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Highly Efficient Suzuki–Miyaura Coupling of Aryl Tosylates and Mesylates Catalyzed by Stable, Cost-Effective [1,3-Bis(diphenylphosphino)propane]nickel(II) Chloride [Ni(dppp)Cl_2] with only 1 mol% Loading

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Abstract: We present a highly active, inexpensive, universally applicable, and markedly stable [1,3-bis(diphenylphosphino)propane]nickel(II) chloride [Ni(dppp)Cl_2] catalyst that is capable of effecting the Suzuki–Miyaura cross-coupling of the inherently less reactive but readily available aryl tosylates and mesylates with only 1 mol% loading and in the absence of extra supporting ligand. Under the optimized reaction conditions, cross-coupling of a wide range of activated, non-activated, and deactivated, as well as sterically hindered and heteroaromatic substrates (36 examples) could proceed efficiently to afford the coupled products in 53–99% yields. Consequently, the results presented in this work provide a significant advance in Suzuki–Miyaura cross-coupling in terms of generality, practicality, and cost which are key concerns in recent research regarding transition metal-catalyzed cross-couplings.

Keywords: aryl sulfonates; biaryls; boronic acids; nickel catalyst; Suzuki–Miyaura coupling

The Suzuki–Miyaura cross-coupling of aryl halides and pseudo-halides (OTf, OTs, OMs, etc.) with arylboronic acids has been recognized as one of the most powerful and straightforward methods for the construction of biaryls and heterobiaryls[1] that constitute the main scaffolds in numerous polymers,[1c] bioactive compounds,[2] ligands,[3] and other functional materials.[4] In this transformation, phenol derivatives such as triflates,[5] tosylates[6] and mesylates[6d–g] have been extensively studied, among which the aryl tosylates and mesylates are the most appealing coupling partners because of their wide availability, low cost, and high stability. Unfortunately, these electrophiles are generally less reactive which has therefore led to considerable efforts towards the development of highly active catalysts over the past years.

Recently, remarkable progress has been achieved that allows the reaction to be carried out at room temperature,[6c,7] and to handle sterically hindered substrates.[8] However, extensive use of these catalyst systems is somewhat restricted owing to the several main concerns: First, the high cost of the frequently used Pd catalysts both for the palladium source[9] and the supporting ligands[10] limits their general use in commercial synthesis, e.g., the antihypertensive drug valsatan, and the fungicide boscalid.[11] Second, following the pioneering work on a $NiCl_2$(dppf)/Zn system-catalyzed Suzuki–Miyaura coupling of aryl sulfonates by Percec,[12] several nickel-based Zn-free catalysts such as $NiCl_2$(dppe), $NiCl_2(PCy_3)_2$, Ni(cod)$_2$, and Ni-NHC complex have been developed to effect the Suzuki–Miyaura coupling of aryl tosylates and mesylates,[6] ethers,[13] esters,[14] carbamates,[15] carbonates,[15a] and sulfamates.[15a] However, high catalyst loading (typically 3–10 mol%) paired with the requirement of an extra addition of 1–5 equivalents of phosphine ligands, which are even much more expensive than the nickel source, made the Ni-based catalysts also costly.[16] Finally, many of the Pd- and Ni-based catalysts suffer from poor stability and sensitivity to air and moisture, which strongly restricts their industrial application.[17]

Due to the aforementioned shortcomings *versus* the rapid increase of Suzuki–Miyaura coupling in practicality, new catalyst systems that combine a greater degree of activity and stability, low cost, and general applicability are highly desirable. Herein, we disclose that the $NiCl_2$(dppp) complex, as an unprecedented catalyst in Suzuki–Miyaura reaction, is not only a stable and cheap, but also a highly active, catalyst to catalyze the cross-coupling of unreactive aryl tosylates and mesylates with only 1 mol% loading and, more importantly, in the absence of extra supporting ligands.

