Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5343

www.rsc.org/obc

**COMMUNICATION**

# Novel α-arylnitriles synthesis *via* Ni-catalyzed cross-coupling of α-bromonitriles with arylboronic acids under mild conditions†

**Yingying Yang,[a] Shan Tang,[a] Chao Liu,[a] Huimin Zhang,[a] Zhexun Sun[a] and Aiwen Lei*[a,b]**

***Received 1st March 2011, Accepted 12th May 2011***
**DOI: 10.1039/c1ob05326d**

**An applicable and easy-handling Ni-catalyst can be used to promote direct arylation of α-bromonitriles with various arylboronic acids to construct α-arylnitriles under mild conditions. The methodology tolerates β-hydrogens and functional groups in the substrates.**

The α-aryl substituted nitrile moieties are very important constituents in many medicinal and natural products.[1] With their impressive bioactivities, they are extensively used as synthetic intermediates in the pharmaceutical industry.[2–4] For example, Ariflo (Cilomilast) has been used in the clinic for bronchial asthma and chronic obstructive pulmonary disease (COPD).[5–6] However, only limited methods for the synthesis of α-aryl nitriles have been reported until recently. An early result was reported in 1996, in which the electrochemical reduction of 1-bromo-3-(trifluoromethyl)benzene with 2-chloropropanenitrile led to the cross-coupled product in 62% yield in the presence of nickel catalyst.[7] Later on, Pd-catalyzed protocols were demonstrated with aryl halides and nitriles in the presence of a strong base.[8–12] A milder process for the synthesis of α-aryl nitrile compounds was recently reported in which α-silyl nitriles and zinc cyanoalkyls were directly coupled with aryl halides in the presence of a palladium catalyst.[6] In these cases, the aryl group all acted as an electrophile (Fig. 1, Path I). Normally, a strong base has to be employed for the deprotonation of nitriles to form the active nucleophiles, resulting in the limitation of the functional groups tolerance.

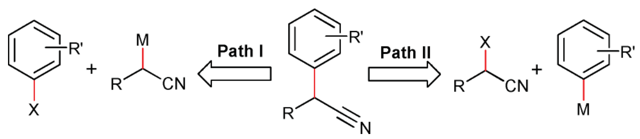


**Fig. 1** Two possible approaches to obtain α-aryl nitriles.

However, from the disconnection of the designed products α-aryl nitriles, an alternative approach also has high potentials (Fig. 1, Path II),[13] in which aryl groups are used as nucleophiles, such as aryl triflorosilanes, aryl boronic acids and aryl zinc reagents. From the nature of these two approaches, the advantages of the second one are very obvious. The reaction conditions are milder. Strong bases are avoided in the deprotonation of the nitriles, hence the functional groups tolerance is highly improved. However, very few results have been reported by this protocol. In 2007, aryl triflorosilanes were reported to couple with α-halonitriles,[14] and arylboronic acids were employed in the α-arylation of α-halocarbonyl compounds.[15]

To explore new entries toward the synthesis of α-arylnitrles, we envisioned that arylboronic acids would be proper choices to react with α-halocarbonyl compounds in the presence of transition metal catalysts (Fig. 1, Path II). As the Suzuki coupling normally leads to a mild method for such transformation, and have better functional groups tolerance.[16–20] Herein, we communicate our recent efforts for the α-arylation of nitrles.

$Ni(PPh_3)_4$ was firstly applied as the catalyst to achieve the coupling between arylboronic acids and α-bromonitriles in the presence of $K_3PO_4$ in toluene. Surprisingly, it worked very well with not only simple α-bromoacetonitrile, but also the α-bromobutanenitrile **2b** and α-bromopentanenitrile **2c** bearing β-hydrogens (Table 1). Various arylboronic acids could be introduced. The bulky *o*-tolylboronic acid proceeded well to afford the desired product. Aryl bromides were also well tolerated, indicating the potential for further functionalization.

$Ni(PPh_3)_4$ is not air-stable and normally requires inert atmosphere operations such as glove box techniques, which limits the application of this protocol. On the other hand, $Ni(PPh_3)_4$ is usually prepared by the reduction of the mixture of $Ni(acac)_2$ and $PPh_3$ with DIBAL-H.[21] To improve the operability of this transformation, we tried to use the air-stable $Ni(acac)_2$ and $PPh_3$ directly as catalyst precursor to achieve this cross-coupling process. Fortunately, it works as well as the $Ni(PPh_3)_4$. This result encouraged us to further optimize the catalyst system.

First, we tried to optimize the ratio of the $Ni(acac)_2$ and $PPh_3$. α-Bromovaleronitrile and phenylboronic acid were used in the model reactions. The reactions were analyzed by GC in a span of 25 h (Fig. 2, and see ESI†). The results showed that when the ratio of $Ni(acac)_2$ and $PPh_3$ is 1 : 2, it gave the highest yield (92%) and finished in the shortest time (1 h).

