

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2019, 9, 29424Received 22nd August 2019
Accepted 10th September 2019

DOI: 10.1039/c9ra07216k

rsc.li/rsc-advances

Efficient synthesis of spirooxindolyl oxazol-2(5H)-ones *via* palladium(II)-catalyzed addition of arylboronic acids to nitriles†

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A versatile synthesis of spirooxindolyl oxazol-2(5H)-ones *via* palladium(II)-catalyzed addition of arylboronic acids to nitriles is described. A wide range of spirooxindolyl oxazol-2(5H)-ones and other spirocyclic frameworks incorporating the oxazol-2(5H)-one unit can be readily prepared in good to high yields under the optimal conditions.

Rapid and efficient construction of pharmaceutical and biologically relevant compounds plays a very important role in modern organic synthesis, and constitutes the original impetus for the development of various novel synthetic approaches. The efficient construction of spirocyclic frameworks has been a topic of great relevance in organic synthesis due to their inherent three-dimensional architectures and the pronounced biological activities.¹ In particular, the spirocyclic oxindoles have emerged as attractive synthetic targets because of their prevalence in numerous natural and unnatural products.² Notably, the enhanced biological activities have been observed by the incorporation of a spiro five-membered azaheterocyclic ring at the C3 position of the oxindole core (Fig. 1).³ Thereby, a variety of synthetic methods have been developed to access analogous compounds possessing such privileged structure moieties.⁴

As one of the important N–O heterocyclic compounds, oxazolidinones and their derivatives have been widely used not only as synthetic building blocks,⁵ but also as pharmaceuticals⁶ and agrochemicals,⁷ owing to a diverse range of biological activities.⁸ Although great contributions have been made to access these valuable scaffolds,⁹ the construction of structurally diverse spirooxindolyl oxazol-2(5H)-ones, characterized by a spiro ring fusion at the C3 position of the oxindole core with oxazol-2(5H)-one motif, has received less attention from synthetic community,¹⁰ despite the fact that these spirocyclic heterocycles could be promising candidates possessing biological responses. In 2017, He and co-workers reported a formal [3 + 2] cycloaddition reaction of *in situ* generated azaoxyallyl

cation with cyclic ketones for the synthesis of spiro-4-oxazolidinones.^{11a} In 2018, Alla and co-workers described a copper-catalyzed one-pot multicomponent protocol for the synthesis of spiro(indoline-3,5'-oxazolidine)-2,2'-diones starting from ketones, arylacetylenes and isocyanates.^{11b}

Recently, the transition-metal-catalyzed addition of organoboron reagents to nitriles has received remarkable progress,¹² since the elegant works on the addition of arylpalladium species to the cyano group reported by Larock and Lu *et al.*,¹³ in which nitriles served as C building blocks and provided aryl ketones. In virtue of palladium-catalyzed tandem addition of organoboron reagents to nitriles/cyclization protocol, this approach enabled the combination of organoboron reagents and nitriles to construct a diversity of nitrogen-containing heterocycles such as 2-aminobenzophenones, benzofurans, and indoles, in which nitrile serves as C–N synthon instead and is incorporated into heterocyclic frameworks in an atom-economical fashion.¹⁴ However, the development of transition-metal-catalyzed tandem sequence involving the addition of organoboron reagents to nitriles to construct structural novel three-dimensional architectures such as spirocyclic systems is still undeveloped.

We have recently developed both intramolecular and intermolecular cyclization approaches to prepare indole and thiophene fused polycyclic derivatives *via* Pd-catalyzed direct C–H bond addition to nitriles.¹⁵ Given the promising biological

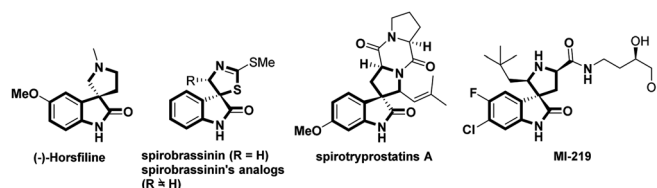


Fig. 1 Examples of spiro oxindoles containing natural products and biological relevant compounds.

