

## Accepted Manuscript

Palladium catalyzed addition of arylboronic acid or indole to nitriles: Synthesis of aryl ketones

Tuluma Das, Amarnath Chakraborty, Amitabha Sarkar

PII: S0040-4039(14)01882-6  
DOI: <http://dx.doi.org/10.1016/j.tetlet.2014.11.009>  
Reference: TETL 45393

To appear in: *Tetrahedron Letters*

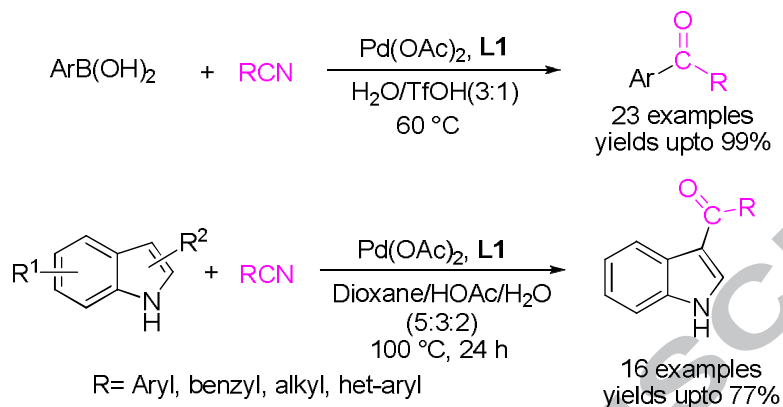
Received Date: 9 October 2014  
Revised Date: 3 November 2014  
Accepted Date: 3 November 2014

Please cite this article as: Das, T., Chakraborty, A., Sarkar, A., Palladium catalyzed addition of arylboronic acid or indole to nitriles: Synthesis of aryl ketones, *Tetrahedron Letters* (2014), doi: <http://dx.doi.org/10.1016/j.tetlet.2014.11.009>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



## Graphical Abstract.



**Palladium catalyzed addition of arylboronic acid or indole to nitriles: Synthesis of aryl ketones**

Tuluma Das, Amarnath Chakraborty, Amitabha Sarkar\*

Department of Organic Chemistry, Indian Association for the Cultivation of Science,

Jadavpur, Kolkata 700032, India

[ocas@iacs.res.in](mailto:ocas@iacs.res.in), Fax: +91 33 2473 2805; Tel: +91 33 2473 4971.

**Abstract.** Aryl ketones can be synthesized conveniently by a palladium catalyzed addition of arylboronic acid to nitriles in aqueous triflic acid. This catalytic system was extended to the addition of unprotected indoles to nitriles under a slightly modified condition to produce 3-acyl indoles in good yield.

*Keywords:* Palladium, Pyrazolylpyridine, Addition reaction, Aryl ketone, 3-Acyl-indole

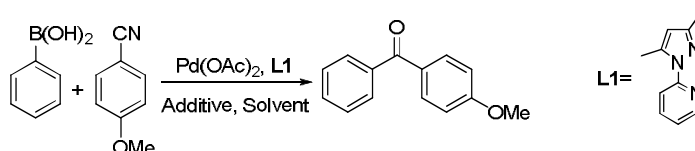
Aryl ketones are important building blocks for bioactive compounds<sup>1</sup> and natural products.<sup>2</sup> Conventional synthetic methods for aryl ketones involve Friedel-Craft acylation,<sup>3</sup> oxidation of secondary alcohols<sup>4</sup> and reaction of nitrile with Grignard<sup>5</sup> or organolithium reagents.<sup>6</sup> Discovery of catalytic transformation, especially transition metal catalyzed C-C bond formation have largely replaced such stoichiometric reactions for the commercial production of important molecules. For instance, transition metal catalyzed addition of aryl boronic acid to nitriles emerged as an improvement over the traditional method of synthesis of aryl ketones because of wider functional group tolerance and ease of handling.<sup>7</sup> In the first example of addition reaction of boronic acid to nitriles Larock utilized a Pd(II) catalyst.<sup>7h</sup> Lu *et al.* later expanded the scope of the reaction.<sup>7f,g</sup> Miura<sup>7e</sup> used sodium tetraphenylboron as

the organoboron reagent and Murakami<sup>7d</sup> described an analogous Rh catalyzed addition reaction of boronic acid to nitriles.