This finding promoted us to apply this new catalyst system to the above-mentioned arylation of α-bromonitriles. Fortunately, most of the substrates worked well with high yields in the presence of 5%

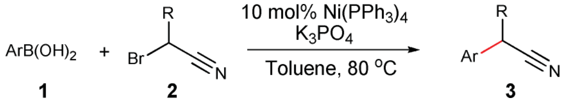
---

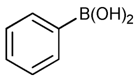
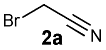
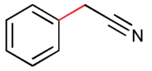
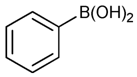
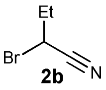
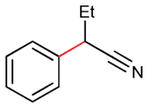
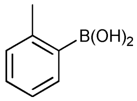
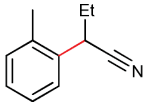
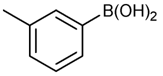
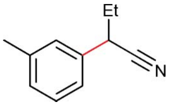
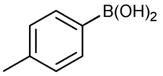
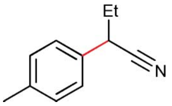
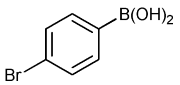
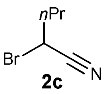
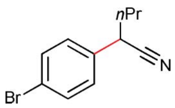
[a] *College of Chemistry and Molecular Sciences, Wuhan University, P. R. China. E-mail: Aiwenlei@whu.edu.cn; Fax: (+86)-27-68754067; Tel: (+86)-27-68754672*

[b] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, 730000, Lanzhou*

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c1ob05326d

**Table 1** Arylation of α-bromonitriles with $ArB(OH)_2$ by using $Ni(PPh_3)_4$ as the catalyst precursor[a]



| Entry | $ArB(OH)_2$ | α-Bromonitrile | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 |  |  2a |  | 67[c] |
| 2 |  |  2b |  | 76 |
| 3 |  | 2b |  | 75 |
| 4 |  | 2b |  | 81 |
| 5 |  | 2b |  | 78 |
| 6 |  |  2c |  | 86 |

[a] Conditions: See ESI.† [b] Isolated yield. [c] GC yield.

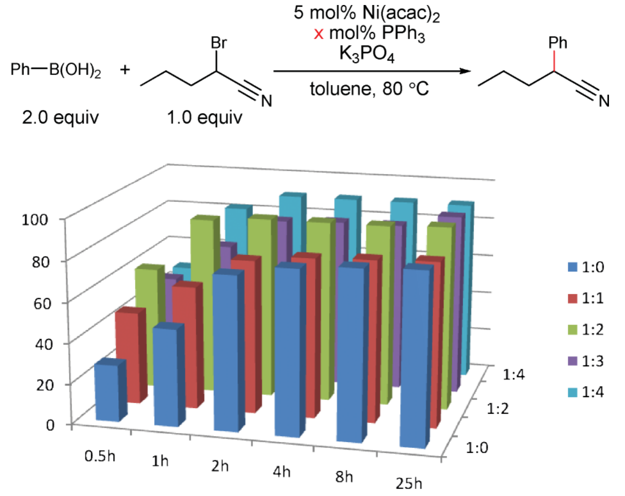
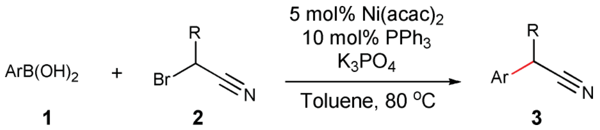
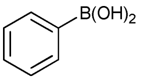
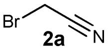
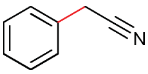
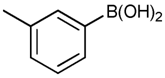
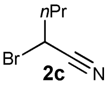
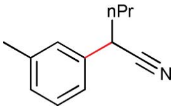
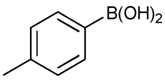
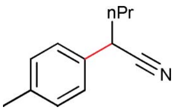
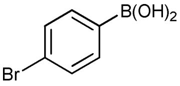
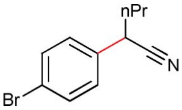
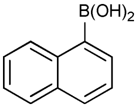
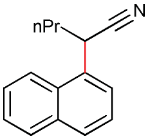
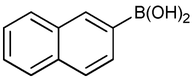
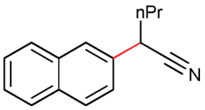


**Fig. 2** Arylation of α-bromovaleronitrile with phenylboronic with different ratios of $Ni(acac)_2$ and $PPh_3$ (x = 0, 5, 10, 15, 20).

of $Ni(acac)_2$ and 10% of $PPh_3$ as catalyst and $K_3PO_4$ as additive (Table 2). Moreover, naphthalen-2-ylboronic acid and naphthalen-1-ylboronic acid also gave good results (Entry 5 and Entry 6 in Table 2).

