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Mn(III)-Mediated Radical Cyclization of *o*-Alkenyl Aromatic Isocyanides with Boronic Acids: Access to N-Unprotected 2-Aryl-3-cyanoindoles

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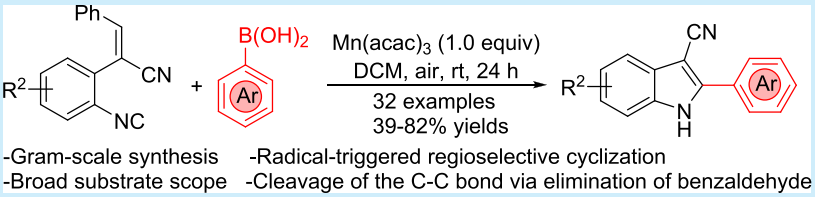

ABSTRACT: The synthesis of N-unprotected 2-aryl-3-cyanoindoles was realized via the Mn(III)-mediated radical cascade cyclization of *o*-alkenyl aromatic isocyanides with boronic acids. A possible mechanism involving a sequential intermolecular radical addition, intramolecular cyclization, and cleavage of the C−C bond under mild reaction conditions is proposed. Mechanism studies show that H_2O or O_2 might provide the oxygen source for the elimination of benzaldehyde.

The indole skeleton is a fundamental structure unit of numerous biologically active molecules and natural products.[1] Among them, 3-cyanoindole is a "privileged structure" that has excellent pharmacological properties, including IMPDH inhibition,[2] acetyl-CoA carboxylase inhibition,[3] HCV NS4B inhibition,[4] xanthine oxidase inhibition,[5] and estrogen receptor ligands[6] (Figure 1). Further, 3-

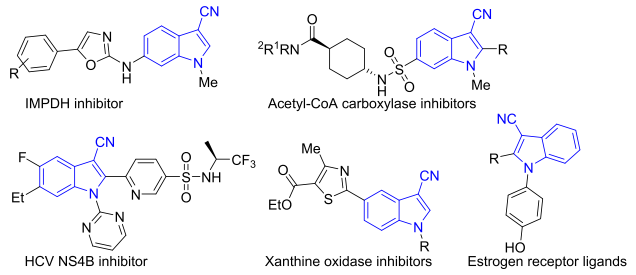

Figure 1. Representative biologically active compounds containing the 3-cyanoindole core.

cyanoindoles have applications as precursors for various drug syntheses.[7] Owing to their fascinating and important biological activities, various synthetic methodologies were developed over the years to construct these scaffolds.[8−10] The need to explore various efficient methodologies toward 3-cyanoindoles under mild conditions still remains.

The use of *o*-alkenyl aromatic isocyanides for the construction of N-heterocycles via base-mediated domino reactions,[11] transition-metal-catalyzed annulations,[12] and radical cyclization reactions[13,14] has been well-established. Notably, the radical cyclization of *o*-alkenyl aromatic isocyanides is an effective method to synthesize indole derivatives. In these transformations, *o*-alkenyl aromatic isocyanides are usually the radical acceptors reacting with heteroatom or carbon-centered radicals to generate the corresponding imidoyl radicals, which subsequently undergo intramolecular cyclization to eventually afford indole skeletons (Scheme 1a). Recently, a new strategy of indirect 6-*endo*-trig radical cyclization pioneered by Alabugin was developed for six-membered aromatic compounds following a sequential 5-*exo*-trig addition/3-*exo*-trig cyclization/ring expansion and C−C fragmentation process (Scheme 1b).[14a,b] Subsequently, Yu and co-workers and our research group achieved progress in the direct 6-*endo*-trig radical cyclization strategy of *o*-alkenyl aromatic isocyanides for the regiospecific synthesis of quinolines (Scheme 1b).[14c,d] Inspired by these results, we envisioned that 2-aryl-3-cyanoindoles can be constructed from the reaction of *o*-alkenyl aromatic isocyanides with arylboronic acids as aryl radical precursors through a sequential intermolecular radical addition, intramolecular cyclization, and cleavage of the C−C bond under suitable conditions. As a part of our research results on the synthesis of heterocyclic compounds,[14d,15] we reported the Mn(III)-mediated radical cyclization reaction of *o*-alkenyl aromatic isocyanides with

