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Nickel-Mediated *N*-Arylation with Arylboronic Acids: An Avenue to Chan–Lam Coupling

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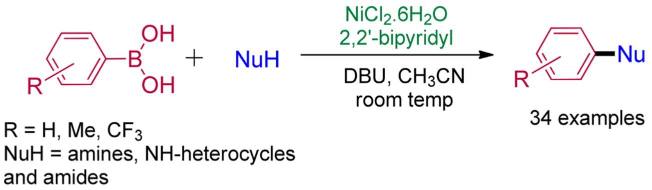
ABSTRACT



An efficient use of $NiCl_2 \cdot 6H_2O$, for the cross-coupling of arylboronic acids with various *N*-nucleophiles, has been demonstrated. The method is practical and offers an alternative to the corresponding Cu-mediated Chan–Lam process for the construction of the C–N bond.

Transition-metal-catalyzed carbon-heteroatom cross-coupling reactions have made a great contribution to the recent growth of organic synthesis. A great diversity of carbon–nitrogen bonds can now be easily generated by transition-metal-catalyzed protocols that find wide applications in the synthesis of substances such as natural products, agrochemicals, materials, dyes, and pharmaceuticals.[1] The Pd and Cu catalyzed coupling of electrophilic aryl halides and nucleophilic primary or secondary amines, pioneered by Buchwald, Hartwig, and others, is a hallmark reaction in this field.[2–6] In 1998, the groups of Chan, Evans, and Lam independently developed Cu-mediated oxidative amination of arylboronic acids with amines and other nucleophiles,[7–9] providing a valuable alternative to traditional cross-couplings in the construction of carbon–heteroatom bonds. Many extensions and applications of this new method have been reported, including the catalytic version of the reaction,[10] arylation of amines under base and ligand-free conditions,[11] tandem cross-coupling reactions,[12] and solid-phase chemistry.[13] The reaction has been applied to a variety of substrates for carbon–heteroatom bond formation, but in almost all cases, copper salts are the only choice to promote the reaction and have been repeatedly

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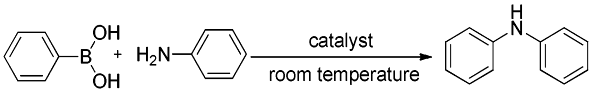
used in combination with different ligands, bases, and solvents.[1m,14] To the best of our knowledge, no other metal is described in the literature to bring about the Chan–Lam reaction except for an unpublished report using stoichiometric amount of gold(III) acetate to afford merely a 26% product yield.[1m] Therefore, it is a highly exigent and preferred endeavor to find a readily available, inexpensive, and efficient alternative transition metal catalyst for the C–N cross-coupling of boronic acids.

Nickel-based catalysts are well-recognized in C–C bond-forming reactions and have also been expanded for C–N bond creation by means of halide amination.[15–20] It was therefore imperative to exploit the catalytic potential of nickel along with other unexplored metals for Chan–Lam type *N*-arylation using arylboronic acid and *N*-nucleophiles as coupling partners. As a part of our ongoing program to develop viable and efficient synthetic protocols,[21] we disclose herein our results on the Ni-catalyzed *N*-arylation using the reaction of arylboronic acids with amines, amides, and *N*-heterocycles under atmospheric conditions.

To explore a new catalytic system for Chan–Lam C–N cross-coupling, a model reaction using easily accessible phenylboronic acid and aniline was investigated in detail by varying different parameters such as catalyst, ligand, base, and solvent to develop appropriate reaction conditions for this transformation (Table 1). At the outset, different transition metal catalysts, viz. $FeCl_3$, $CoCl_2$, $CdCl_2$, $RuCl_3 \cdot xH_2O$, and $Ni(NO_3)_2 \cdot 6H_2O$, were screened using 2,2′-bipyridyl as ligand and DBU as a base in acetonitrile to determine their catalytic efficacy (Table 1, entries 1–5). We were astonished to see that only the nickel salt could bring about the desired conversion (entry 5), and therefore the studies were directed to look at the prospective of other nickel salts too. All the nickel salts tried, viz. $Ni(NO_3)_2 \cdot 6H_2O$, $NiSO_4$, $Ni(OAc)_2 \cdot 4H_2O$, $NiCl_2$, and $NiCl_2 \cdot 6H_2O$, invariably worked well (entries 5–9), but the performance of $NiCl_2 \cdot 6H_2O$ was maximum, providing the *N*-aryl product **3a** in 78% yield at rt (entry 9). As evident, the yield of **3a** was not enhanced at all when anhydrous $NiCl_2$ was used (entry 8). The experiment under identical conditions without the aid of a nickel salt ended with no conversion (entry 10). To exclude the role of a Cu contaminant in the present reaction, some control experiments for the model reaction were carefully investigated using 1, 5, and 10 ppm of $Cu(OAc)_2$ (entry 11) leading to no reaction at all, which conclusively discards any possible role of Cu contaminant catalysis under the

