and phosphonium salts,[13] although several groups have shown that dppp was inefficient in nickel-catalyzed Suzuki–Miyaura coupling either as an external ligand or when prior complexed with nickel.[7b,9a,14a,b] On the basis of our recent results and our long-standing interest in the development of highly active catalysts based on the inexpensive and readily available first-row transition metals, herein, we disclose the $NiCl_2$(dppp)-catalyzed Suzuki–Miyaura coupling of aryl halides. Our results showed that this catalyst is a highly active, stable, cheap, and universally applicable catalyst, which allows for the efficient cross-coupling of a rich variety of aryl halides, particularly, the more challenging aryl chlorides with a catalyst loading of lower than 1 mol% without the need of external ligands. Moreover, the practicality of the catalyst was further exemplified by the efficient elaboration of several commercial drug motifs on a gram-scale.

Table 1. Suzuki–Miyaura coupling of 1-bromonaphthalene (**1a**) with various arylboronic acids.[a]



1a **2a** R = *p*-OMe; **2b** R = *m*-NH_2; **2c** R = *p*-Me; **2d** R = *o*-Me; **2e** R = H; **2f** R = *p*-CO_2Me; **2g** R = *p*-C(O)Me; **2h** R = *p*-OH; **3**

Entry	$(HO)_2$BAr	Product	Yield[b]
1	**2a**		90%
2	**2b**		92%
3	**2c**		92%[c]
4	**2d**		94%[c]
5	**2e**		88%[c]
6	**2f**		89%
7	**2g**		83%[d]
8	**2h**		48%

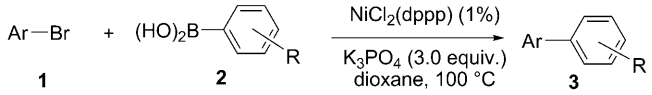
[a] *Reaction conditions:* 1-bromonaphthalene **1a** (1.0 mmol), boronic acid **2** (1.5 mmol), $NiCl_2$(dppp) (1.0 mol%), K_3PO_4 (3.0 equiv.), dioxane (4 mL), 100 °C, 2–12 h.
[b] Isolated yield.
[c] Yield was determined by ^{1}H NMR analysis due to the contamination of a small amount of inseparable by-product produced from homo-coupling of boronic acids.
[d] A mixture of dioxane and DMF (v/v = 8:1) was used as solvent.

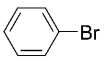
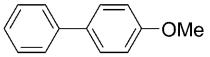
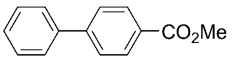
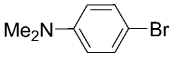
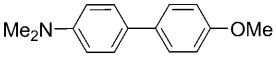
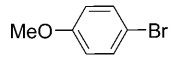
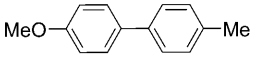
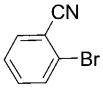
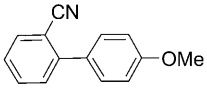
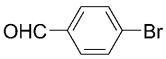
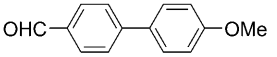
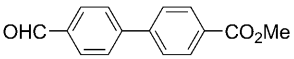
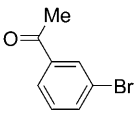
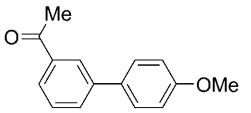
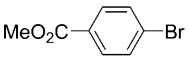
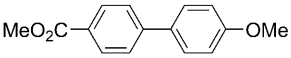
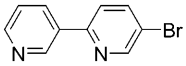
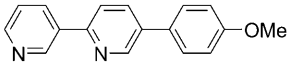
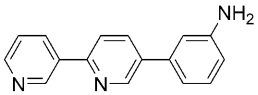
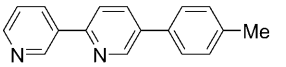
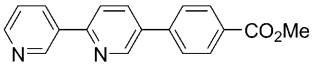
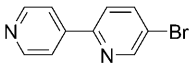
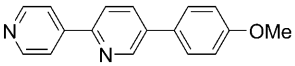
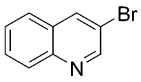
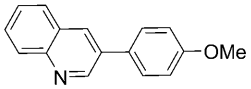
Results and Discussion