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† Electronic supplementary information (ESI) available. CCDC 1943540. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra07216k

activities of spirooxindoles-containing molecules in medicinal chemistry and our ongoing interest in the development of efficient catalytic processes to prepare diverse aza-heterocyclic frameworks, herein, we report an efficient synthetic approach to prepare spirooxindolyl oxazol-2(5*H*)-ones *via* palladium(II)-catalyzed addition of arylboronic acids to nitriles.

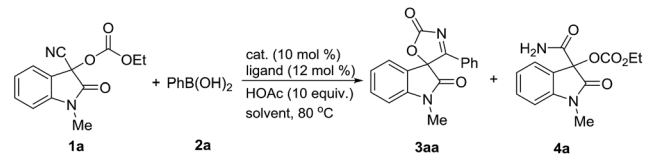
As functionalized nitriles, cyanohydrins which are readily prepared from ketones and aldehydes have demonstrated considerable synthetic potential as useful building blocks.¹⁶ We chose the Pd(II)-catalyzed reaction of 3-cyano-1-methyl-2-oxindolin-3-yl ethyl carbonate **1a**, which is readily prepared from isatin and ethyl cyanoformate, and phenylboronic acid **2a** as a model reaction for the optimization of the reaction conditions (Table 1). Initially, we examined the reactions in various solvents in the presence of Pd(OAc)₂ (10 mol%), 2,2'-bipyridine (**L1**: bpy) (12 mol%) and HOAc (10 equiv.) at 80 °C. To our delight, the desired spirooxindolyl oxazol-2(5*H*)-one **3aa** was observed in range of solvents, in which low yield was obtained in less polar solvent along with the small amount of byproduct **4a** (Table 1, entry 1), while moderate yields were obtained in polar solvents in general (Table 1, entries 2–5). Replacing Pd(OAc)₂ with Pd(acac)₂ afforded the cyclized product **3aa** in the increased yield in NMP, while Pd(TFA)₂ gave the slightly

decreased yield (Table 1, entries 6 and 7). Subsequently, the effect of ligands was evaluated in the presence of Pd(acac)₂. The similar results were obtained when 4,4'-dimethyl-2,2'-bipyridine (**L2**) and 1,10-phenanthroline (**L4**) were employed respectively, while 5,5'-dimethyl-2,2'-bipyridine (**L3**) gave the marginal reducing yield of **3a** (Table 1, entries 8–10). Notably, the similar efficiency can be observed in prolonged reaction time by using Pd(OAc)₂, in which 91% yield can be obtained in the presence of Pd(OAc)₂ (5 mol%) and HOAc (5.0 equiv.) for 36 hours (Table 1, entry 11). The obvious decline in the yield of product **3aa** was observed without HOAc (Table 1, entry 12), while HOAc cannot promote this reaction alone (Table 1, entry 15). Both ligand and Pd(II) catalyst proven to be essential to this transformation since no reaction happened without them (Table 1, entries 13 and 14). The attempt to reducing the amount of **2a** resulted in the decreased yield (Table 1, entry 16). Further survey on other reaction parameters such as additives, reaction temperature and concentration did not improve the chemical outcome of this transformation (for details see the ESI†). In addition, the reaction also was evaluated with Ni(II) catalyst system. However, Ni(II)-catalyzed reaction gave the inferior to that of Pd(II) catalytic system (Table 1, entry 17), and delivered the desired product **3aa** in moderate yield under the optimized reaction conditions (Ni(acac)₂ (10 mol%) **L2** (12 mol%) and MTBE) (for details see the ESI†).