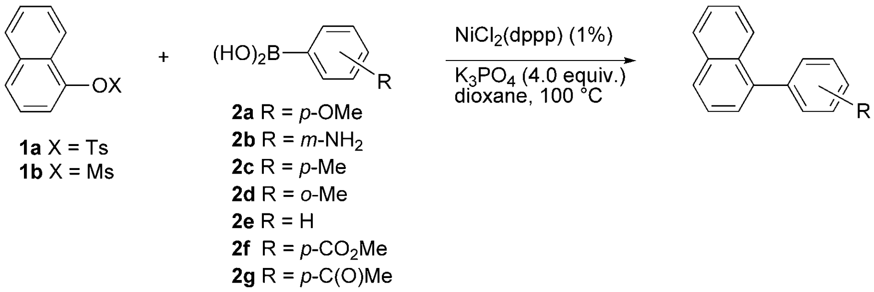
As groundwork for this study, we had previously demonstrated that a simple combination of $NiCl_2$ and dppp in a 1:2 molar ratio could catalyze the Suzuki–Miyaura reaction of aryl phosphoramides.[18] Although a high catalyst loading (10 mol% of $NiCl_2$, and 20 mol% of dppp) was required in that coupling reaction, the important advantages that pertain to using $NiCl_2$ and dppp, i.e., the low cost and high stability of both $NiCl_2$ metal source[9] and dppp ligand,[10] as well as the excellent functional group tolerance of the catalyst system stimulated us to further develop an $NiCl_2$-dppp-based new catalyst system that is capable of catalyzing the Suzuki–Miyaura reaction of the inherently less reactive aryl tosylates and mesylates. Accordingly, extensive experiments were carried out using 1-naphthyl tosylate (**1a**) and 4-methoxylphenylboronic acid (**2a**) as a reference reaction in order to optimize the reaction conditions (Table 1). Much to our delight, a systematic survey of various reaction parameters including the form of the $NiCl_2$/dppp complex [e.g., $NiCl_2(dppp)_2$, $NiCl_2$(dppp), and $NiCl_2$ $(dppp)_{1/2}$], bases (e.g., K_3PO_4, K_2CO_3, Na_2CO_3, KOAc), ligands (dppp, dppe, dppp, PCy_3), solvent, and temperature eventually revealed that $NiCl_2$ (dppp)[19] is a promising catalyst to catalyze the cross-coupling of **1a** and **2a** even in the absence of extra phosphine ligands. For instance, the cross-coupling of **1a** and **2a** could proceed very smoothly to afford the desired biaryl in 91% yield (entry 1) under the optimized conditions, that is, $NiCl_2$(dppp) (1 mol%) and K_3PO_4 (4.0 equiv.) in dioxane at 100 °C. Equal efficiently, the coupling of 1-naphthyl mesylate (**1b**) with boronic acid **2a** afforded the desired product in 99% yield under identical reaction conditions (entry 2).

To confirm that the cross-coupling is veritably catalyzed by the Ni-based catalyst rather than trace amounts of other metal impurities since $NiCl_2$ with 98% purity was used in our experiments,[19] a control experiment was carried out by using $NiCl_2$ with 99.999% purity purchased from Acros. A high yield (95%) was obtained for the coupling of **1a** and **2a** (entry 3). In addition, we also tested the purity of the $NiCl_2$(dppp) complex by using inductively coupled plasma atomic emission spectrometry (ICP-AES, Prodigy, LEEMAN). The results showed a very high purity, no other metal impurities such as palladium and copper were detected. These results firmly confirmed that $NiCl_2$(dppp) presented herein is a highly active catalyst that is capable of catalyzing the Suzuki–Miyaura coupling of less reactive aryl sulfonates.

Thus, with the optimized reaction conditions available, we first examined the feasibility of this transformation by varying the boronic acids. The results are shown in Table 1. In general, the cross-coupling of both 1-naphthyl tosylate and mesylate (**1a** and **1b**) proceeded very smoothly with various boronic acids (**2b–g**) whose structures are modified by electron-rich NH_2 (entries 4 and 5), neutral Me and H (entries 6–11), and electron-deficient CO_2Me and C(O)Me groups (entries 12–15). In addition, a sterically hindered boronic acid **2d** was also a viable coupling partner, affording the product in high yields (entries 8 and 9). Of particularly note is that for the boronic acid having an unprotected NH_2 substituent (**2b**), the reaction occurred exclusively at the boronic acid group with the naked NH_2 functionality remaining uncontaminated (entries 4 and 5). To the best of our knowledge, such a highly chemoselective cross-coupling has not been observed in the known protocols. Indeed, we have noted that a similar coupling catalyzed by Pd(0) was unsuccessful and required a prior protection of the amino group.[20] Thus, as one of the foreseeable advantages of this discovery, the orthogonal use of the $NiCl_2$(dppp)-catalyzed Suzuki–Miyaura protocol presented herein with the Buchwald–Hartwig coupling[21] would provide a straightforward pathway for the selective C−C (sp^2-sp^2) and C(sp^2)−N bond formation reaction *via* a proper control of the catalysts and the reaction sequences.