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield[b] (%)
1	$FeCl_3$	DBU	CH_3CN	nr[c]
2	$CoCl_2$	DBU	CH_3CN	nr
3	$CdCl_2$	DBU	CH_3CN	nr
4	$RuCl_3 \cdot xH_2O$	DBU	CH_3CN	nr
5	$Ni(NO_3)_2 \cdot 6H_2O$	DBU	CH_3CN	60
6	$NiSO_4$	DBU	CH_3CN	65
7	$Ni(OAc)_2 \cdot 4H_2O$	DBU	CH_3CN	68
8	$NiCl_2$	DBU	CH_3CN	77
9	**$NiCl_2 \cdot 6H_2O$**	**DBU**	**CH_3CN**	**78 (76)**[d]
10	–	DBU	CH_3CN	nr
11[e]	$Cu(OAc)_2$	DBU	CH_3CN	nr
12	$NiCl_2 \cdot H_2O$	DBU	CH_3CN	65[f]
13	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	70[g]
14	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	14[h]
15	$NiCl_2 \cdot 6H_2O$	Et_3N	CH_3CN	nr
16	$NiCl_2 \cdot 6H_2O$	KOH	CH_3CN	44
17	$NiCl_2 \cdot 6H_2O$	*t*-BuOK	CH_3CN	48
18	$NiCl_2 \cdot 6H_2O$	K_3PO_4	CH_3CN	52
19	$NiCl_2 \cdot 6H_2O$	–	CH_3CN	nr
20	$NiCl_2 \cdot 6H_2O$	DBU	DMSO	45
21	$NiCl_2 \cdot 6H_2O$	DBU	CH_2Cl_2	48
22	$NiCl_2 \cdot 6H_2O$	DBU	CH_3OH	nr
23	$NiCl_2 \cdot 6H_2O$	DBU	–	40
24	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	77[i]
25	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	78[j]
26	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	60[k]
27	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	42[l]
28	$NiCl_2 \cdot 6H_2O$	DBU	CH_3CN	58[m]

[a] Reaction conditions: Phenylboronic acid (1 mmol), aniline (2 mmol), catalyst (20 mol %), 2,2′-bipyridyl as ligand (20 mol %), base (2 equiv) at rt for 20 h. [b] Isolated yield based on arylboronic acid. [c] No reaction. [d] Reaction performed at 60 °C. [e] Reaction using 1, 5, and 10 ppm $Cu(OAc)_2$. [f] 1,10-Phenanthroline as ligand. [g] Tetramethylethylenediamine as ligand. [h] Reaction performed without ligand. [i] 20 mol % of $NiCl_2 \cdot 6H_2O$, 40 mol % of 2,2′-bipyridyl were used. [j] 25 mol % of $NiCl_2 \cdot 6H_2O$, 25 mol % of 2,2′-bipyridyl were used. [k] 10 mol % of $NiCl_2 \cdot 6H_2O$, 10 mol % of 2,2′-bipyridyl were used. [l] 1.0 equiv of aniline was used. [m] 1.5 equiv of aniline was used.