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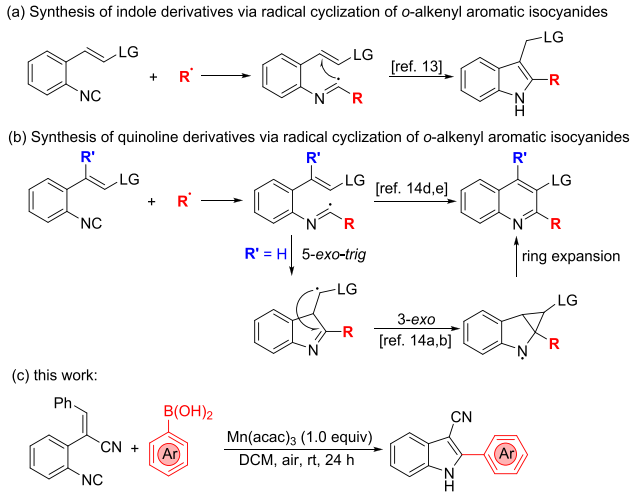
Scheme 1. Radical Cycloaddition of *o*-Alkenyl Aromatic Isocyanides

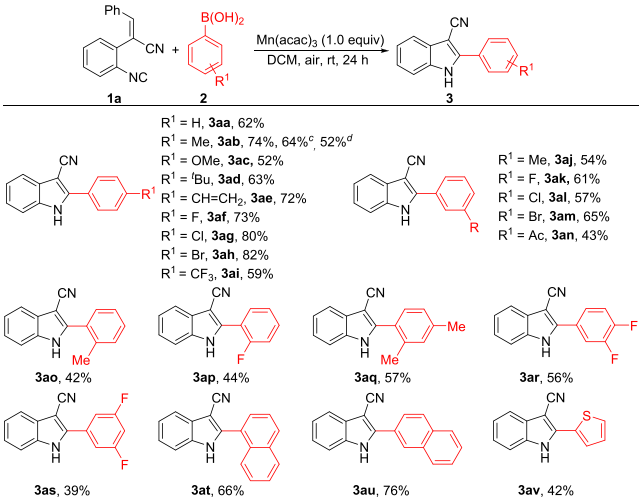


arylboronic acids to access 2-aryl-3-cyanoindoles under mild conditions.

Initially, the reaction of (*E*)-2-(2-isocyanophenyl)-3-phenylacrylonitrile **1a** and *p*-tolylboronic acid **2b** in the presence of 1.0 equiv of $Mn(acac)_3$ in CH_3CN in air was selected as the model reaction. The desired product **3ab** was isolated in 63% yield along with quinoline **4ab** in 12% yield (see SI, Table S1, entry 1). Further optimization of the solvents revealed that DCM was better suited than toluene, THF, 1,4-dioxane, DMSO, DMF, and DCE, giving a 74% yield of **3ab** with a 7% yield of **4ab** (see SI, Table S1, entries 2−8). Examination of the effect of the reaction temperature revealed that elevating the temperature was detrimental to the reaction efficiency (see SI, Table S1, entry 9). Next, lowering the amount of boronic acid to 2.5 equiv resulted in a diminished yield and selectivity (see SI, Table S1, entry 10). A similar yield with entry 7 was obtained increasing the amount of $Mn(acac)_3$ to 2.0 equiv (see SI, Table S1, entry 11). Finally, poor or no conversion was observed when $Mn(acac)_3$ was replaced by other catalysts such as $Mn(OAc)_3{\cdot}2H_2O$, $Mn(OAc)_2{\cdot}4H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $CuCl_2$, or $Co(acac)_3$ (see SI, Table S1, entries 12−16).