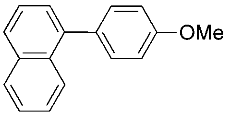
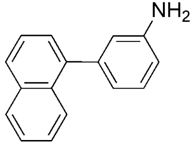
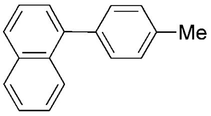
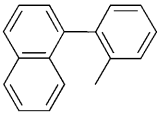
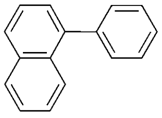
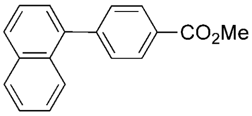
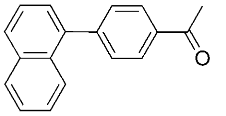
Next, we examined the general applicability of this technology for a broad range of phenols. As listed in Table 2, tosylate and mesylate derived from 2-naphthol underwent smooth coupling to afford the desired product in almost quatitative yields (entries 1 and 2). The reaction was also tolerant of naphthol analogues either substituted by a strong electron-donating OMe group (entries 3 and 4) or a strong electron-withdrawing CN group (entries 5 and 6). Moreover, the non-fused (i.e., less electron-deficient) aryl tosylate and mesylate derivatives are also competent coupling partners, affording the cross-coupled products in good to excellent yields for a range of substrates whose structures are modified by electron-rich (entries 7 and 8), neutral (entries 9 and 10), and electron-deficient groups (entries 11–18).[22] In addition, the heteroaromatic tosylate and mesylate derived from 3-hydroxypyridine were also highly effective, delivering the corresponding heterobiaryls in 98% and 96% yields, respectively (entries 19 and 20). Finally, coupling of the

Table 1. Suzuki–Miyaura cross-coupling of 1-naphthyl tosylates (**1a**) and mesylates (**1b**) with various boronic acids.[a]



1a X = Ts
1b X = Ms

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

Entry	$(HO)_2BAr$	Product	Yield [%][b]
1	**2a**		91 (X = Ts)
2			99 (X = Ms)
3			95 (X = Ts)[c]
4	**2b**		98 (X = Ts)
5			90 (X = Ms)
6	**2c**		92 (X = Ts)[d]
7			90 (X = Ms)[d]
8	**2d**		92 (X = Ts)[d]
9			75 (X = Ms)[d]
10	**2e**		90 (X = Ts)[d]
11			91 (X = Ms)[d]
12	**2f**		97 (X = Ts)
13			81 (X = Ms)
14	**2g**		91 (X = Ts)[e]
15			81 (X = Ms)[e]

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[a] *Reaction conditions:* 1-naphthyl tosylate (**1a**) or mesylate (**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.

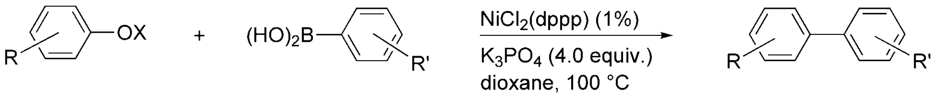
[c] $NiCl_2$ with 99.999% purity was used.