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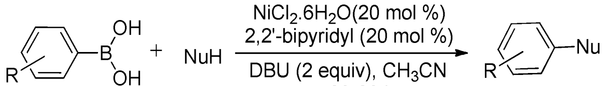
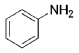
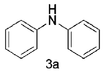
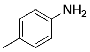
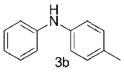
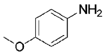
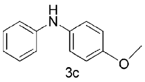
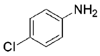
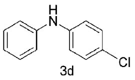
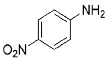
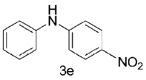
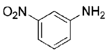
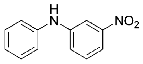
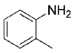
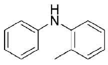
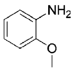
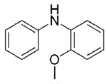
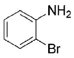
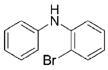
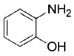
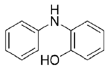
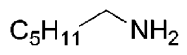
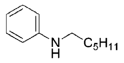
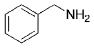
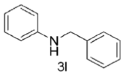
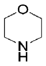
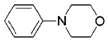
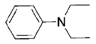
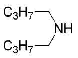
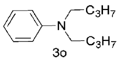
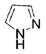
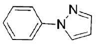
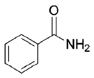
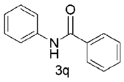
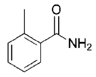
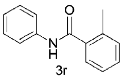
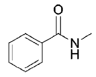
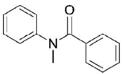
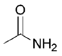
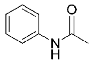
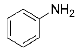
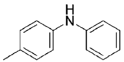
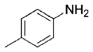
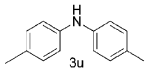
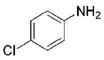
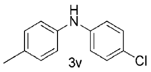
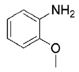
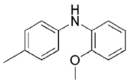
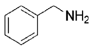
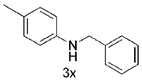
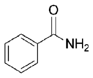
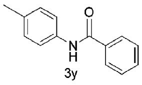
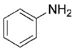
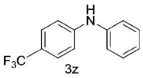
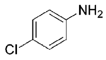
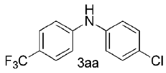
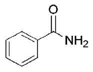
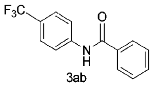
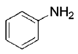
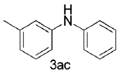
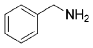
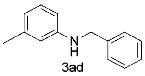
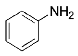
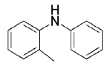
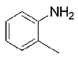
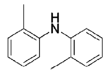
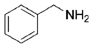
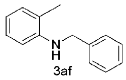
Table 2. Coupling of Arylboronic Acid with a Range of *N*-Nucleophiles[a]



1 2 3

entry	R	2	product 3	yield[b] (%)
1.	H		 3a	78
2.	H		 3b	82
3.	H		 3c	80
4.	H		 3d	75
5.	H		 3e	65[c]
6.	H		 3f	62[c]
7.	H		 3g	68
8.	H		 3h	70
9.	H		 3i	62
10.	H		 3j	70
11.	H		 3k	78
12.	H		 3l	85 (70)[d]
13.	H		 3m	68
14.	H		 3n	Trace
15.	H		 3o	nr[e]
16.	H		 3p	60[c]
17.	H		 3q	74

entry	R	2	product 3	yield[b] (%)
18.	H		 3r	55[c]
19.	H		 3s	nr[e]
20.	H		 3t	76
21.	4- Me		 3b	78
22.	4- Me		 3u	75
23.	4- Me		 3v	80
24.	4- Me		 3w	73
25.	4- Mc		 3x	83
26.	4- Me		 3y	72
27.	4- CF3		 3z	70
28.	4- CF3		 3aa	74
29.	4- CF3		 3ab	64[c]
30.	3- Me		 3ac	68
31.	3- Me		 3ad	65
32.	2- Me		 3h	60[c]
33.	2- Me		 3ae	50[c]
34.	2- Mc		 3af	54[c]

[a] Reaction conditions: Arylboronic acid (1 mmol), *N*-nucleophile (2 mmol), $NiCl_2 \cdot 6H_2O$ (20 mol %), 2,2′-bipyridyl (20 mol %), CH_3CN (1 mL), rt, 20 h. [b] Isolated yield based on arylboronic acid. [c] Reaction carried out at 60 °C for 28 h. [d] Phenylboronic acid (20 mmol), benzylamine (40 mmol), $NiCl_2 \cdot 6H_2O$ (20 mol %), 2,2′-bipyridyl (20 mol %), CH_3CN (20 mL). [e] No reaction.

investigated reaction conditions. The outcome approves the sole contribution of $NiCl_2 \cdot 6H_2O$ as a catalyst in the present study.

