Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901300

Link to VoR: http://dx.doi.org/10.1002/adsc.201901300

10.1002/adsc.201901300

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Mn(III)-Mediated Regioselective 6-*endo*-trig Radical Cyclization of *o*-Vinyl Arylisocyanides to Access 2-Funtionalized Quinolines

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A Mn(III)-mediated radical cyclization reaction of *o*-vinyl arylisocyanides and arylboronic acids or diphenylphosphine oxides to access various 2-funtionalized quinolines under mild conditions was developed. With the introduction of radical stabilizing substituents (e.g. aryl and methyl group) on vinyl group, this reaction provides a regiospecific 6-*endo*-trig radical cyclization of *o*-vinyl arylisocyanides, giving a number of structurally unique and biologically potential 2-functionalized quinoline derivatives.

Keywords: Mn(III)-mediated; regioselective; 6-*endo*-trig radical cyclization; 2-funtionalized quinolines; *o*-vinyl arylisocyanides

Isocyanides, owing to their unique structures and reactivities, have been applied as versatile building blocks for the construction of nitrogen-containing compounds, especially amides and heterocycles, which are of great significance in biological and pharmaceutical chemistry.[1] For instance, isocyanide-involved multicomponent reactions,[2] such as Passerini and Ugi reactions, provide rapid access to a large array of druglike molecules.[3] Over the past decades, transition-metal-catalyzed isocyanide insertion chemistry have been well developed.[4] Notably, *ortho*-functionalized aromatic isocyanides have been applied as valuable synthons in radical cascade reactions for the synthesis of *N*-heterocycle scaffolds, due to their capability to incorporate various substituents simultaneously with the construction of ring systems, showing remarkable operational simplicity and atom-/step-economy.[5] For instance, a number of *ortho*-functionalized aromatic isocyanides have been employed as radical acceptors reacting with heteroatom (P, S, Si, *etc*.)- or carbon (aryl or alkyl)-centered radicals to generate corresponding imidoyl radicals, which subsequently undergo intramolecular cyclization after addition to their adjacent functionalities to eventually afford various *N*-heterocycles, including phenanthridines,[6] quinolines,[7] quinoxalines,[8] benzimidazoles,[9] benzothiazoles,[10] benzoselenazoles,[11] *etc* (Figure 1).

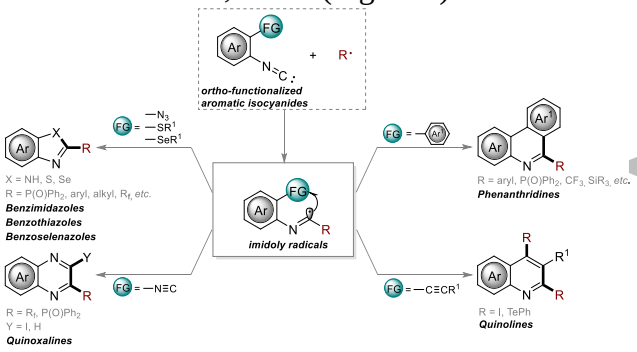

Figure 1. Radical Cascade Cyclization Involving *ortho*-Functionalized Aromatic Isocyanides.