Cross-Coupling of Aryl Bromides

In our initial studies, we carried out the optimization of the reaction conditions using the coupling of 1-bromonaphthene **1a** and **2a** as a model reaction (Table 1). On the basis of our previous experience in Ni-catalyzed Suzuki–Miyaura cross-coupling of phenols,[7h,12,13] we quickly established that the optimized conditions, after examining various reaction parameters including solvent, base, temperature, and precatalyst, were $NiCl_2$(dppp)[17] (1 mol%), boronic acid (1.5 equiv.), and K_3PO_4 (3.0 equiv.) in dioxane at 100 °C. Under these conditions, the reaction of **1a** and **2a** proceeded smoothly to afford the desired product in 90% isolated yield (Table 1, entry 1). In addition, complete conversion as well as excellent yields was also observed for various boronic acids (**2b–g**) whose structures are decorated by a strong electron-donating OMe and NH_2 (entries 1 and 2), simple Me and H (entries 3–5), and electron-withdrawing CO_2Me and C(O)Me functional groups (entries 6 and 7). Notably, the tolerance of a free NH_2 group offers an opportunity for the straightforward synthesis of polyaromatic amines (see also entry 11 in Table 2 and entry 2 in Table 3). The reaction also tolerates *ortho*-substituted boronic acids (entry 4). It should be mentioned that the somewhat diminished yield (48%) for unprotected 4-hydroxyphenylboronic acid (**2h**) is due most proba-

Table 2. Suzuki–Miyaura cross-coupling of various aryl bromides with arylboronic acids.[a]



Entry	Ar–Br	$ArB(OH)_2$	Product	Yield[b]
1		**2a**		82%
2		**2f**		78%
3		**2a**		75%
4		**2c**		53%
5		**2a**		91%
6		**2a**		95%
7		**2f**		87%
8		**2a**		80%
9		**2a**		89%
10		**2a**		97%
11		**2b**		83%
12		**2c**		88%
13		**2f**		85%
14		**2a**		94%
15		**2a**		98%

[a] *Reaction conditions:* aryl bromide **1** (1.0 mmol), boronic acid **2** (1.5 mmol), $NiCl_2$(dppp) (1.0 mol%), K_3PO_4 (3.0 equiv.), dioxane (4 mL), 100 °C, 2–12 h.

[b] Isolated yield.

bly to the formation of potassium phenoxide salt that is less soluble in the dioxane solvent used (entry 8).

The broad applicability of this transformation was further exemplified by examining the scope of aryl bromides. As summarized in Table 2, the unactivated (entries 1 and 2), deactivated (entries 3 and 4), and the activated aryl bromides (entries 5–9) could be coupled successfully with various boronic acids to generate the desired biaryls in high yields. In addition, the reaction tolerates not only *ortho*-substituents on the boronic acids (Table 1, entry 4), but also the same steric hindrance on the aryl bromides (Table 2,

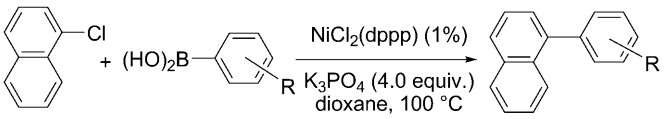
entry 5). The examples from entries 10 to 15 demonstrate the viability of heteroaryl bromides in this transforamtion. For instance, bipyridines and fused quinoline derivatives underwent smooth coupling with various boronic acids, affording the desired polyheteroaromatic compounds in excellent yields. These results are attractive since polypyridyl compounds are ubiquitous structural scaffolds found in polymers, bioactive compounds, coordination complexes, catalysis and supramolecular materials.

