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N-(Pyridin-2-yl)benzamide: efficient ligand for the nickel catalyzed Chan–Lam cross-coupling reaction

Srinivas Keesara

School of Chemistry, University of Hyderabad, Hyderabad 500046, India

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An efficient protocol for the Chan–Lam cross-coupling reactions of arylboronic acids with aryl or alkyl amines has been developed by employing simple *N*-(pyridin-2-yl)benzamide ligand with Ni(OAc)$_2$·4H$_2$O in the presence of TMG base. The reaction proceeded well with high yields by employing various *N*-nucleophiles at low catalytic loadings.

Introduction

The discovery of the transition-metal-catalyzed Chan–Lam cross-coupling reaction has taken innovative progress in synthetic organic chemistry by providing highly applicable C–N bond formations via the coupling of arylboronic acids with *N*-nucleophiles.[1] *N*-Aryl scaffold involving C–N bond forming reactions are of high synthetic significance for various natural products, agrochemicals, and pharmaceutical materials.[2] Ullmann coupling was the traditional method for the C–N bond forming reactions between *N*-nucleophiles and aryl halides using stoichiometric amounts of Cu salts at higher temperatures.[3] Stille, Hartwig, and Buchwald reported the C–N coupling of aryl halides and nucleophilic primary/secondary amines by using Pd catalysts.[4] Significant progress has been achieved in the past decade in the copper and palladium catalyzed C–N bond forming reactions. The high cost of palladium catalysts restricts their usage in industrial applications. Some of the reported methods employed stoichiometric amounts of Cu for different active aryl donor reagents like aryl silanes,[5] aryl stannanes,[6] aryl bismuth,[7] and aryl lead triacetates.[8]

In 1998, Chan and Lam reported the preparation of *N*-arylimines from arylboronic acids using Cu catalysts under mild reaction conditions providing a valuable alternative to traditional cross-couplings in the construction of C–N bonds.[9] The use of low toxic arylboronic acids has found wide applications in modern organic synthesis.[10] No other transition metal catalysts are as popular as copper catalysts for Chan–Lam coupling reactions. We found some reports with mixed transition metal catalysts. Sawant and co-workers described Cu–Mn bimetallic catalyst for *N*-arylated amine synthesis from arylboronic acids and amines.[11] Nasrollahzadeh and co-workers reported copper and ligand free catalyst Fe@Pd nanowires for the Chan–Lam coupling reaction.[12] They used 3.0 mol % of the expensive Pd catalyst for efficient coupling of aryl boronic acids with aryl amine. Until recently, nickel-based catalysts were successfully applied to the above coupling reactions, which are equal to copper catalysts in their catalytic activity. Singh and co-workers developed the first Ni catalyst for the Chan–Lam coupling reaction of arylboronic acids with *N*-nucleophiles using bipyridyl ligand and DBU base.[13] Singh and co-workers reported the C–N coupling reaction with Ni(II) complexes of bis-(2-acetylthiophene)oxaloyldihydrazone.[14] Shi and co-workers reported the arylation of amines by Ni(II)-thiolate complexes.[15] All the reported methods used 15–20 mol % of Ni catalyst for biarylamine synthesis. Few reports on the above named reaction offer a wide scope for researchers to improve the efficiency of the Ni catalyst. Therefore, it is essential to develop more simple and efficient Ni catalytic systems for Chan–Lam cross coupling reaction. Herein, we report *N*-(pyridin-2-yl)benzamide as efficient ligand for the Ni-catalyzed Chan–Lam cross-coupling reaction of amines with arylboronic acids.