Our ongoing research seeks to explore pyrazole tethered donors as effective ligands<sup>8</sup> in metal catalyzed reactions. In this context, the ligand **L1** was identified as a non-phosphorus, inexpensive ligand<sup>9</sup> that can coordinate with palladium and catalyze an addition reaction of arylboronic acid to aryl aldehydes.<sup>10</sup> Extending the reaction to nitriles instead of aldehydes, we expected, we would have a general synthesis of aryl ketones. We report herein the successful outcome of this reaction and our fruitful attempt to extend this chemistry to achieve convenient synthesis of 3-acylindoles.

. Initially we chose 4-methoxybenzonitrile and phenylboronic acid as reaction partners to optimize the reaction. When the reaction was performed in dioxane and water at 80 °C no product was obtained. An equivalent amount of Sc(OTf)<sub>3</sub> as additive was necessary (Table 1, compare entry 2 with 3) to obtain high yield of the addition product. In presence of trifluoroacetic acid (TFA) or triflic acid the reactivity was greatly enhanced compared to HOAc allowing the reaction to be performed at 60 °C. Triflic acid afforded slightly better yield than TFA (Table 1, compare entry 12 with 11). Omission of additive left no impact on product yield (Table 1, entry 14). Also, the reaction did not proceed in absence of the ligand; the reaction mixture immediately turned black indicating precipitation of palladium black (Table 1, entry 15). Significantly, **L1** ensured less time and lower temperature than the precedents.<sup>7</sup> An important advantage is the use of aqueous medium without an organic solvent.

**Table S1. Optimization of addition of arylboronic acid to nitrile<sup>a</sup>**

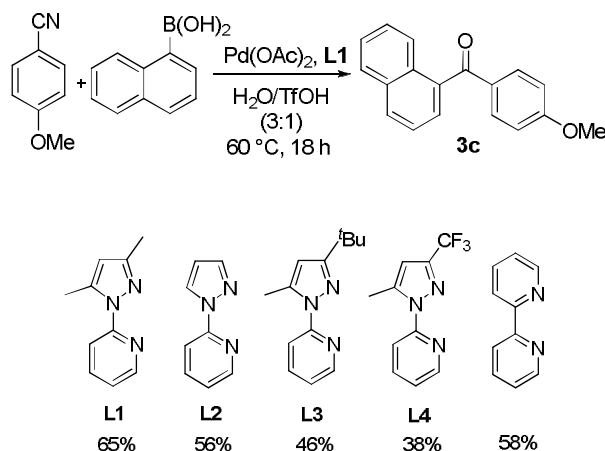


entry	solvent	time(h)	additive	yield(%) <sup>b</sup>
1	Dioxane/H <sub>2</sub> O(0.6 mL/0.2 mL)	20	KF	0
2 <sup>c</sup>	Dioxane/H <sub>2</sub> O(0.6 mL/0.2 mL)	12	-	90
3 <sup>d</sup>	Dioxane/H <sub>2</sub> O(0.6 mL/0.2 mL)	12	-	72
4	H <sub>2</sub> O/THF/HOAc(0.2 mL/0.3mL/0.3mL)	20	KF	89
5	HOAc(0.5 mL)	20	KF	90
6	H <sub>2</sub> O/HOAc(0.2 mL/0.6 mL)	20	KF	95
7	H <sub>2</sub> O/HOAc(0.2 mL/0.6 mL)	12	KF	88
8	H <sub>2</sub> O/HOAc(0.2 mL/0.6 mL)	12	CsF	97
9	H <sub>2</sub> O/HOAc(0.6 mL/0.2 mL)	12	CsF	96
10	H <sub>2</sub> O/TFA(0.6 mL/0.2 mL)	1	CsF	96
11 <sup>e</sup>	H <sub>2</sub> O/TFA(0.6 mL/0.2 mL)	3.5	CsF	93
12 <sup>e</sup>	H <sub>2</sub> O/TfOH(0.6 mL/0.2 mL)	3.5	CsF	98
13	H <sub>2</sub> O/TfOH/CH <sub>3</sub> NO <sub>2</sub> (0.6 mL/0.2 mL/0.2mL)	20	CsF	0
<b>14<sup>e</sup></b>	<b>H<sub>2</sub>O/TfOH(0.6 mL/0.2 mL)</b>	<b>3.5</b>	<b>-</b>	<b>98</b>
15 <sup>e,f</sup>	H <sub>2</sub> O/TfOH(0.6 mL/0.2 mL)	3.5	-	0

<sup>a</sup>Reaction condition: PhB(OH)<sub>2</sub> (0.6 mmol), 4-methoxybenzonitrile (0.5 mmol), additive (1.5 mmol), Pd(OAc)<sub>2</sub> (5 mol%), **L1** (5 mol%), under air. <sup>b</sup>Isolated yield. <sup>c</sup>Sc(OTf)<sub>3</sub> (0.5 mmol). <sup>d</sup>Sc(OTf)<sub>3</sub> (20 mol%). <sup>e</sup>60 °C & 4 mol% [Pd]. <sup>f</sup>no ligand used.