**Table 2** Arylation of α-bromonitriles with $ArB(OH)_2$ by using $Ni(acac)_2$ and $PPh_3$ as the catalyst precursor[a]



| Entry | $ArB(OH)_2$ | α-Bromonitrile | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 |  |  2a |  | 68[c] |
| 2 |  |  2c |  | 81 |
| 3 |  | 2c |  | 88 |
| 4 |  | 2c |  | 89 |
| 5 |  | 2c |  | 75 |
| 6 |  | 2c |  | 86 |

[a] Conditions: See ESI.† [b] Isolated yield. [c] GC yield.

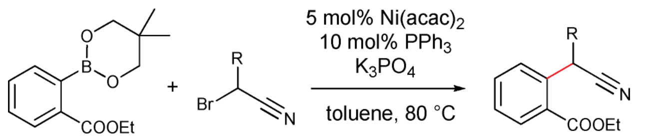
Since arylboronic acid esters can be easily prepared by direct borylation of arenes, they have been increasingly used in coupling reactions.[22] A sample arylboronic ester was appiled to this arylation reaction to couple with the α-bromonitriles (Table 3). The catalyst system gave us very positive results. Even though it is a hindered arylboronic ester, it can couple with the nitriles bearing β-hydrogens (Entry 2 and 3, Table 3) in high yields (95% and 87%).

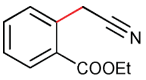
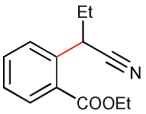
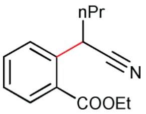
In conclusion, we reported the Ni-catalyzed α-arylation of nitriles by using readily prepared α-bromonitriles and arylboronic acids or esters which are being widely used in synthetic chemistry for the first time. The use of $Ni(acac)_2$ and $PPh_3$ as the catalyst precursor has a significant practical advantage over the reported methods.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (21025206, 20832003, 20972118 and 20772093) and the "973" Project from the MOST of China (2011CB808600). We also thank the support from "the Fundamental Research Funds

**Table 3** Arylation of α-bromonitriles with ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate by using Ni(acac)$_2$ and PPh$_3$ as the catalyst precursor[a]



| Entry | α-Bromonitrile | Product | Yield [%][b] |
|---|---|---|---|
| 1 | **2a** |  | 63 |
| 2 | **2b** |  | 95 |
| 3 | **2c** |  | 87 |

[a] Conditions: See ESI.† [b] Isolated yield.

for the Central Universities", and Program for New Century Excellent Talents in University (NCET).

## Notes and references

1 S. Caron, E. Vazquez and J. M. Wojcik, *J. Am. Chem. Soc.*, 2000, **122**, 712.
2 S. B. Christensen, A. Guider, C. J. Forster, J. G. Gleason, P. E. Bender, J. M. Karpinski, W. E. DeWolf, M. S. Barnette, D. C. Underwood, D. E. Griswold, L. B. Cieslinski, M. Burman, S. Bochnowicz, R. R. Osborn, C. D. Manning, M. Grous, L. M. Hillegas, J. O. L. Bartus, M. D. Ryan, D. S. Eggleston, R. C. Haltiwanger and T. J. Torphy, *J. Med. Chem.*, 1998, **41**, 821.
3 S. Dei, M. N. Romanelli, S. Scapecchi, E. Teodori, A. Chiarini and F. Gualtieri, *J. Med. Chem.*, 1991, **34**, 2219.
4 L. J. Theodore and W. L. Nelson, *J. Org. Chem.*, 1987, **52**, 1309.
5 P. Jeffery, *Pulm. Pharmacol. Ther.*, 2005, **18**, 9.
6 L. Wu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 15824.
7 M. Durandetti, J.-Y. Nedelec and J. Perichon, *J. Org. Chem.*, 1996, **61**, 1748.
8 D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 9330.
9 J. You and J. G. Verkade, *Angew. Chem., Int. Ed.*, 2003, **42**, 5051.
10 J. You and J. G. Verkade, *J. Org. Chem.*, 2003, **68**, 8003.
11 R. Shetty and K. K. Moffett, *Tetrahedron Lett.*, 2006, **47**, 8021.
12 F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082.
13 G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2002, **41**, 953.
14 N. A. Strotman, S. Sommer and G. C. Fu, *Angew. Chem., Int. Ed.*, 2007, **46**, 3556.
15 C. Liu, C. He, W. Shi, M. Chen and A. Lei, *Org. Lett.*, 2007, **9**, 5601.
16 D. C. Gerbino, S. D. Mandolesi, H.-G. Schmalz and J. C. Podesta, *Eur. J. Org. Chem.*, 2009, 3964.
17 G. A. Molander and N. Ellis, *Acc. Chem. Res.*, 2007, **40**, 275.
18 Z. Weng, S. Teo and T. S. A. Hor, *Acc. Chem. Res.*, 2007, **40**, 676.
19 G. A. Molander and B. Canturk, *Angew. Chem., Int. Ed.*, 2009, **48**, 9240.
20 X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2010, **49**, 9047.
21 E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn and N. Okukado, *J. Am. Chem. Soc.*, 1987, **109**, 2393.
22 I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890.