After establishing the optimized reaction conditions, the scope and generality of boronic acid **2** in the cascade cyclization reaction were explored (Scheme 2). It was found that electron-donating (Me, OMe, ^{t}Bu, CH=CH_2), halogen (F, Cl, Br), and electron-withdrawing substituents (CF_3) at the *para*-position of aryl boronic acids were all smoothly converted into indole products (**3ab**−**3ai**) in 52%−82% yields. The use of *ortho*- and *meta*-substituted aryl boronic acids was also compatible with these reaction conditions, and target products **3aj**−**3ap** were obtained in moderate to good yields. The disubstituted substrates were fully tolerated, furnishing target products **3aq**−**3au** in 39%−76% yields. Notably, the thiophene heterocycle worked well to provide a product **3av** in 42% yield. To further demonstrate the synthesized application of this cascade cyclization reaction, the gram-scale reaction of **1a** with **2b** was performed under the standard reaction conditions. The reaction proceeded smoothly to afford desired product **3ab** in 64% yield along with quinoline **4ab** in 12% yield. When the $Mn(acac)_3$ was reduced to 50 mol % in a pure O_2 atmosphere, we obtained **3ab** in 52% yield and **4ab** in 19% yield.

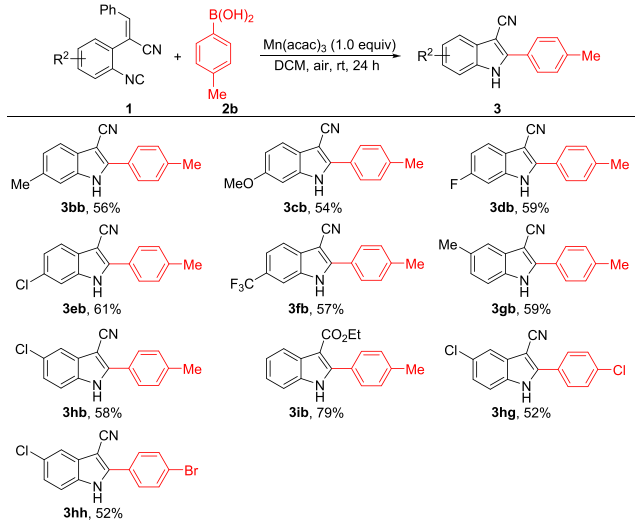
Scheme 2. Substrate Scope of Boronic Acid[a,b]



[a]Reactions were carried out using **1a** (0.2 mmol), **2** (0.6 mmol), and $Mn(acac)_3$ (0.2 mmol) in DCM (2 mL) at room temperature for 24 h in air. [b]Isolated yield. [c]Reaction was performed with 4.4 mmol of **1a**. [d]Reaction was performed with 4.4 mmol of **1a**.

We next explored the scope of *o*-alkenyl aromatic isocyanides under the standard conditions (Scheme 3). The

Scheme 3. Substrate Scope of *o*-Alkenyl Aromatic Isocyanides[a,b]



[a]Reactions were carried out using **1a** (0.2 mmol), **2** (0.6 mmol), and $Mn(acac)_3$ (0.2 mmol) in DCM (2 mL) at room temperature for 24 h in air. [b]Isolated yield.

functional groups such as methyl, methoxy, fluoro, chloro, and trifluoro methyl introduced at different positions of *o*-alkenyl aromatic isocyanides reacted smoothly with boronic acids. In all the cases, target products **3bb**−**3hb** were obtained in moderate yields. Substrate **1i** was also utilized for this transformation, and desired product **3ib** was isolated in 79% yield. Furthermore, boronic acids **2g** and **2h** also reacted with 4-Cl-substituted aromatic isocyanide **1o** to produce desired products **3hg** and **3hh** in 52% and 52% yields, respectively.