It was also found that, among analogous ligands<sup>11</sup> **L1-L4** (bipyridyl was also used for comparison), the dimethyl substituted **L1** afforded the highest yield for addition reaction of  $\alpha$ -naphthylboronic acid to 4-methoxybenzonitrile under optimized condition (Scheme 1). Hence **L1** was used for all subsequent reactions.

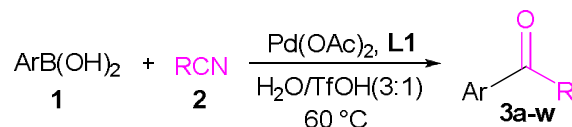
**Scheme 1. Effect of ligands in addition reaction of  $\alpha$ -naphthylboronic acid to 4-methoxybenzonitrile**

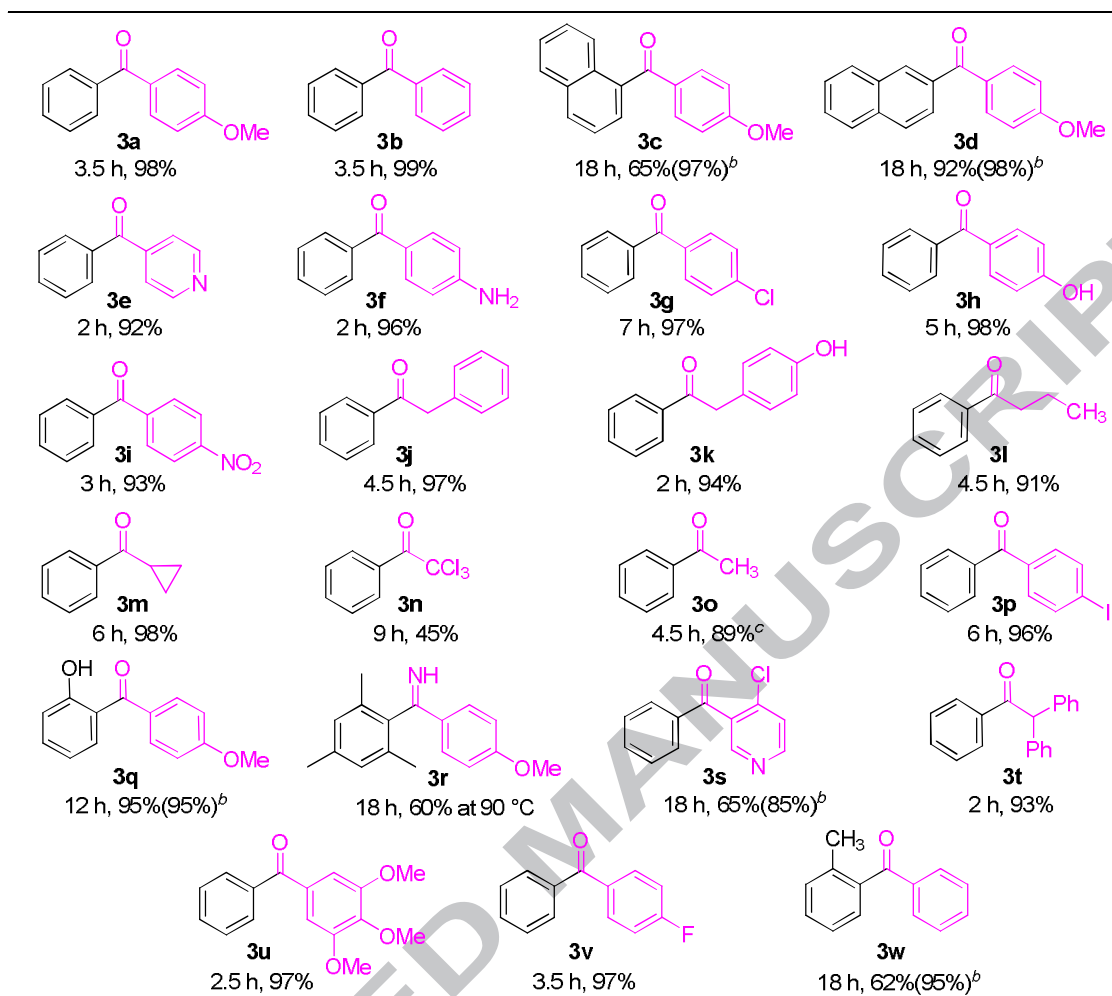


Under the optimized condition at hand with Pd(OAc)<sub>2</sub> (4 mol%), **L1** (4 mol%) in H<sub>2</sub>O/TfOH (3:1) we examined the addition reaction of arylboronic acids to different kinds of nitriles (Scheme 2).. A variety of nitriles were screened In most cases, the aryl ketone was obtained in excellent yield. Despite heating in a strongly acidic medium, it is remarkable to note that the desired ketones were obtained from -NH<sub>2</sub>, -Cl, -OH and -NO<sub>2</sub> substituted benzonitriles in high yield (**3f**, **3g**, **3h** and **3i** respectively). This offers a clear opportunity for these substrates to undergo further transformations. Steric factor appears to impede the reaction and reduce the yield (**3c**, **3d**, **3q** and **3w**). However, the adverse impact can be minimized to a large extent by increasing the temperature to 90 °C. In case of **3r**, steric hindrance around the imine group inhibited hydrolysis to ketone (for a similar observation, see ref.7h).

Alkyl nitriles were also tested in this reaction and they afforded excellent yields of products (**3l** and **3o**). Ethyl 2-cyanoacetate afforded acetophenone (**3o**) *via* in *situ* decarboxylation of the initially formed  $\beta$ -keto ester. Cyclopropanecarbonitrile and trichloroacetonitrile underwent addition reaction to afford products **3m** and **3n** though **3n** was obtained in lower yield. Absence