With the optimized reaction conditions in hand, the generality of the Pd-catalyzed addition/cyclization sequence for the preparation of spirooxindolyl oxazol-2(5*H*)-ones was evaluated by employing various isatin based-*O*-ethoxycarbonyl cyanohydrins **1** and phenylboronic acid **2a** first (Scheme 1). Other than *N*-methyl substrate **1a**, cyanohydrin analogues **1** bearing different *N*-substituents such as phenyl, benzyl, *p*-methoxybenzyl and *p*-nitrobenzyl can give the desired products **3ba–3ea** in high yields. The substitution pattern at the benzene ring of cyanohydrins **1** has little influence on the results, and high yields could be obtained (**3fa–3ia**). In addition, the reactions between substrates possessing both electron-donating (MeO and Me) and electron-withdrawing (NO₂, Br, Cl and I) substituents at the benzene ring and phenylboronic acid **2a** proceeded well, and gave the corresponding products with excellent yields (**3ja–3oa**). The structures of spirooxindolyl oxazol-2(5*H*)-ones were unambiguously confirmed by the exemplification of X-ray crystal structural analysis of product **3aa**.¹⁷

Next, the substrate scope with respect to arylboronic acids was also investigated, the results of which are summarized in Scheme 2. Arylboronic acids bearing both electron-donating (**3ab–3ad**) and electron-withdrawing substituents (**3ae–3ag**) at the benzene ring were tolerated, affording the desired products in good to high yields, exception for strong electron-withdrawing substituent such as nitro group (**3ah**), which did not react with 3-cyano-1-methyl-2-oxindolin-3-yl ethyl carbonate **1a**. It is noteworthy that the reaction also proceeded smoothly when a substituent was situated at the ortho position of the arylboronic acid, albeit with the slightly decreased yield (**3ai**). As expected, meta- and di-substituted analogues afforded products (**3aj** and **3ak**) in high yields. Additionally, aryl boronic acids with fused ring also gave their corresponding products

Table 1 Effects of reaction parameters^a



| Entry | Cat. | Ligand | Solvent | <i>t</i> (h) | Yield ^b (%) |
|---------------------|-----------------------|-----------|---------|--------------|------------------------|
| 1 | Pd(OAc) ₂ | L1 | Toluene | 24 | 27 |
| 2 | Pd(OAc) ₂ | L1 | THF | 24 | 77 |
| 3 | Pd(OAc) ₂ | L1 | DMF | 24 | 79 |
| 4 | Pd(OAc) ₂ | L1 | DMSO | 24 | 71 |
| 5 | Pd(OAc) ₂ | L1 | NMP | 24 | 82 |
| 6 | Pd(TFA) ₂ | L1 | NMP | 24 | 77 |
| 7 | Pd(acac) ₂ | L1 | NMP | 24 | 88 |
| 8 | Pd(acac) ₂ | L2 | NMP | 24 | 86 |
| 9 | Pd(acac) ₂ | L3 | NMP | 24 | 73 |
| 10 | Pd(acac) ₂ | L4 | NMP | 24 | 88 |
| 11 ^{c,d} | Pd(OAc) ₂ | L1 | NMP | 36 | 91 |
| 12 ^{c,e} | Pd(OAc) ₂ | L1 | NMP | 36 | 83 |
| 13 ^e | — | L1 | NMP | 24 | nd |
| 14 ^e | Pd(OAc) ₂ | — | NMP | 24 | nd |
| 15 ^d | — | — | NMP | 24 | nd |
| 16 ^{c,d,f} | Pd(OAc) ₂ | L1 | NMP | 36 | 79 |
| 17 ^g | Ni(acac) ₂ | L2 | MTBE | 24 | 67 |

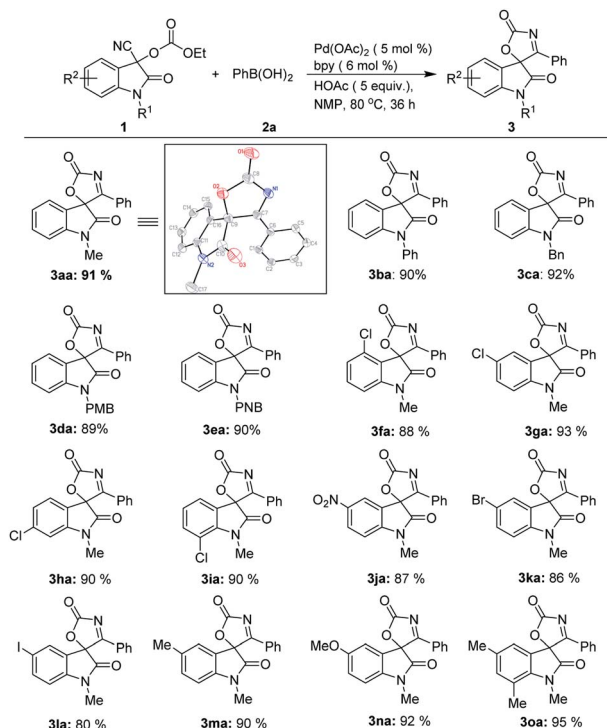
^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (10 mol%), ligand (12 mol%) and HOAc (10 equiv.) in solvent (1 mL) at 80 °C.