Subsequent investigation on the role of ligands for the aforementioned reaction revealed 2,2′-bipyridyl as the most favored one to push the reaction forward (entries 9, 12, and 13). In the absence of a ligand under the same set of conditions, considerably lower conversion was observed (entry 14). As the nature of the base is assumed to have a marked impact on the overall process, different bases such as Et_3N, KOH, *t*-BuOK, K_3PO_4, and DBU were also examined. Whereas triethylamine did not afford any product (entry 15), the other bases, *viz.* KOH, *t*-BuOK, and K_3PO_4, gave rise to 44%, 48%, and 52% product yields respectively (entries 16–18). The use of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) in acetonitrile enhanced the product yield significantly (78%, entry 9), which may be attributed to the very strong basicity of DBU in acetonitrile (pK_a 24.33).[22] For maximum conversion, 2 equiv of the base were needed, and no reaction was observed in the absence of base (entry 19). To advance the process further, the optimized catalytic reaction was also probed in different solvents, such as DMSO, dichloromethane, and methanol at rt, in addition to acetonitrile, which categorically approved acetonitrile as the most appropriate choice (entries 9, 20–22). The absence of the solvent diminished the product yield considerably (entry 23). In another endeavor, a 20 mol % catalyst loading with a 1:1 molar ratio of metal to ligand was found to be optimal, and no improvement was noticed on raising the ratio from 1:1 to 1:2 (entries 9, 24–26). When the reaction temperature was elevated to 60 °C (entry 9), no remarkable change was observed in the product yield. Regarding the reactant ratio, 2 equiv of aniline were needed and found sufficient to gain the utmost conversion (entry 9); a lower reactant ratio decreased the product yield (entries 27, 28).

With the stipulated conditions in hand, the scope of this method was extended to the reaction of a wide range of diverse N–H substrates including *o*/*m*/*p* substituted arylamines, alkylamines, amides, and *N*-heterocycles with different boronic acids, *viz.* phenylboronic acid, *o*/*m*/*p*-tolylboronic acids, and 4-(trifluoromethyl)boronic acid (Table 2). The findings reveal that all sorts of aromatic amines undergo reaction smoothly, although the anilines containing a nitro group required a higher temperature and longer reaction time (Table 2, entries 1–10). Aliphatic amines also work well (entries 11–13), though diethylamine and dibutylamine were surprisingly reluctant (entries 14, 15). Pyrazole was found to couple sluggishly to a small extent even at higher temperature (entry 16). To our delight, poorly nucleophilic amides also underwent this C–N cross-coupling reaction proficiently (entries 17, 18), albeit *N*-methylbenzamide showed no reactivity (entry 19). The versatility of the reaction was further demonstrated for the coupling of different amines and benzamide with *o*/*m*/*p*-tolylboronic acids and 4-(trifluoromethyl)boronic acid (entries 21–34); nonetheless, the reaction of benzamide with 4-(trifluoromethyl)boronic acid and that of *o*-tolylboronic acid with amines necessitated a longer reaction time and higher temperature (entries 29, 32–34).

More importantly, a scale-up experiment for the coupling of phenylboronic acid with benzylamine on a 20 mmol (gram) scale was carried out to show the practicability of the method, which gave rise to a 70% isolated product yield (Table 2, entry 12), exhibiting this protocol to be appropriate for industrial applications.

In conclusion, nickel-catalyzed C–N bond formation has been developed employing a range of *N*-nucleophiles and arylboronic acids. The protocol embodies the first time use of Ni salts, is efficient and versatile, and renders a new way of Chan–Lam coupling. Further assessment regarding the scope and limitations of the reaction is currently underway.

Acknowledgment. We are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for financial assistance.

Supporting Information Available. Detailed experimental procedure and spectral data of all the products along with copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] Ishikawa, T. *Superbases for Organic Synthesis*; John Wiley & Sons: Chichester, U.K., 2009.