of competitive Suzuki-Miyaura coupling product or homocoupling product from 4-iodobenzonitrile expands the scope of the reaction (**3p**). Excellent yield of products from the reaction of arylboronic acid with benzyl cyanides proves the versatility of this synthetic methodology (**3j**, **3k** and **3t**).

Scheme 2. Arylboronic acid addition to nitriles<sup>a</sup>





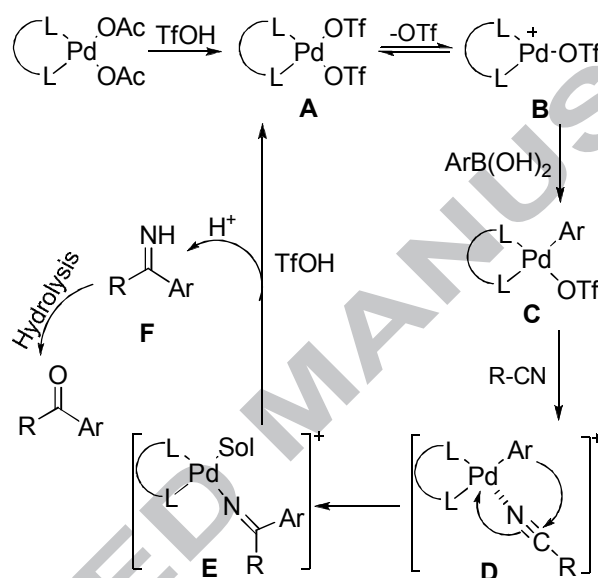
<sup>a</sup>Reaction condition: ArB(OH)<sub>2</sub> (1.2 mmol), RCN (1 mmol), H<sub>2</sub>O/TfOH (1.2 mL/0.4 mL), Pd(OAc)<sub>2</sub> (4 mol%), **L1** (4 mol%), under air, all yields are isolated yields. <sup>b</sup>At 90 °C, 1.5 h. <sup>c</sup>Ethyl 2-cyanoacetate was used, decarboxylation product obtained.

Transmetalation, which is one of the most fundamental processes in carbon-carbon bond formation reaction, is sluggish with boron reagents.<sup>12</sup> In absence of a base, use of cationic transition metal complex<sup>12,13</sup> not only makes the transmetalation step more facile, but also activates the nitrile group through coordination to metal. In aqueous TfOH, it is likely that the reaction involves cationic palladium species. This Pd-catalyzed addition reaction does not need any preformed catalyst,<sup>7g</sup> thus making the synthetic procedure operationally simple.

Considering all these factors and on the basis of suggestions made in earlier reports<sup>7</sup> a possible reaction mechanism is depicted in Scheme 3. First, electrophilic transmetalation of

the aromatic boronic acid occurs by cationic Pd(II) species (**B**)<sup>14</sup> to generate **C**. Then nitrile group coordinates to the vacant coordination site of Pd giving intermediate **D**. Intramolecular migration of the aryl group from Pd centre to the activated cation of the nitrile would result in the new C-C bond formation to afford intermediate **E**. Finally protonolysis of **E** affords **F** and regenerates the [Pd] catalyst.