^b Isolated yields. ^c Pd(OAc)₂ (5 mol%) and bpy (6 mol%) were used.

^d HOAc (5.0 equiv.) was used. ^e Without HOAc. ^f **2a** (0.4 mmol) was used.

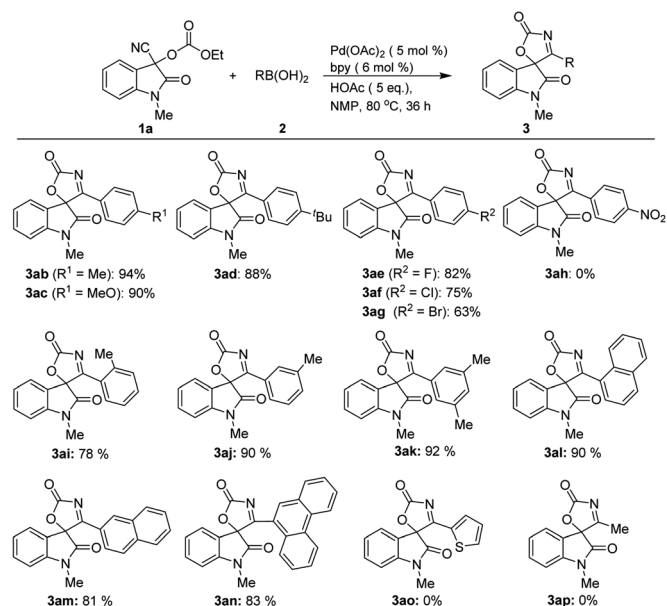
^g Ni(acac)₂ (10 mol%), **L2** (12 mol%) and Cs₂CO₃ (20 mol%) in MTBE (1 mL) at 110 °C. **L1**: 2,2'-bipyridine; **L2**: 4,4'-dimethyl-2,2'-bipyridine; **L3**: 5,5'-dimethyl-2,2'-bipyridine; **L4**: 1,10-phenanthroline.





Scheme 1 Substrate scope for preparation of spirooxindolyl oxazol-2(5H)-ones^a. ^aReaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), Pd(OAc)₂ (5 mol%), bpy (6 mol%), HOAc (5 equiv.) in NMP (1.5 mL) at 80 °C for 36 h. Yields shown are of isolated products. PMB = *p*-methoxybenzyl; PNB = *p*-nitrobenzyl.

with high yields. For examples, treatment of both α -naphthyl and β -naphthyl boronic acids with **1a** can deliver the corresponding products (**3al–3am**) in high yields under the



Scheme 2 Substrate scope with respect to boronic acids^a. ^aReaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), Pd(OAc)₂ (5 mol%), bpy (6 mol%), HOAc (5 equiv.) in NMP (1.5 mL) at 80 °C for 36 h. Yields shown are of isolated products.

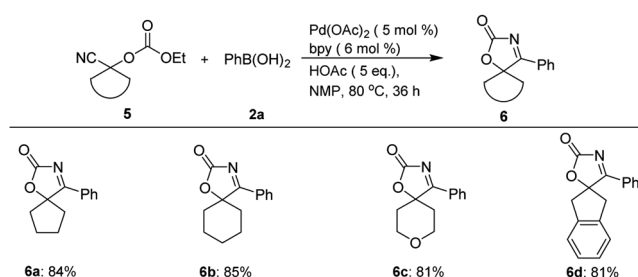
optimized reaction conditions, while 9-phenanthreneboronic acid gave spirooxindolyl product **3an** in 83% yield. However, hetero-aromatic boronic and alkyl boronic acid did not provided any desired products (**3ao–3ap**).