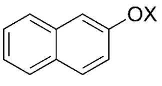
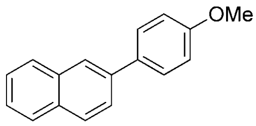
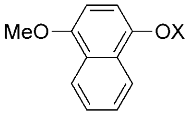
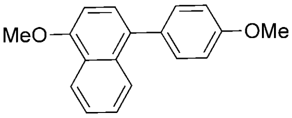
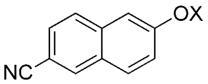
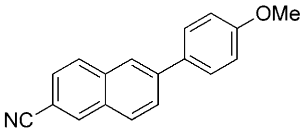
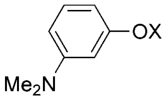
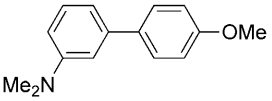
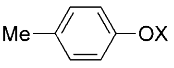
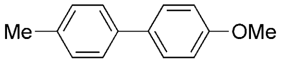
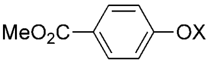
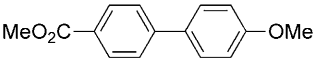
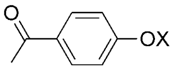
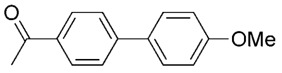
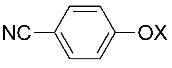
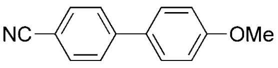
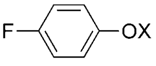
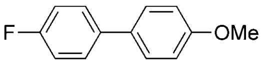
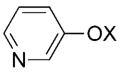
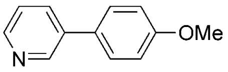
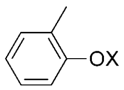
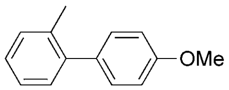
[d] Yield was determined by ^1H NMR spectroscopy due to the contamination of a small amount of hard-to-separate by-product derived from homo-coupling of boronic acids.

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

sterically hindered aryl sulfonates was somewhat challenging, affording the corresponding cross-coupled product in moderate yields (entries 21 and 22). These results indicate that the steric hindrance on the aryl sulfonates exhibits a greater effect on the coupling efficiency than that on the boronic acids as shown by a comparison of the results in entries 8 and 9 in Table 1 with entries 21 and 22 in Table 2.

Table 2. Suzuki–Miyaura Cross-coupling of various aryl tosylates and mesylates with boronic acids.[a]

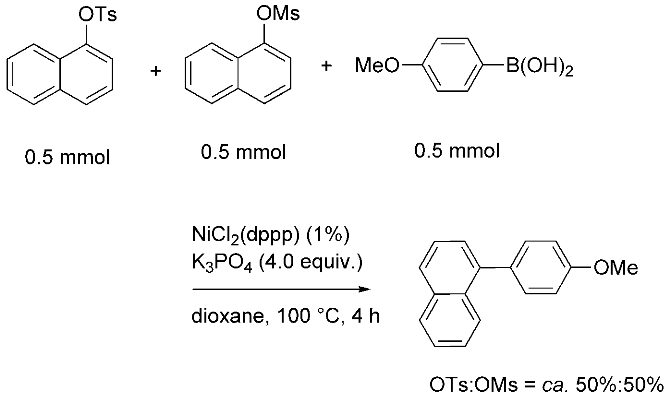


Entry	ArOX	(HO)$_2$BAr	Product	Yield [%][b]
1 2		**2a**		97 (X = Ts) 98 (X = Ms)
3 4		**2a**		73 (X = Ts) 78 (X = Ms)
5 6		**2a**		95 (X = Ts) 90 (X = Ms)
7 8		**2a**		57 (X = Ts) 80 (X = Ms)
9 10		**2a**		88 (X = Ts) 73 (X = Ms)
11 12		**2a**		73 (X = Ts) 88 (X = Ms)
13 14		**2a**		94 (X = Ts) 91 (X = Ms)
15 16		**2a**		97 (X = Ts) 83 (X = Ms)
17 18		**2a**		87 (X = Ts) 88 (X = Ms)
19 20		**2a**		98 (X = Ts) 96 (X = Ms)
21 22		**2a**		53 (X = Ts) 56 (X = Ms)

[a] *Reaction conditions:* aryl tosylate or mesylate (1.0 mmol), boronic acid (2.0 mmol), $NiCl_2$(dppp) (1.0 mol%), K_3PO_4 (4.0 equiv.), dioxane (4 mL), 100–110 °C, 2–20 h.

[b] Isolated yield.