Boronic acids as radical precursors are widely applied in radical cascade cyclization in the presence of Mn salt.[16]

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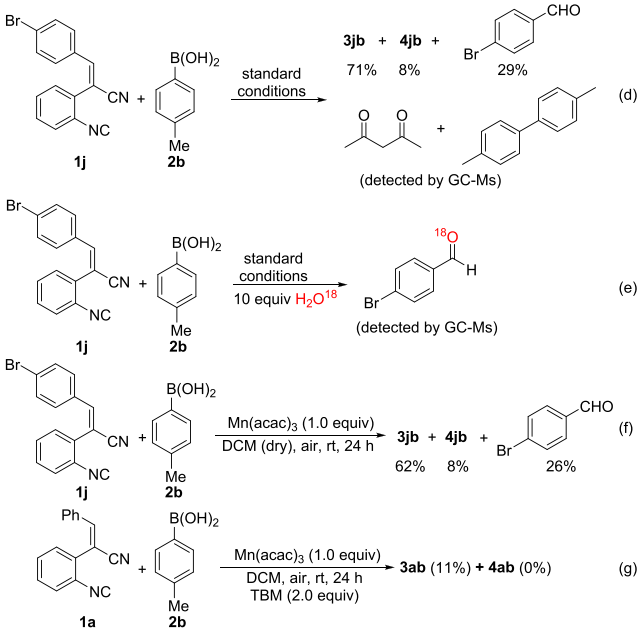
However, in the reported transformations, usually, the use of more than 2 equiv of the Mn salt was required for the corresponding reactions. Until recently, Lei's group reported a Mn(III)-catalyzed electrochemical assistance cascade cyclization reaction of N-substituted 2-arylbenzoimidazoles with alkylboronic acids.[16g] Note that 1 equiv of Mn salt was used to drive the reaction to completion in our reported experimental results. To gain mechanistic insight into this transformation, some control experiments were designed and investigated (Schemes 4, S1, and S2). First, the reaction was performed in