In addition, besides spirooxindolyl oxazol-2(5H)-one frameworks, this approach is also applicable to the construction of other spirocyclic frameworks incorporating oxazol-2(5H)-one unit *via* palladium-catalyzed tandem sequence (Scheme 3). For example, treatment of 1-cyanocyclopentyl ethyl carbonate **5a** with **2a** can furnish 4-phenyl-1-oxa-3-azaspiro[4.4]non-3-en-2-one **6a** in 84% yield, while six-membered-ring analogues delivered the corresponding six-membered ring fused spiro-products (**6b–6c**) in high yields. Cyanohydrin **5d** derived from 2-indanone can also serve as a suitable substrate for this tandem sequence, and provided the desired spiro-product **6d** in 81% yield.

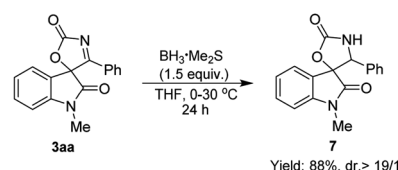
Finally, the synthetic utility of this Pd-catalyzed cyclization was demonstrated (Scheme 4). The reduction of **3aa** by using BH₃·SMe₂ readily gave spirooxindolyl product **7** bearing the oxazolidine unit in good yield with an excellent diastereoselectivity.

On the basis of these results and other processes involving the addition of arylpalladium species to nitrile,^{14,15} a plausible mechanism was illustrated in Scheme 5. First, the transmetalation of arylboronic acid by Pd(II) catalyst **A** generates arylpalladium species **B**. Then coordination of the nitrile provides intermediate **C**, which undergoes a carbopalladation of the cyano group to result in formation of the corresponding ketimine Pd(II) complex **D**. The intramolecular cyclization of the intermediate **D** to form palladium complex **E** which affords product and regenerates the Pd(II) catalyst.

In summary, we have demonstrated an efficient protocol for the synthesis of spirooxindolyl oxazol-2(5H)-ones *via* Pd(II)-catalyzed addition of arylboronic acids to nitriles. A diversity of

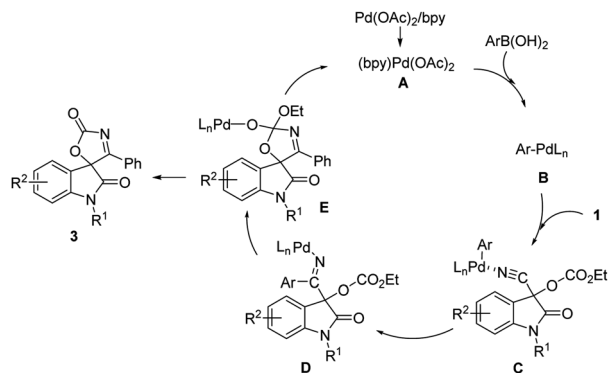


Scheme 3 Preparation of other spirocyclic frameworks^a. ^aReaction conditions: **5** (0.3 mmol), **2a** (0.9 mmol), Pd(OAc)₂ (5 mol%), bpy (6 mol%), HOAc (5 equiv.) in NMP (1.5 mL) at 80 °C for 36 h. Yields shown are of isolated products.



Scheme 4 Synthetic transformation.





Scheme 5 Proposed mechanism.

functionalized spirooxindolyl oxazol-2(5H)-ones can be prepared in good to high yields under the optimal conditions. Furthermore, by the virtue of this Pd-catalyzed sequence, other five- and six-membered ring fused spiro-oxazol-2(5H)-ones can be readily prepared in good yields. Further studies on the application of this synthetic method are currently under investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The NSFC (No. 21772063) and the Open Project of State Key Laboratory for Supramolecular Structure and Materials (sklssm2019016) are acknowledged. This research was supported by China Scholarship Council.

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