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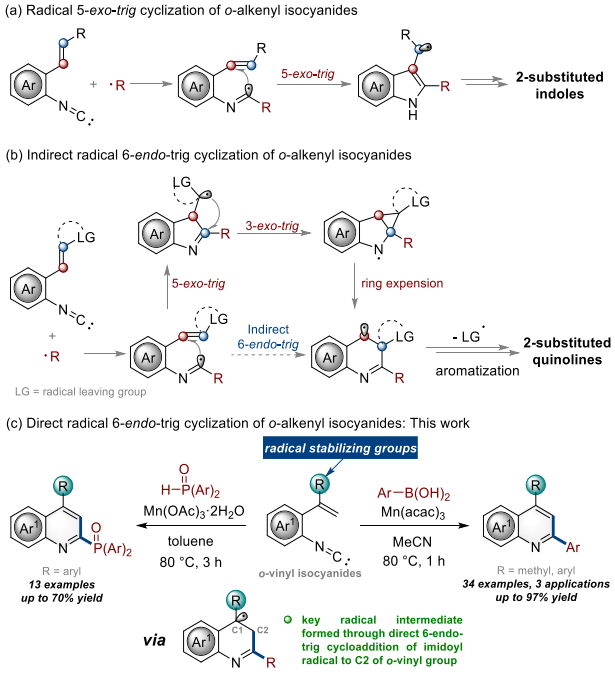
Unlike the above-listed radical cycloadditions, as for *o*-alkenyl arylisocyanides, there are two possible cyclization pathways according to Baldwin's rules, *i.e.*, 5-*exo*-trig and 6-*endo*-trig, to deliver corresponding *N*-heterocyclic scaffolds (*i.e.*, indoles and quinolines), respectively. However, on the basis of the previous reports,[12] 5-*exo*-trig radical cyclization seems more stereoelectronically favored and kinetically preferred comparing with 6-*endo*-trig cyclization. As a result, the formation of five-membered indole rings is often observed in radical cyclization reactions of *o*-alkenyl arylisocyanides (Scheme 1a). For example, Ogawa and coworkers synthesized bisthiolated indoles *via* 5-*exo*-trig radical cyclization from *o*-ethenyl arylisocyanides with disulfide reagents.[13] Afterwards, Studer *et al* constructed mono- and bis-trifluoromethylated indoles by adjusting the substituents on *o*-alkenyl groups from *o*-alkenyl arylisocyanides and Togni's reagent.[14] Furthermore, the photoredox synthesis of 2-phosphinoylindoles though 5-*exo*-trig radical annulation/hydrogen atom transfer (HAT) process was disclosed by Yang's group.[15] Very recently, Reiser's group utilized Br-/OMe-group promoted umpolung electron transfer to synthesize a series of 2-substituted indole-3-glyoxylates.[16]



Scheme 1. Radical Cycloaddition of *o*-Alkenyl Arylisocyanides.

In comparison of 5-*exo* cyclization, 6-*endo* ring closure seems inaccessible from the aspect of stereoelectronic and kinetic control. While, the indirect 6-*endo*-trig radical cyclization was reported by Alabugin's group[17] and Shi's group[18], respectively, through a domino sequence consisting of 5-*exo*-trig addition/3-*exo*-trig cyclization/ring expansion (Scheme 1b). Despite those significant progress, the direct 6-*endo*-trig radical cyclization strategy of *o*-alkenyl arylisocyanides for regiospecific synthesis of quinolines remains in demand. We hypothesized that the introduction of a radical stabilizing substitution (*e.g.* phenyl) on C1 position of *o*-vinyl group in arylisocyanide might stabilize the key radical intermediate rendering the direct 6-*endo*-trig cycloaddition of imidoyl radical to the terminal C2 of *o*-vinyl group (Scheme 1c). Herein, we reported a Mn(III)-mediated regioselective 6-*endo*-trig radical cyclization of C1 aryl/methyl-modified *o*-vinyl arylisocyanides with arylboronic acids or diphenylphosphine oxides to access 2-funtionalized quinolines under mild conditions.

Results and Discussion

Diverse methodologies have been established toward the synthesis of 2-aryl substituted quinoline derivatives since 1800s, among which, the representative methods approximately include classical name reactions,[19] A^3 coupling reactions,[20] dehydrogenative coupling of aminobenzyl alcohols and amines,[21] and transition-metal-catalyzed cross-dehydrogenative coupling (CDC).[22] Although they can provide easy accesses to targets, the development of remarkably efficient and practical strategies though radical cascade cyclization remains highly desirable. In 2012, Chatani and coworkers disclosed that with the oxidation of Mn(III) salts arylboronic acids could generate aryl radical for the synthesis of phenanthridines.[23] Afterward, the generation of aryl radical form arylboronic acids to initiate cascade cyclization of isocyanides for the synthesis of functionalized heterocycles has also been reported.[9-10, 24] We initiated this study by establishing optimal experiment conditions using the model reaction of 1-isocyano-2-(1-phenylvinyl)benzene **1a** with phenylboronic acid **2a** in the presence of manganese (III) salts. After extensive screening of various reaction parameters including catalyst loadings, solvents, temperature, *etc.*, the