**Scheme 3. Proposed mechanism**



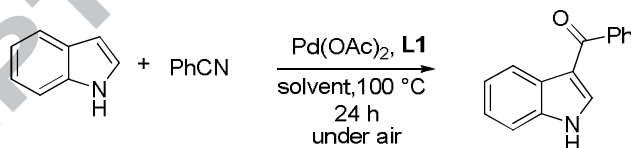
If **B** indeed was a putative cationic intermediate, we surmised, in principle, with a different nucleophile. Since nucleophilic attack by C-3 of an indole nucleus is well-known<sup>15</sup> we wanted to explore whether indole would participate in this reaction to afford 3-acyl indoles which are common molecular fragments in biologically active compounds<sup>16</sup> and natural products.<sup>17</sup> Such compounds are also versatile starting materials for the syntheses of a wide range of indole derivatives. Synthesis of 3-acyl indoles are generally accomplished by Friedel-Craft acylation,<sup>18</sup> Vilsmeier-Haack type reaction,<sup>19</sup> and indole Grignard reaction.<sup>20</sup> The most frequently used Friedel-Craft reactions require *N*-protection (especially for indoles bearing an electron-donating group), use of stoichiometric Lewis acid, strict exclusion of moisture, and suffers from side reactions such as N1-acylation or N1/C3



diacylation.<sup>18</sup> Moreover, acylating reagents themselves are normally hazardous. Therefore, a desirable procedure is one which is versatile, highly regio- and chemoselective, operationally simple and relatively non-hazardous. Pd-catalyzed acylation of unprotected indoles with nitriles redresses majority of the difficulties but is less explored.<sup>21</sup> Our catalytic system is active enough to conduct the reaction at lower temperature and within a comparatively short reaction time.

Reaction conducted under the same condition as described above, however, led to extensive decomposition of the reaction component (Table 2, entry 1). In dioxane/MeSO<sub>3</sub>H/H<sub>2</sub>O (0.7/0.1/0.2 mL) system at 100 °C only 20% yield of product was observed with some decomposition (Table 2, entry 2). Gratifyingly, 70% yield was obtained when HOAc was used (Table 2, entry 4). Yield remained unaffected even after doubling the amount of catalyst (Table 2, entry 5). Use of different solvents *e. g.* DMF, NMP, DMAc had no significant impact on the yield of the reaction. Here also **L1** afforded the highest yield among all the ligands (compare entry 4 with 9, 10 and 11 of Table 2).

**Table 2. Optimization of addition of indole to nitrile<sup>a</sup>**

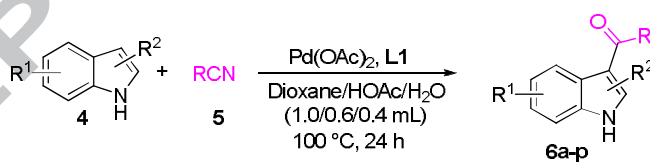


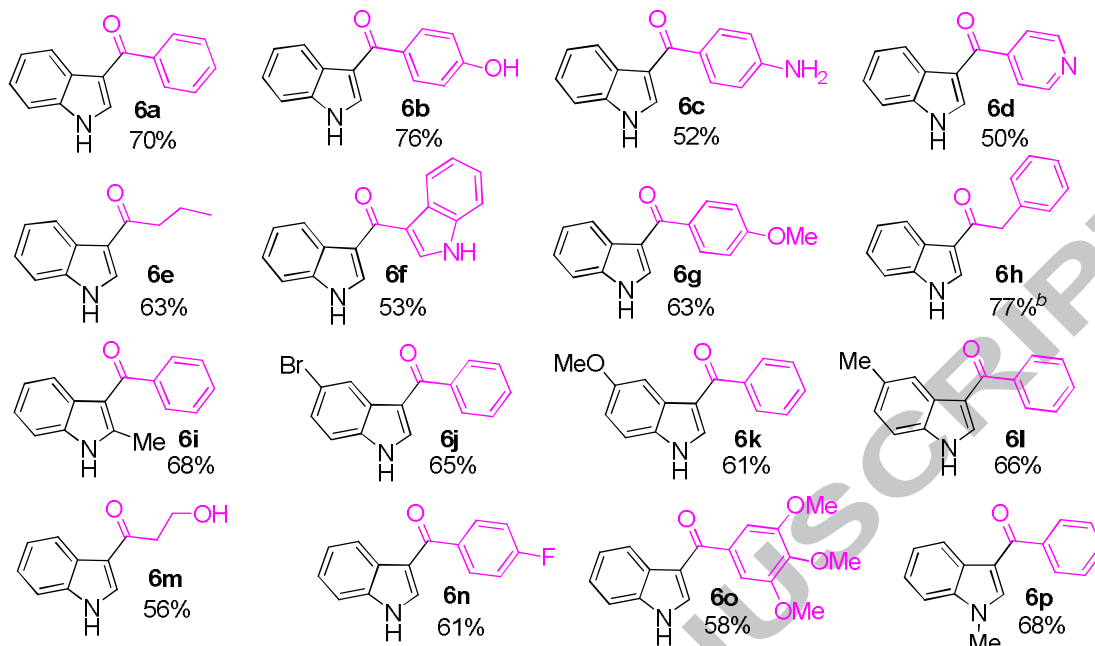
entry	solvent	yield <sup>b</sup>
1 <sup>c</sup>	H <sub>2</sub> O/TfOH (0.6/0.2 mL)	Decomposed
2	Dioxane/MeSO <sub>3</sub> H/H <sub>2</sub> O (0.7/0.1/0.2 mL)	20
3	Dioxane/HOAc/H <sub>2</sub> O (0.3/0.5/0.2 mL)	60
4	<b>Dioxane/HOAc/H<sub>2</sub>O (0.5/0.3/0.2 mL)</b>	<b>70</b>
5 <sup>d</sup>	Dioxane/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	71
6	DMF/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	28
7	NMP/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	45
8	DMAc/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	41
9 <sup>e</sup>	Dioxane/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	41
10 <sup>f</sup>	Dioxane/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	60
11 <sup>g</sup>	Dioxane/HOAc/H <sub>2</sub> O (0.5/0.3/0.2 mL)	25