To develop an efficient Ni catalytic system for Chan–Lam coupling reaction, initially we studied the different Ni(II)-salts with *N*-(pyridin-2-yl)benzamide ligand (**1a**) using TMG (1,1,3,3-tetramethylguanidine) as base in toluene at 60 °C. For this purpose, we

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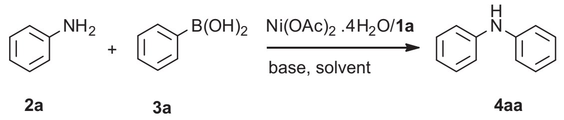
0040-4039/

Table 1
Optimization of the N-arylation reaction of phenylboronic acid with aniline[a]



Entry	Ni(II) salt/**1a**	Base	Solvent	Yield[b] (%)
1	$NiCl_2{\cdot}6H_2O$/**1a**	TMG	Toluene	5
2	$Ni(NO_3)_2{\cdot}6H_2O$/**1a**	TMG	Toluene	40
3	$NiSO_4{\cdot}7H_2O$/**1a**	TMG	Toluene	10
4	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	Toluene	84
5	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	K_3PO_4	Toluene	Nr
6	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	K_2CO_3	Toluene	Nr
7	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	$LiOH{\cdot}H_2O$	Toluene	Nr
8	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	Dabco	Toluene	Nr
9	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	Et_3N	Toluene	Nr
10	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	–	Toluene	Nr
11	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	CH_3CN	73
12	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	Dioxane	31
13	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	Methanol	Nr
14	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	Water	Nr
15	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	DMSO	Nr
16	$Ni(OAc)_2{\cdot}4H_2O$/**1a**	TMG	–	22

[a] Reaction conditions: Phenylboronic acid (1 mmol), aniline (2 mmol), nickel(II) salt (10 mol %), ligand **1a** (20 mol %), base (2 mmol), solvent (1 mL) at 60 °C for 24 h.
[b] Isolated yield based on arylboronic acid. Nr = no reaction.

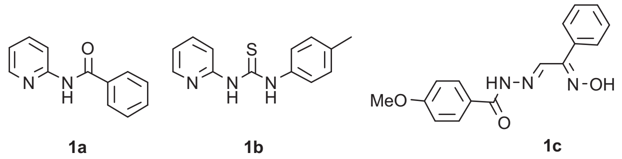


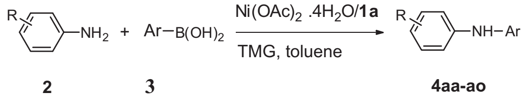
Figure 1. Structures of the designed amine ligands.

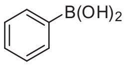
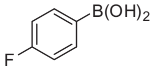
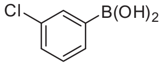
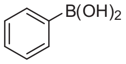
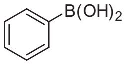
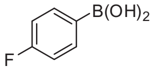
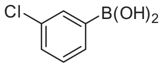
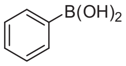
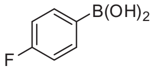
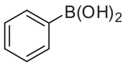
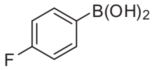
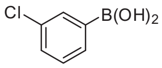
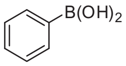
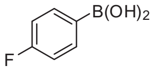
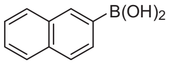
Table 2
$Ni(OAc)_2{\cdot}4H_2O$ /ligand catalyzed N-arylation reaction of phenylboronic acid with aniline[a]

Entry	Ni(II) salt (mol %)	Ligand (mol %)	Time (h)	Temp (°C)	Yield[b] (%)
1	10	**1a** (20)	24	60	84
2	10	**1b** (20)	24	60	40
3	10	**1c** (20)	48	60	25
4	5	**1a** (10)	24	60	52
5	10	**1a** (20)	15	80	86
6	10	**1a** (20)	24	28	Nr
7	10	**1a** (20)	24	60	44[c]
8	10	**1a** (20)	24	60	80[d]

[a] Reaction conditions: Phenylboronic acid (1 mmol), aniline (2 mmol), catalyst ($Ni(OAc)_2$. $4H_2O$/L 1:2), TMG (2 mmol), toluene (1 mL).
[b] Isolated yield based on arylboronic acid.
[c] Reaction with 1 equiv of aniline.
[d] Reaction under nitrogen atmosphere.