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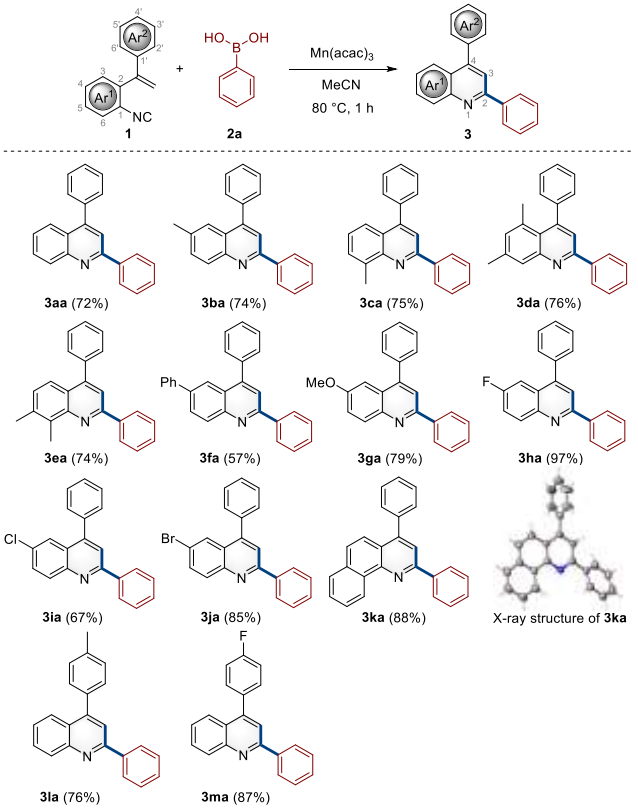
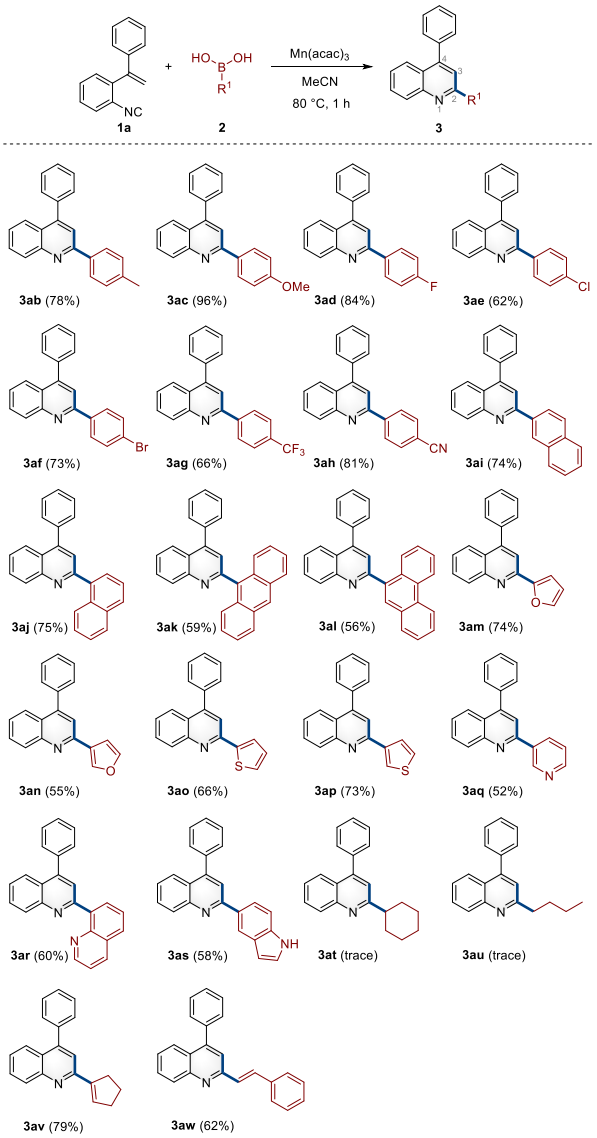
optimized reaction conditions were established as follows: **1a** (0.2 mmol), **2a** (2.0 equiv), and $Mn(acac)_3$ (2.0 equiv) were mixed in MeCN (2 mL) at 80 °C for 1 h (see the Supporting Information for more details).



Scheme 2. Substrate Scope of Isocyanides.[a] [a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and $Mn(acac)_3$ (0.4 mmol) in MeCN (2 mL) at 80 °C for 1 h. Isolated yields were given based on substrate **1**.