<sup>a</sup>Reaction condition : indole (0.5 mmol), benzonitrile (0.6 mmol), Pd(OAc)<sub>2</sub> (5 mol%), **L1** (5 mol%). <sup>b</sup>Isolated yield. <sup>c</sup>at 60 °C. <sup>d</sup>10 mol% Pd(OAc)<sub>2</sub> used. <sup>e</sup>**L2** used. <sup>f</sup>**L3** used. <sup>g</sup>**L4** used.

We explored the substrate scope with variously substituted indoles and nitriles. Indoles with electron rich (**6k** and **6l**), electron poor (**6j**), and sterically hindered (**6i**) groups, smoothly underwent reaction with benzonitriles affording the 3-acylated products in good yield.

**Scheme 4. Addition of indoles to nitriles<sup>a</sup>**



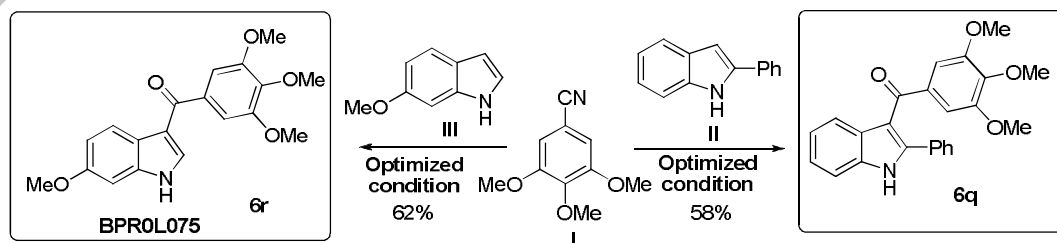


<sup>a</sup>Reaction Condition: Indole (1.0 mmol), nitrile (1.2 mmol), Pd(OAc)<sub>2</sub> (5 mol%), **L1** (5 mol%), under air, all yields are isolated yields. <sup>b</sup>At 70 °C.

This reaction condition is compatible with a variety of functional groups such as -OH, -NH<sub>2</sub>, -OMe (**6b**, **6c**, and **6g**). Heteroaryl nitrile like 4-cyanopyridine afforded the expected product **6d**. For benzyl cyanide, reaction was performed at 70 °C to prevent decomposition at higher temperature (**6h**). A notable advantage of the reaction is that acylation of 3-position of indole can be carried out without protecting the -NH group.

Exploiting this methodology we have synthesized two reported anti-cancer agents (**6q**)<sup>22</sup> and (**6r**)<sup>23</sup> by reacting 3,4,5-trimethoxybenzonitrile (**I**) with 2-phenylindole (**II**) and 6-methoxyindole (**III**) respectively (Scheme 5).

**Scheme 5. Synthesis of biologically active compounds (6q and 6r)**



In conclusion, we have developed a protocol for addition of arylboronic acid to nitrile that is efficiently catalyzed by a complex of palladium coordinated to ligand **L1**, a pyrazole-pyridine analogue of bipyridyl. This protocol has several advantages in terms of reaction time, temperature, yield, and convenience. The method also permits acylation of indoles at C-3 position without protection of the -NH group.