Table 3
Coupling reactions of arylboronic acids with a variety of *N*-nucleophiles[a]



Entry	R	Ar	Product	Yield[b] (%)
1	H		**4aa**	84
2	H		**4ab**	80
3	H		**4ac**	74
4	4-OMe		**4ad**	72
5	3-Me		**4ae**	78
6	3-Me		**4af**	75
7	3-Me		**4ag**	70
8	2-Me		**4ah**	76
9	2-Me		**4ai**	72
10	2-Ac		**4aj**	71
11	2-Ac		**4ak**	72
12	2-Ac		**4al**	68
13	2-Br		**4am**	74[c]
14	2-Br		**4an**	70[c]
15	H		**4ao**	80

[a] Reaction conditions: arylboronic acid (1 mmol), *N*-nucleophile (2 mmol), catalyst 10 mol % ($Ni(OAc)_2{\cdot}4H_2O$/1a 1:2), TMG (2 mmol), toluene (1 mL) at 60 °C for 24 h.
[b] Isolated yield based on arylboronic acid.
[c] Reaction time 30 h.

chose phenylboronic acid and aniline as model substrates for the above coupling reaction and the results are summarized in Table 1. All the reactions were conducted with 10 mol % of Ni(II) salts and 20 mol % of ligand **1a**. To find out a best combination, we have screened various Ni(II) salts ($NiCl_2{\cdot}6H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $NiSO_4{\cdot}7H_2O$ and $Ni(OAc)_2{\cdot}4H_2O$) with ligand **1a**. Among these Ni(II) salts, $Ni(OAc)_2{\cdot}4H_2O$ was found to be most suitable for the combination of ligand **1a** with desired product yield of 84% (entry 4). We also screened the coupling reaction with a variety of inorganic and organic bases (entries 5–9). The organic non nucleophilic base TMG was found to be the best for our reaction conditions. We observed from the above results that the TMG base has much affect on the coupling. In contrast to other bases, the high p*K*a value and strong basic nature of TMG might be the responsible factor for efficient coupling.[16] However, no reaction occurred in the absence of base (entry 10). This clearly shows that the base plays a major role in the coupling reaction. Next, we focused on the role of solvent for this coupling reaction. It was observed that, among the various solvents screened, only toluene, acetonitrile, and dioxane promoted the coupling reaction (entries 4, 11, and 12). Poor or no coupling product formation was observed in the presence of polar protic solvents (like methanol, water) and DMSO (entries 13–15). Low yields were observed, in the absence of solvent (entry 16). Thus toluene found to be the best solvent to promote the coupling reaction.

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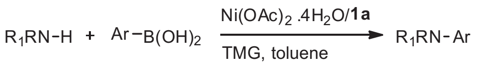
Further, we studied the catalytic activity of $Ni(OAc)_2{\cdot}4H_2O$ with different types of ligands (**1a**–**1c**)[17–19] (Fig. 1) for the Chan–Lam coupling reaction between phenylboronic acid and aniline using the above optimized conditions (Table 2). Among the screened ligands, **1a** resulted in high yield of the Chan–Lam coupling product (entry 1). In the case of ligands **1b** and **1c** low yields were observed even after longer reaction times (entries 2 and 3). The reaction proceeds smoothly at 60 °C temperature, subsequently we calculated the catalytic performance comparatively at low and high temperatures. The isolated yield of the coupled product was 86% at 80 °C temperature (entry 5). No coupling product was observed at room temperature conditions (entry 6). We found that 10 mol % of $Ni(OAc)_2{\cdot}4H_2O$ and 20 mol % of ligand **1a** was sufficient for the formation of diphenylamine product in high yield using TMG base with toluene solvent at 60 °C.