Cross-Coupling of Aryl Chlorides

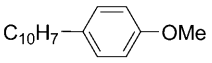
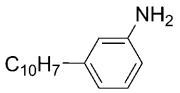
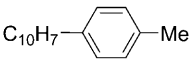
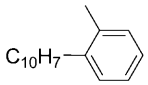
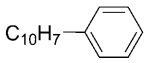
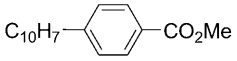
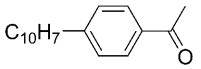
With the robust cross-coupling conditions for aryl bromides established, we further examined the catalytic efficacy of the catalyst by executing the cross-coupling of aryl chlorides. This class of substrates is more appealing as coupling partner in comparison with the analogous aryl bromides and iodides due to the lower cost and the wider availability. However, the notoriously unreactive nature of aryl chlorides makes their coupling reactions considerably more challenging.[2–5,7g,14] The low reactivity is attributed to the much higher bond energy of the C–Cl bond than those of the C–Br and C–I bonds,[18] which results in their reluctance to participate in oxidative addition. Much to our delight, we found that $NiCl_2$(dppp) is a prominent catalyst to couple aryl chlorides under the similar conditions as used to couple aryl bromides, except for a slightly increased molar equivalent of arylboronic acids and K_3PO_4 base. As shown in Table 3, 1-chloronaphthalene underwent smooth coupling with a range of boronic acids whose structures are substituted by versatile functional groups such as electron-rich OMe and the unprotected NH_2, neutral Me and H, and electron-deficient CO_2Me and C(O)Me groups (entries 1–7). Boronic acids with an unprotected amino group and an *ortho*-substituted boronic acid also serve as superb coupling partners, affording the corresponding coupled products in high yields (entries 2 and 4).

Next, the catalytic efficiency of $NiCl_2$(dppp) was further confirmed by varying the structure of the aryl chlorides. Thus, 2-chloronaphthalene could be transformed into the desired product in 95% yield (Table 4, entry 1). Most importantly the non-fused aryl chlorides, whose coupling under Suzuki–Miyaura conditions often appears to be very challenging due to the less delocalized nature, are also viable substrates, affording the desired biaryls in good to excellent yields. For instance, reaction of the non-activated phenyl chloride with 4-methoxyphenylboronic acid provided the biaryl in 94% yield (entry 2). The deactivated 3-*N,N*-dimethylaminophenyl chloride underwent smooth cross-coupling, affording the desired product in 71% yield (entry 3). In addition, the reaction was also tolerant of various activated aryl chlorides, encompassing a range of functional groups including *ortho*- and *para*-substituted aldehydes (entries 4 and 5), as well as cyano groups (entries 6–9), ketone (entry 10), and ester (entry 11). It is noteworthy that the substrates with a cyano or aldehyde group at the *ortho*-position of the aryl chloride provided the coupled biaryls in excellent yields (entries 5, 8 and 9). These results, together with that observed from the sterically hindered boronic acid (Table 3, entry 4), indicate that the transformation exhibits good tolerance of steric hindrance not only on aryl chlorides but also on boronic acids. As important applications for the couplings of these sterically hindered substrates, they offer practical pathways for the synthesis of several core motifs of commercialized drugs and bioactive compounds (*vide infra*). Finally,

Table 3. Suzuki–Miyaura Cross-coupling of 1-chloronaphthalene (**1b**) with various arylboronic acids.[a]



1b **2** **4**

Entry	$(HO)_2BAr$	Product	Yield[b]
1	**2a**		96%
2	**2b**		98%[c]
3	**2c**		94%[d]
4	**2d**		80%[d]
5	**2e**		96%[d]
6	**2f**		90%
7	**2g**		90%[e]

[a] *Reaction conditions:* 1-chloronaphthalene **1b** (1.0 mmol), boronic acid **2** (2.0 mmol), $NiCl_2$(dppp) (1.0 mol%), K_3PO_4 (4.0 equiv.), dioxane (4 mL), 100 °C, 2–20 h.

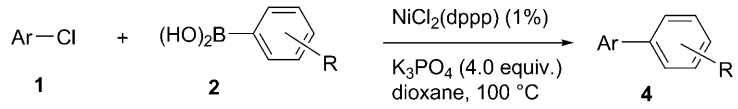
[b] Isolated yield.