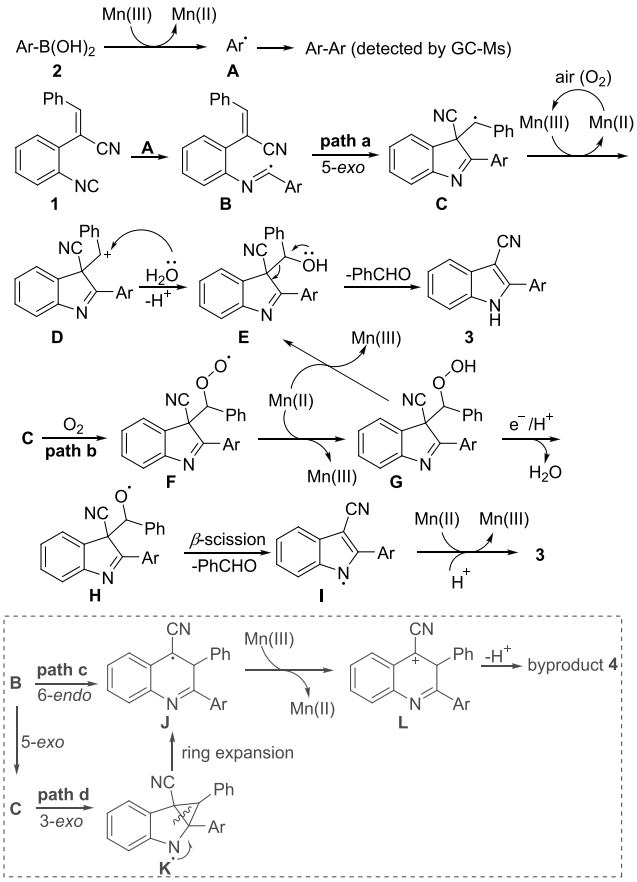
Scheme 4. Control Experiments



an inert Ar atmosphere, resulting in a drastic decrease in the yield. When the reaction proceeded in pure O_2 atmosphere or in Ar atmosphere in the presence of 2 equiv of $Mn(acac)_3$, the products **3ab** and **4ab** were isolated in comparable yields (Scheme S1). Therefore, we hypothesized that the radical cyclization reaction might be related with the presence of air (O_2 from air). As far as we know, β-dicarbonyl compounds are effective radical acceptors,[17] but the adduct of the aryl radical with the acac ligand of $Mn(acac)_3$ was not observed in this transformation. In addition, we analyzed the 4-bromobenzaldehyde coproduct in 29% yield in the coupling of **1j** and **2b**. Meanwhile, the acetylacetone and 4,4′-dimethylbiphenyl were already detected by GC-MS (Scheme 4d). Next, a H_2O^{18}-labeling experiment has been carried out (Scheme 4e). The observed ^{18}O incorporation into 4-bromobenzaldehyde was detected by GC-Ms. Next, the reaction was performed in DCM (dry) and resulted in a diminished yield along with 4-bromobenzaldehyde in 26% yield (Schemes 4f and S1). These results imply that the oxygen atom of 4-bromobenzaldehyde might come from H_2O or O_2. The reaction was inhibited with a dramatic decrease of the yield when *tert*-butylmercaptan (TBM) was used as the radical inhibitor under the standard conditions.[18] Radical inhibition experiments suggested a possible radical process for this reaction (Schemes 4g and S2).

On the basis of our preliminary results, a plausible mechanism was proposed (Scheme 5). The reaction is initiated by a single-electron transfer from both boronic acids **2** and $Mn(acac)_3$ to afford an aryl radical **A**, which undergoes an

Scheme 5. Plausible Mechanism



intermolecular addition to *o*-alkenyl aromatic isocyanide **1** to deliver an imidoyl radical **B**. Subsequently, a 5-*exo*-trig cyclization involving an intramolecular radical addition generates a radical intermediate **C**, providing two possible pathways for the formation of 2-aryl-3-cyanoindoles. Radical intermediate **C** was oxidized to a carbocation intermediate **D** by the Mn(III)/air (O_2).[16] Next, the nucleophilic attack of H_2O on the carbocation intermediate **D** and deprotonation deliver an intermediate **E**. Finally, the cleavage of the C−C bond via elimination of benzaldehyde gives the desired 2-aryl-3-cyanoindoles (path a). Another pathway involves molecular oxygen addition to furnish a peroxy radical **F**, which undergoes a reduction by Mn(II) to afford an alkoxy radical **H**.[19] Subsequent β-scission of the alkoxy radical **G** is followed by extrusion of benzaldehyde to produce a radical intermediate **I**. Finally, product **3** is obtained by the single-electron oxidation and protonation from intermediate **I** (path b). In addition, the hydroperoxide intermediate **G** could be reduced by Mn(II) to generate intermediate **E**.[20] Meanwhile, the radical intermediate **B** undergoes an indirect or direct 6-*endo*-trig cycloaddition to generate an intermediate **J**.[14d] The byproduct **4** is eventually released by the single-electron oxidation of **L** by Mn(III) followed by deprotonation (paths c and d).

In summary, a Mn(III)-mediated radical cascade cyclization of *o*-alkenyl aromatic isocyanides with boronic acids to synthesize N-unprotected 2-aryl-3-cyanoindoles is reported herein. The reaction involves a sequential intermolecular radical addition, intramolecular cyclization, and cleavage of the C−C bond. The radical cascade cyclization reaction has attractive features such as synthetic simplicity, broad scope of

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substrates, and excellent functional group compatibilities under mild reaction conditions. Furthermore, the synthetic utility was showcased by gram-scale synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01979.

Experimental procedures, mechanistic experiments, and characterization data for all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3av**, **3bb**−**3ib**, **3hg**, **3hh**, and **4ab** (ZIP)

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Notes

The authors declare no competing financial interest.

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