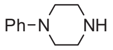
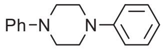
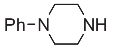
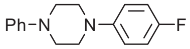
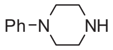
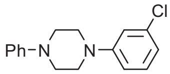
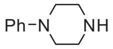
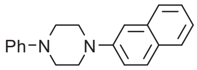
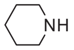
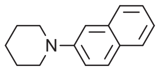
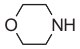
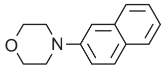
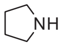
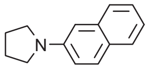
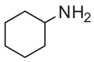
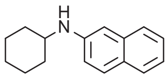
The scope and feasibility of the above-mentioned optimized reaction conditions applied to substituted anilines with different arylboronic acids.[20] The results are listed in Table 3. It is interesting to observe that the reactions of *para* and *meta* substituted arylboronic acid derivatives were easily performed with aniline and produced the corresponding *N*-arylated products **4ab** and **4ac** in 74–80% yields (entries 2 and 3). The reaction of *p*-anisidine with phenylboronic acid afforded the corresponding coupled product **4ad** in moderate yield (entry 4). The coupled products of *meta* substituted aniline **4ae**–**4ag** were obtained in good yields (entries 5–7). The reaction of *o*-toluidine and 2-aminoacetophenone was not influenced by the steric hindrance (entries 8–12). 2-bromoaniline easily converted to 2-bromo-*N*-arylaniline (**4am**–**4an**) in 70–74% yield irrespective of the *ortho* bromide effect (entries 13 and 14). However the coupling reaction of 2-naphthylboronic acid with aniline proceeded well with moderate yields of the corresponding products (entry 15).

Table 4

Coupling reactions of 2-naphthylboronic acid with various *N*-nucleophiles[a]



2 **3** **4ap-aw**

Entry	R_1RNH	Product	Yield[b] (%)
1		 **4ap**	82
2		 **4aq**	80
3		 **4ar**	78
4		 **4as**	74
5		 **4at**	66[c]
6		 **4au**	62[c]
7		 **4av**	56[c]
8		 **4aw**	70

[a] Reaction conditions: 2-naphthylboronic acid (1 mmol), *N*-nucleophile (2 mmol), catalyst 10 mol % ($Ni(OAc)_2{\cdot}4H_2O$/**1a** 1:2), TMG (2 mmol), toluene (1 mL) at 60 °C for 24 h.

[b] Isolated yield based on 2-naphthylboronic acid.

[c] Reaction time 30 h.

Further, we extended this optimized conditions to the coupling reaction of arylboronic acids with a variety of cyclic secondary amine derivatives (Table 4).[20] *N*-Phenylpiperazine was effectively converted to the coupled product in high yields (74–82%) with various boronic acids (entries 1–4), whereas the coupling reactions of piperidine, morpholine, and pyrrolidine derivatives with 2-naphthylboronic acid requires a longer reaction time to complete the reaction and produced the corresponding products in moderate yields (entries 5–7). Furthermore, cyclohexylamine produced the corresponding product in 70% yield with 2-naphthylboronic acid (entry 8).

Upto to now, the mechanism of the Ni catalyzed Chan–Lam coupling was not proposed. According to our study, there is not much change observed in product formation when the reaction is conducted either in the presence of air (Tables 1–4) or nitrogen atmosphere (Table 2, entry 9). This indicates an oxidative process was not involved in the formation of the product.[12] The possible resonance of TMG base in reaction between imine nitrogen and other two nitrogen atoms at 1, 3 positions may well affect the boron group of phenylboronic acid for efficient coupling with *N*-nucleophile.[21,22] No coupling product was observed with saturated amine bases (Et_3N and DABCO Table 1 entries 8 and 9). Experiments related to this coupling are under progress in our laboratory.

Conclusions

In summary, we have developed a new synthetic method for nickel-catalyzed Chan–Lam cross-coupling reactions of various amines and arylboronic acids. This method shows broad substrate scope and produces all the corresponding coupling products in moderate to good yields with low catalytic loadings. Further investigation into the use of other amine sources for above coupling reaction is currently ongoing in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.047.