With the optimized reaction conditions established, we firstly explored the substrate scope of arylisocyanides **1**, which were synthesized though chemoselective *ortho*-alkenylation of anilines (see Supporting Information for synthetic procedure), and the results were illustrated in Scheme 2. As it can be seen, a broad range of *o*-(1-phenylvinyl)arylisocyanides **1** bearing different electron-donating groups (4-Me, 6-Me, 3,5-dimethyl, 5,6-dimethyl, 4-Ph, and 4-MeO) on Ar^1 rings could react smoothly with **2a** to afford the corresponding 2-phenyl substituted quinolines **3ba**-**3ga** in 57-79% yields. Meanwhile, **1** bearing electron-withdrawing groups (−F, −Cl, and −Br) on 4-position of Ar^1 rings also performed well giving products **3ha**-**3ja** in yields of 97%, 67%, and 85%, respectively. No obvious electronic effect was observed when different substituents were present on Ar^1 rings. Additionally, 1-isocyano-2-(1-phenylvinyl)naphthalene (**1k**) was also a well-suitable substrate resulting in the successful synthesis of fused framework benzo[*h*]quinoline **3ka** in high yield (88%). Furthermore, **1l** and **1m**, with −Me and −F groups on 4-position of Ar^2 rings, could also react with **2a** smoothly to provide the corresponding products **3la** and **3ma** in good yields (76% and 87%). Among the target products, the structure of **3ka** was further confirmed by X-ray diffraction.[25]



Scheme 3. Substrate Scope of Boronic Acids.[a] [a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), and $Mn(acac)_3$ (0.4 mmol) in MeCN (2 mL) at 80 °C for 1 h. Isolated yields were given based on substrate **1a**.

We then continued to evaluate the substrate scope of boronic acids **2**. As it can be seen in Scheme 3, phenylboronic acids bearing electron-

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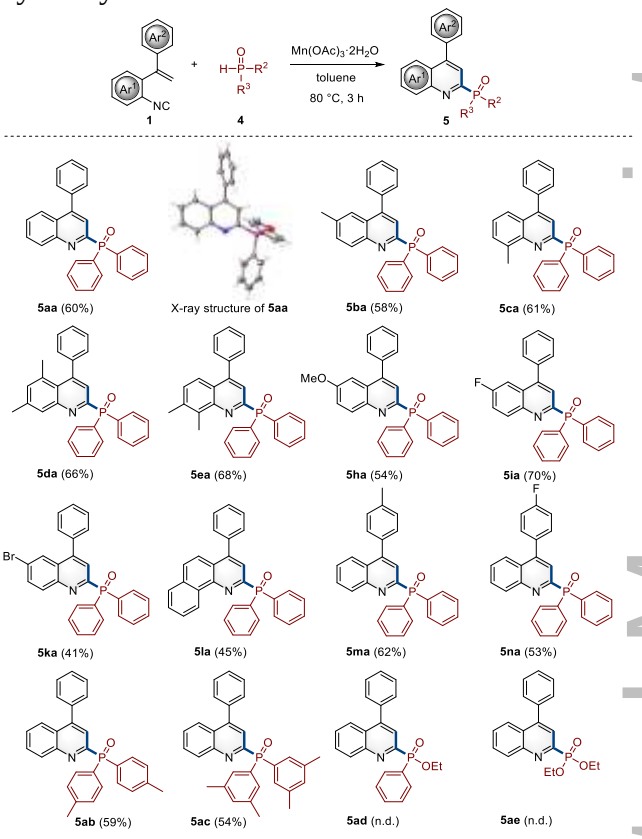
donating and electron-withdrawing groups on *para*-position were well tolerated affording the corresponding products **3ab**-**3ah** in moderate to excellent yields (62-96%). Boronic acids with fused arenes, including 2-naphthyl, 1-naphthyl, 9-anthracenyl, and 9-phenanthrenyl, were also compatible under the standard conditions (**3ai**-**3al**). Heteroarenes substituted boronic acids, such as 2-furanyl-, 3-furanyl-, 2-thienyl-, 3-thienyl-, 3-pyridyl-, 8-quinolinyl-, 5-indolyl-substituted boronic acids **2m-2s**, were converted into the corresponding quinoline derivatives **3am**-**3as** in comparable yields as well. However, cyclohexyl and *n*-butyl substituted boronic acids (**2t** and **2u**) only gave trace amount of desired products **3at** and **3au**, demonstrating that alkylboronic acids have relatively poor reactivities in this 6-*endo*-trig radical annulation.[24b] Besides, two alkenyl bronic acids were further evaluated under the standard conditions to afford the corresponding 2-alkenylquinolines **3av** and **3aw** in yields of 79% and 62%.