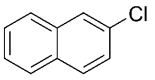
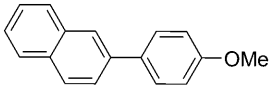
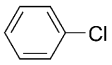
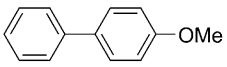
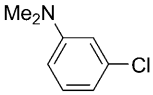
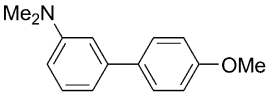
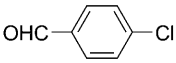
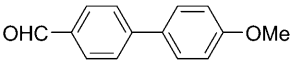
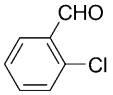
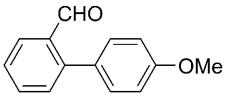
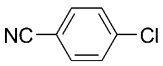
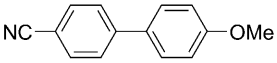
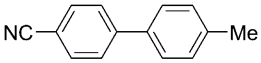
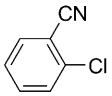
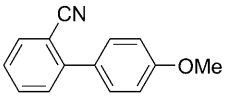
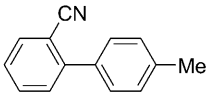
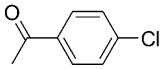
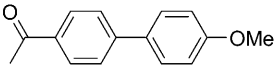
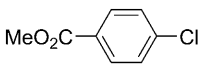
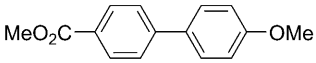
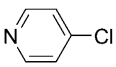
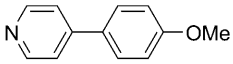
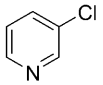
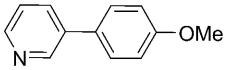
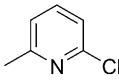
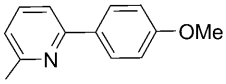
[c] Reaction was run at 110 °C.

[d] Yield was determined by ^{1}H NMR analysis due to the contamination of a small amount of inseparable by-product derived from homo-coupling of boronic acids.

[e] A mixture of dioxane and DMF (v/v = 8:1) was used as solvent.

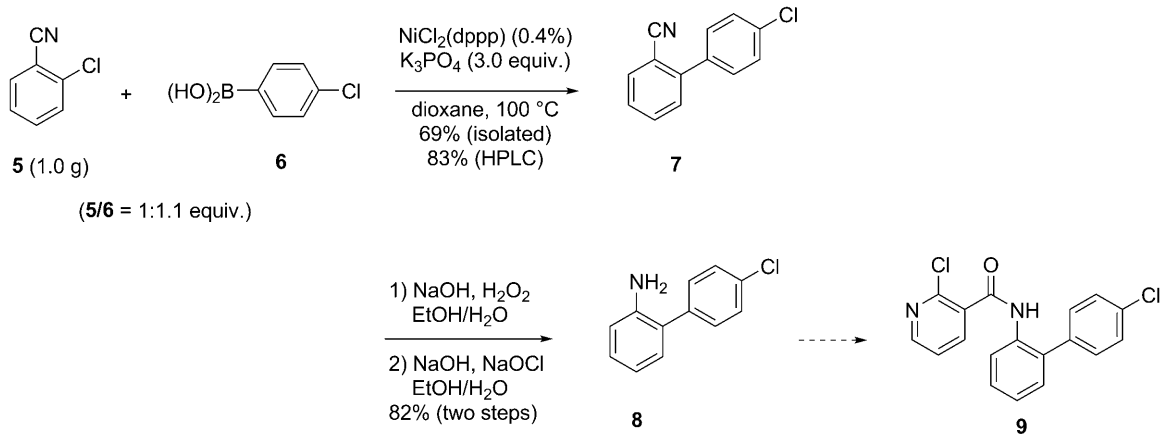
Table 4. Suzuki–Miyaura cross-coupling of various aryl chlorides with arylboronic acids.[a]



Entry	ArCl	$(HO)_2BAr$	Product	Yield[b]
1		**2a**		95%
2		**2a**		94%
3		**2a**		71%
4		**2a**		89%
5		**2a**		89%
6		**2a**		97%
7		**2c**		94%
8		**2a**		96%
9		**2c**		94%
10		**2a**		88%
11		**2a**		98%
12		**2a**		95%
13		**2a**		98%
14		**2a**		79%

[a] *Reaction conditions:* aryl chloride **1** (1.0 mmol), boronic acid **2** (2.0 mmol), $NiCl_2$ (dppp) (1.0 mol%), K_3PO_4 (4.0 equiv.), dioxane (4 mL), 100–110 °C, 2-18 h.
[b] Isolated yield.