### Acknowledgement

We thank Dr. Koena Ghosh for her valuable input in this work. T. D. and A. C. are thankful to CSIR, India and IACS, Kolkata respectively for research fellowships.

**Supplementary data.** Supplementary data (experimental procedure, optimization of reaction conditions and characterisation data of all products listed in the tables) associated with this article are provided as a separate file and can be found in online version.

### References:

1. (a) Arenas, P.; Peña, A.; Ríos, D.; Benites, J.; Muccioli, G. G.; Calderon, P. B.; Valderrama, J. A. *Molecules* **2013**, *18*, 9818-9832. (b) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441-4447. (c) Batt, D. G.; Goodman, R.; Jones, D. G.; Kerr, J. S.; Mantegna, L. R.; McAllister, C.; Newton, R. C.; Nurnberg, S.; Welch, P. K.; Covington, M. B. *J. Med. Chem.* **1993**, *36*, 1434-1443.
2. (a) Chang, Y. M.; Yin, W. F.; Ho, C. Y.; Mustafa, M. R.; Hadi, A. H. A.; Awang, K.; Narrima, P.; Koh, C.; Appleton, D. R.; Chan, K. *J. Nat. Prod.* **2011**, *74*, 2261-2264. (b) Battaglia, U.; Moody, C. J. *J. Nat. Prod.* **2010**, *73*, 1938-1939. (c) Wang, W.; Zeng, Y. H.; Osman, K.; Shinde, K.; Rahman, M.; Gibbons, S.; Mu, Q. *J. Nat. Prod.* **2010**, *73*, 1815-1820. (d) Veda, J.; Takagi, M.; Shin-Ya, K. *J. Nat. Prod.* **2009**, *72*, 2181-2183.

3. (a) Ianni, A.; Waldvogel, S. R. *Synthesis* **2006**, 2103-2112. (b) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316-1327. (c) Sarvari, M. H.; Sharghi, H. *Synthesis* **2004**, 2165-2168. (d) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953-6956. (e) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219-2222. (f) Ross, J.; Xiao, J. *Green Chem.* **2002**, *4*, 129-133. (g) Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417-420. (h) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616-8620. (i) Gooßen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458-3460. (j) Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *Chem. Commun.* **2000**, 1695-1696.

4. (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750-6755. (b) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332-1334. (c) Hirao, T.; Misu, D.; Agawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 7179-7181. (d) Hudlicky, M. *In Oxidations in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, DC, 1990. (e) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p 591.

5. (a) Malamas, M. S.; Erdei, J.; Gunawan, I.; Barnes, K.; Jhonson, M.; Hui, Y.; Turner, J.; Hu, Y.; Wagner, E.; Fan, K.; Olland, A.; Bard, J.; Robichaud, A. J. *J. Med. Chem.* **2009**, *52*, 6314-6323. (b) Kharasch, M. S.; Reimuth, O. *Grignard reactions of non-metallic substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954; p 138-528.

6. (a) Jie, S.; Zhang, S.; Sun, W. *Eur. J. Inorg. Chem.* **2007**, 5584-5598. (b) Ball, S. C.; Davies, R. P.; Raithby, P. R.; Shields, G. P.; Snaith, R. *J. Organomet. Chem.* **1998**, *550*, 457-461.

7. (a) Wang, X.; Wang, X.; Liu, M.; Ding, J.; Chen, J.; Wu, H. *Synthesis*, **2013**, *45*, 2241-2244. (b) Wong, Y.; Parthasarathy, K.; Cheng, C. *Org. Lett.* **2010**, *12*, 1736-1739. (c) Yu, A.;

- Li, J.; Cui, M.; Wu, Y. *Synlett* **2007**, 3063-3067. (d) Shimizu, H.; Murakami, M. *Chem. Commun.* **2007**, 2855-2857. (e) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, 691, 2821-2826. (f) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, 47, 6765-6768. (g) Zhao, B.; Lu, X. *Org. Lett.* **2006**, 8, 5987-5990. (h) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, 71, 3551-3558. (i) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, 126, 2302-2303.
8. (a) Mukherjee, A.; Sarkar, A. *Tetrahedron Lett.* **2004**, 45, 9525-9528. (b) Mukherjee, A.; Subramanyam, U.; Puranik, V. G.; Mohandas, T. P.; Sarkar, A. *Eur. J. Inorg. Chem.* **2005**, 1254-1263. (c) Pal, A.; Ghosh, R.; Adarsh, N. N.; Sarkar, A. *Tetrahedron* **2010**, 66, 5451-5458.
9. Saha, N.; Kar, S. K.; *J. Inorg. Nucl. Chem.* **1977**, 39, 1238-1239.
10. Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, 55, 5174-5178.
11. Synthesis of ligand **L2**: Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, 76, 654-660. Procedure for synthesis of **L3** and **L4** were adopted from this paper (see supporting information).
12. Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, 23, 4317-4324.
13. (a) Yamamoto, A. *J. Organomet. Chem.* **1995**, 500, 337-348. (b) Ludwig, M.; Strömberg, S.; Svensson, M.; Kermark, B. *Organometallics* **1999**, 18, 970-975. (c) Alcazar-Rman, L. M.; Hartwig, J. F. *Organometallics* **2002**, 21, 491-502. (d) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, 35, 905-913. (e) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2003**, 42, 2768-2770.
14. (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, 287, 1992-1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara,

Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252-7263. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633-639 and references therein.

15. (a) Chen, Y.; Guo, S.; Li, K.; Qu, J.; Yuan, H.; Hua, Q.; Chena, B. *Adv. Synth. Catal.* **2013**, *355*, 711-715. (b) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529-5535. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174. (d) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415-2419.

16. (a) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5365-5369. (b) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119-7137. (c) Wu, Y.; Coumar, M. S.; Chang, J.; Sun, H.; Kuo, F.; Kuo, C.; Chen, Y.; Chang, C.; Hsiao, C.; Liou, J.; Chen, C.; Yao, H.; Chiang, Y.; Tan, U.; Chen, C.; Chu, C.; Wu, S.; Yeh, T.; Lin, C.; Hsieh, H. *J. Med. Chem.* **2009**, *52*, 4941-4945. (d) Cai, Q.; Zhao, Z.; You, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7428-7431. (e) Barreca, M. L.; Ferro, S.; Rao, A.; Luca, L.; Zappalà, M.; Monforte, A.; Debyser, Z.; Witvrouw, M.; Chimirri, A. *J. Med. Chem.* **2005**, *48*, 7084-7088. (f) Pais, G. C. G.; Zhang, X.; Marchand, C.; Neamati, N.; Cowansage, K.; Svarovskaia, E. S.; Pathak, V. K.; Tang, Y.; Nicklaus, M.; Pommier, Y.; Burke, T. R. Jr. *J. Med. Chem.* **2002**, *45*, 3184-3194.

17. (a) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447-457. (b) Fresneda, P. M.; Molina, P.; Saez, M. A. *Synlett* **1999**, 1651-1653. (c) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053-6058.

18. (a) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4753-4758. (b) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740-5743. (c) Yeung, K. -S.; Qiu, Z.; Farkas, M. E.; Xue, Q.; Regueiro-Ren, A.; Yang, Z.; Bender, J. A.; Good, A. C.; Kadow, J. F. *Tetrahedron Lett.* **2008**, *49*, 6250-6253. (d) Katritzky, A. R.;

- Suzuki, K.; Singh, S. K.; He, H. *J. Org. Chem.* **2003**, *68*, 5720-5723. (e) Ottoni, O.; Neder, A. V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005-1007. (f) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485-1487. (g) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451-5457.
19. a) Anthony, W. C. *J. Org. Chem.* **1960**, *25*, 2049-2053; b) Sundberg, R. J. *The Chemistry of Indoles*, Academic Press, New York, 1970 and references cited therein.
20. Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1987**, *28*, 3741-3744.
21. (a) Jiang, T.; Wang, G. *Org. Lett.* **2013**, *15*, 788-791. (b) Ma, Y.; You, J.; Song, F. *Chem.-Euro. J.* **2013**, *19*, 1189-1193.
22. Regina, G. L.; Bai, R.; Rensen, W. M.; Cesare, E. D.; Coluccia, A.; Piscitelli, F.; Famigliani, V.; Reggio, A.; Nalli, M.; Pelliccia, S.; Pozzo, E. D.; Costa, B.; Granata, I.; Porta, A.; Maresca, B.; Soriani, A.; Iannitto, M. L.; Santoni, A.; Li, J.; Cona, M. M.; Chen, F.; Ni, Y.; Brancale, A.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Martini, C.; Hamel, E.; Lavia, P.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 123-149.
23. Liou, J. -P.; Chang, Y. -Li.; Kuo, F. -M.; Chang, C. -W.; Tseng, H. -Y.; Wang, C. -C.; Yang, Y. -N.; Chang, J. -Y.; Lee, S. -J.; Hsieh, H. -P. *J. Med. Chem.* **2004**, *47*, 4247-4257.