Thus, we have evidence that $NiCl_2$(dppp) is a highly active catalyst for the Suzuki–Miyaura cross-coupling of aryl tosylates and mesylates although the reaction mechanism deserves further clarification. Interestingly, recent studies showed that, being a supporting ligand, the electron-deficient bidentate phosphines such as dppp, dppe, and dppf were inefficient in <br/ Ni(cod)$_2$- and Ni(PCy$_3$)$_2$Cl$_2$-catalyzed Suzuki–Miyaura couplings of aryl tosylates[6c] and esters.[14a] Furthermore, as an added highlight of our catalyst over the reported ones, we should mention that, in addition to the high chemoselectivity for the NH_2-substituted boronic acid (*vide supra*), the new catalyst also exhibits a better functional group compatibility. For instance, the $NiCl_2$(dppp)-catalyzed coupling of CN-substituted aryl tosylates and mesylates could be converted to the



Scheme 1. Competition reaction of 1-naphthyl tosylate *vs.* mesylate.

corresponding CN-substituted biaryls in excellent yields (Table 2, entries 5, 6, 15, and 16). In contrast, as the available examples from literatures, efforts at realizing the similar cross-coupling catalyzed by the $NiCl_2(PCy_3)_2$-PCy_3·HBF_4 system[15b] or by Ni-NHC[6g] afforded only low to moderate yields due to the competing coupling of cyano group with boronic acid, or the low catalytic efficiency.

Finally, to evaluate the reactivity between aryl tosylates and mesylates in $NiCl_2$(dppp)-catalyzed Suzuki–Miyaura reactions, a competition experiment was performed by employing a 1:1:1 molar equivalent of 1-naphthyl tosylate and mesylate, and 4-methoxylphenyl boronic acid (Scheme 1). The results showed that the reactivity between 1-naphthyl tosylate and mesylate was almost identical with approximately 50% *vs.* 50% of the coupled product (as deduced from the recovered starting materials) was formed from 1-naphthyl tosylate and mesylate, respectively.

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 the inherently less reactive aryl tosylates and mesylates. This protocol offers several advantages over the available methods in terms of: (i) the highly catalytic efficacy that allows the coupling reaction to proceed efficiently with only 1.0 mol% catalyst loading as well as in the absence of extra supporting ligand; (ii) the general applicability and good functional group tolerance both for a rich range of aryl sulfonates and boronic acids; (iii) the low cost either compared with the frequently used palladium catalysts attributed to the non-noble metal nature of nickel, or in comparison with the several available nickel catalysts (*vide supra*) due to the significantly lowered catalyst loading, the use of more affordable dppp ligand, and the absence of extra supporting ligands; (iv) the markedly enhanced stability toward air and moisture due to the high stability of the dppp ligand. Thus, we believe that the $NiCl_2$(dppp) catalyst presented in this work is one of the most practical catalysts among a myriad of Suzuki–Muyaura catalysts developed so far. Consequently, this catalyst paired with the use of aryl sulfonates as substrates, which are generally more affordable than aryl halides, would provide a great advance in the transition metal-catalyzed Suzuki–Miyaura cross-coupling toward industrial applications. Furthermore, the high activity of $NiCl_2$ (dppp) as evidenced by the Suzuki–Miyaura reaction suggested that this catalyst is also possibly a suitable catalyst for other couplings such as Heck and Stille reactions. Studies on these reactions along with the large-scale application of $NiCl_2$(dppp) in Suzuki–Miyaura coupling are currently underway in our laboratory.

Experimental Section

General Procedure for Suzuki–Miyaura Cross-Coupling Reactions of Aryl Sulfonates with Arylboronic Acids

To a 25-mL Schlenk tube equipped with a magnetic bar were added $NiCl_2$(dppp) (0.01 mmol, 5.4 mg), aryl sulfonate (1.0 mmol), aryboronic acid (2.0 mmol), and anhydrous K_3PO_4 (4.0 mmol). The tube was then evacuated (3 × 10 min) under vacuum and backfilled with N_2. Dried dioxane (4.0 mL) was injected *via* syringe, and the reaction mixture was stirred at 100–110 °C until the aryl sulfonates had disappeared as monitored by TLC. The reaction mixture was then poured into water (30 mL) and 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.

Acknowledgements

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