the methodology also displays good compatibility to heteroaromatic chlorides (entries 12–14), although a somewhat interesting observation is that the deactivated 3- and 4-chloropyridines (entries 12 and 13) were coupled slightly more efficiently than the activated 2-chloropyridine (entry 14). Such a similar



Scheme 1. Synthesis of core structure **8** of Boscalid® (**9**).

result was also observed in the closely related Stille cross-coupling catalyzed by $Pd_2(dba)_3$.[19]

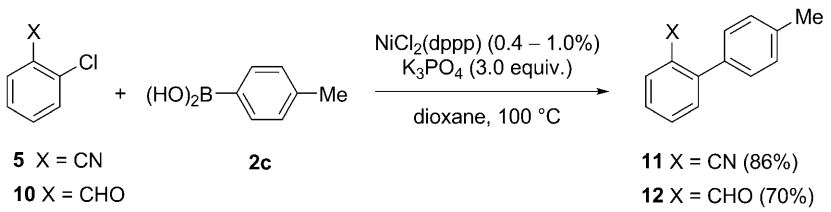
Now, we have clearly demonstrated that by careful optimization of the reaction conditions, $NiCl_2$(dppp) can be a highly active catalyst to effect the cross-coupling of a rich range of aryl halides. In contrast, outcomes from the work of Miyaura[14a] and Indolese[14b] showed that $NiCl_2$(dppp) [or $NiCl_2$(dppe)] was less efficient to couple aryl halides and boronic acids under their reaction conditions either by prior reducing the nickel(II) to nickel(0) with BuLi[14a] or by employing anisole as solvent.[14b] As a plausible explanation, it was suggested that $NiCl_2$ complexes with dppp and dppe could form highly stable six- and five-membered chelates which was unfavourable for the dissociation of one phosphorus during the catalytic cycle. And since then, these two highly stable and readily available catalysts have been less investigated over the past decade in the Suzuki–Miyaura coupling of aryl halides (and pseudohalides).

Potential Applications

To demonstrate the potential utility of our methodology, the synthesis of 2-amino-4′-chlorobiphenyl (**8**) was performed (Scheme 1). This compound is the core motif of a new fungicide, Boscalid® (**9**), which is currently one of the largest industrial applications of Suzuki–Miyaura reaction (*ca.* 1000 tons per year).[16,20] Of the available approaches for accessing **8**, palladium-catalyzed cross-couplings were exclusively used as the key transformation. The industrial process involves the palladium-catalyzed Suzuki coupling of 1-chloro-2-nitrobenzene with 4-chlorophenylboronic acid (**6**), followed by the reduction of the nitro group to an amino group.[21] A similar method *via* the palladim-catalyzed cross-coupling of 2-nitrophenyldiazonium salt and boronic acid **6** was also reported recently.[22] Alternative pathways for the construction of **8** included the palladium-catalyzed cross-coupling of arylgermane and aryl bromides,[23] and free radical-induced cross-coupling of aryldiazonium salts.[24]

To examine the efficiency of our methodology, we synthesized **8** on the gram-scale starting from 2-chlorobenzonitrile (**5**). As outlined in Scheme 1, coupling of **5** with a slightly excess of **6** (1.1 equiv.) proceeded smoothly in the presence of only 0.4 mol% of our $NiCl_2$(dppp) catalyst to afford the coupled product **7** in high yield. Hydrolysis followed by Hofmann rearrangement of **7** gave the desired key structure **8** in 82% yield over two steps (an unoptimized trial showed that the later two-step transformation can be combined into a one-pot operation without decreasing the yield). This approach offers an advantage over the available methods in terms of the cost of catalyst. In addition, the method is environmentally more benign than the reported ones since the subsequent hydrolysis and Hofmann rearrangement of **7** were carried out under clean conditions, avoiding the disposal of iron waste generated from the reduction of the nitro group.[22]

The practicality of this transformation was further exemplified by the synthesis of biphenyl derivatives **11** and **12** in a gram-scale operation (Scheme 2). These two biaryls are key intermediates for the synthesis of antihypertensive drugs such as losartan, irbesartan, and valsartan,[25] or AT II antagonists,[1,16] and also represent one of the most important industrial applications of the Pd-catalyzed Suzuki–Miyaura reaction.[26] Here, by employing only 0.4 and 1.0 mol% of $NiCl_2$(dppp) as catalyst, *ortho*-substituted 2-chlorobenzonitrile (**5**) or 2-chlorobenzaldehyde (**10**) could be coupled efficiently with a slight excess (1.05 equiv.) of 4-methylphenylboronic acid (**2c**) to afford **11** and **12**, respectively, in high yields.