References and notes

1. (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449; (b) Rao, K. S.; Wu, T. S. *Tetrahedron* **2012**, *68*, 7735–7754.
2. (a) Narasimhan, B.; Sharma, D.; Kumar, P. *Med. Chem. Res.* **2011**, *20*, 1119–1140; (b) Chegaev, K.; Lazzarato, L.; Tosco, P.; Cena, C.; Marini, E.; Rolando, B.; Carrupt, P. A.; Fruttero, R.; Gasco, A. *J. Med. Chem.* **2007**, *50*, 1449–1457; (c) Alvarado, P. L.; Avandano, C.; Menendez, J. C. *J. Org. Chem.* **1996**, *61*, 5865–5870; (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626; (e) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209; (f) Chen, T.; Luo, Y.; Hu, Y.; Yang, B.; Lu, W. *Eur. J. Med. Chem.* **2013**, *64*, 613–620.
3. Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211–2212.

4. (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771–1780; (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970; (c) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902.
5. Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; Deshong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600–7601.
6. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674–676.
7. Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137–4144.
8. Alvarado, P. L.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678–5682.
9. (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936; (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
10. (a)*Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; (b) Moon, S. Y.; Nam, J.; Rathwell, K.; Kim, W. S. *Org. Lett.* **2014**, *16*, 338–341; (c) Moon, S. Y.; Kim, U. B.; Sung, D. B.; Kim, W. S. *J. Org. Chem.* **2015**, *80*, 1856–1865; (d) DalZotto, C.; Michaux, J.; Lurin, E. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 3811–3814; (e) Zhang, J. Q.; Huang, G. B.; Weng, J.; Lu, G.; Chan, A. S. C. *Org. Biomol. Chem.* **2015**, *13*, 2055–2063.
11. Nasrollahzadeh, M.; Azarian, A.; Ehsani, A.; Zahraei, A. *Tetrahedron Lett.* **2014**, *55*, 2813–2817.
12. Sawant, S. D.; Srinivas, M.; Kumar, K. A. A.; Reddy, G. L.; Singh, P. P.; Singh, B.; Sharma, A. K.; Sharma, P. R.; Vishw-akarma, R. A. *Tetrahedron Lett.* **2013**, *54*, 5351–5354.
13. Raghuvanshi, D. S.; Gupta, A. K.; Singh, K. N. *Org. Lett.* **2012**, *14*, 4326–4329.
14. Singh, D. P.; Raghuvanshi, D. S.; Singh, K. N.; Singh, V. P. *J. Mol. Catal. A: Chem.* **2013**, *379*, 21–29.
15. Shi, J.; Li, F. L.; Li, H. X.; Wang, F.; Yua, H.; Ren, Z. G.; Zhang, W. H.; Lang, J. P. *Inorg. Chem. Commun.* **2014**, *46*, 159–162.
16. Satish, R. L.; Bhalchandra, M. B. *Appl. Organometal. Chem.* **2013**, *27*, 729–733.
17. Srinivas, K.; Saiprathima, P.; Balaswamy, K.; Rao, M. M. *J. Organomet. Chem.* **2013**, *741–742*, 162–167.
18. Srinivas, K.; Saiprathima, P.; Rao, M. M. *Tetrahedron Lett.* **2014**, *55*, 6769–6772.
19. (a) Zulfikaroglu, A.; Yuksektepe, C.; Bati, H.; Caliskan, N. *Russ. J. Coord. Chem.* **2010**, *36*, 124–127; (b) Ramazan, G.; Emrah, G. *Spectrochim Acta, Part A* **2006**, *65*, 719–726.
20. *General procedure for Chan–Lam cross-coupling reaction:* The 25 mL RB flask was charged with arylboronic acid (1 mmol), *N*-nucleophile (2 mmol), Ni $(OAc)_2 \cdot 4H_2O$/**1a** (10 mol % of Ni(II) salt and 20 mol % of **1a**), TMG (2 mmol), and toluene (1 ml). The reaction mixture was stirred at 60 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with brine water. The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica gel using hexane to afford the Chan–Lam product in high purity.
21. Niedenzu, K. In *Boron-Nitrogen Chemistry* In *Advances in Chemistry*; Am. Chem. Soc.: Washington, DC, 1964; pp 1–16.
22. Dennis, G. H. *Boronic Acids*, 2nd ed.; Springer, 2011.