Scheme 2. Gram-scale synthesis of biphenyls **11** and **12**.

Conclusions

In summary, through an extensive study, we have unambiguously demonstrated that $NiCl_2$(dppp) is a reliable and practical catalyst for Suzuki–Miyaura cross-couplings of aryl bromides and chlorides. The reaction proceeds smoothly with a catalyst loading lower than 1.0 mol% and, more notably, without the need of extra supporting ligands. Moreover, the transformation tolerates a wide variety of aryl bromide and chloride electrophiles, as well as boronic acid nucleophiles, including activated, non-activated, deactivated, and heterocyclic and sterically hindered substrates. Also, a rich range of functional groups such as ether, ester, ketone, aldehyde, cyano and unprotected amino and hydroxy groups are compatible. In addition, the potential application of this methodology was further demonstrated by the elaboration of two core motifs of commercialized sartan-type drugs and a fungicide in gram-scale operations. Consequently, the results presented in this work, along with those disclosed previously by us for the coupling of aryl sulfonates,[7h] phosphoramides,[12] and phosphonium salts[13] clearly exemplified that an appropriate combination of $NiCl_2$ and dppp ligand is a highly active and universally applicable catalyst for Suzuki–Miyaura coupling of both phenol derivatives and aryl halides. These advantages combined with the high stability and ready availability render $NiCl_2$(dppp) one of the few catalysts for practical and reliable Suzuki–Miyaura cross-couplings not only in academic research, but also in industrial applications. Finally, the high activity of $NiCl_2$(dppp) as evidenced by the Suzuki–Miyaura reaction implies that this catalyst may also be suitable for other transition metal-catalyzed reactions such as Heck and Stille cross-couplings. Investigations on these reactions are currently underway in our laboratory.

Experimental Section

General Methods

All reactions were carried out under an N_2 atmosphere. The dioxane solvent was dried over molecular sieves (4 Å), or distilled according to the standard method. Anhydrous $NiCl_2$ and ligand dppp were purchased from J&K Chemical Ltd and Alfa Aesar, respectively. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz (or 600 and 125 MHz), respectively, in $CDCl_3$ with TMS as internal standard. All chemical shifts were given in ppm. All coupling constants (J values) are reported in Hertz (Hz). High resolution mass spectra were measured by using IonSpec 7.0T MALDI-FT-ICRMs. Column chromatography was performed on silica gel 100 mesh. Melting points were obtained on a Laboratory Devices Mel-Temp II instrument and were uncorrected.

General Procedure for the Small Scale Suzuki–Miyaura Cross-Coupling Reactions of Aryl Halides with Arylboronic Acids

To a 25-mL Schlenk tube equipped with a magnetic stir bar were added $NiCl_2$(dppp) (0.01 mmol, 5.4 mg), aryl halides (1.0 mmol), arylboronic acids (1.5 mmol), and anhydrous K_3PO_4 (3.0 mmol) (2.0 and 4.0 mmol of boronic acids and K_3PO_4 were used, respectively, in the case of aryl chlorides). The tube was then evacuated (3 × 10 min) under vacuum and backfilled with N_2. Dried dioxane (4.0 mL) was injected *via* a syringe, and the reaction mixture was stirred at 100–110 °C until the aryl halides had disappeared as monitored by TLC. The reaction mixture was poured into water (30 mL) and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using a mixture of hexane and CH_2Cl_2 (or hexane and ethyl acetate) as eluents to give the desired cross-coupled products. See the Supporting Information for characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra of the coupled products.

Acknowledgements

F.-S. Han is grateful to CAS (Hundred Talent Program) and State Key Laboratory of Fine Chemicals (KF1008) for financial support. Y.-L. Zhao is grateful for the support of CPSF (20090451144)

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[1] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047.
[2] For reviews, see: a) J. S. Blakeney, R. C. Reid, G. T. Le, D. P. Fairlie, *Chem. Rev.* **2007**, *107*, 2960; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; c) M.

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