It is well known that organophosphorus compounds occupy an important position in biochemistry, pharmaceutical chemistry, material science, and organic synthesis, where phosphorus substituents modify biological responses, medicinal properties, and material functions or act as ligands of transition metals.[26] In light of the significance of these compounds, the development of efficient methods for C-P bond construction attracts continuous interests.[27] It has been reported that phosphorus centered radicals can be generated from phosphine oxides *via* homolytic cleavage of H-P bond in the presence of Mn(III) salts.[9-10, 28] To further expand the application of this protocol, the reactions of *o*-vinyl arylisocyanides **1** with diaryl phosphine oxides **4** in the presence of Mn(III)-salt were conducted. To our delight, a number of 2-phosphoryl quinolines **5** were successfully synthesized by using $Mn(OAc)_2{\cdot}2H_2O$ as oxidant at 80 °C for 3 h (Scheme 4, also see Supporting Information for details). A diversity of *o*-vinyl arylisocyanides **1** bearing electron-donating or electron-withdrawing groups on Ar^1 or Ar^2 ring reacted efficiently with diphenyl phosphine oxide **4a** to furnish the corresponding products (**5aa**-**5na**) in moderate to good yields. Additionally, 4-methyl, 3,5-dimethyl substituted diarylphosphine oxides (**5b** and **5c**) were also well tolerated, giving products **5ab** and **5ac** with satisfactory yields. Ethyl phenylphosphinate (**4d**) and dimethyl *H*-phosphonate (**4e**) were also employed was substrate, however, they failed to afford desired products (**5ad** and **5ae**). The poor reactivities of alkyl phenylphosphinate and dialkyl *H*-phosphonates might be due to their higher theoretical bond dissociation energies (BDE) of the P-H bonds.[29] Notably, all the synthesized 2-phosphoryl quinolines **5** are new compounds. Among them, the structure of **5aa** was confirmed by X-ray diffraction.[25]



Scheme 4. Substrate Scope of 2- Phosphoryl-Substituted Quinolines. [a] [a] Reaction conditions: **1a** (0.2 mmol), **4** (0.4 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (0.4 mmol) in toluene (2 mL) at 80 °C for 1 h. Isolated yields were given based on substrate **1**. [b] n.d. = not detected.

To demonstrate the synthetic utility of our strategy, a gram-scale experiment toward 2,4-diphenylquinoline (**3aa**) was carried out. We were delighted to isolate the product **3aa** in 70% yield (Scheme 5a). The practical applicability of this methodology was further extended to the synthesis of biologically active quinoxaline derivatives. As shown in Scheme 5b, the antifungal reagent (**3na**), anticancer reagent (**3ke**), and a DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenger (**3kb**)[30] were synthesized from

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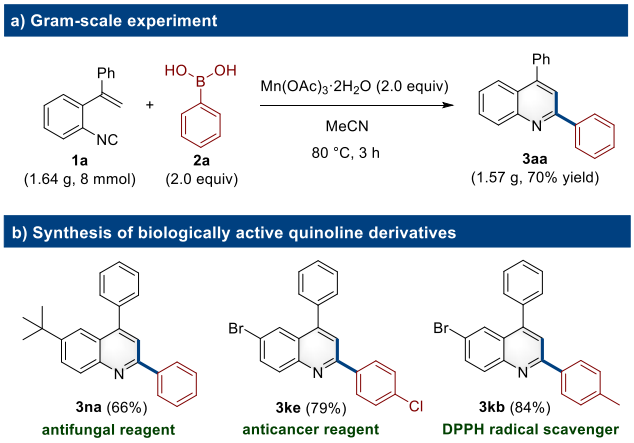
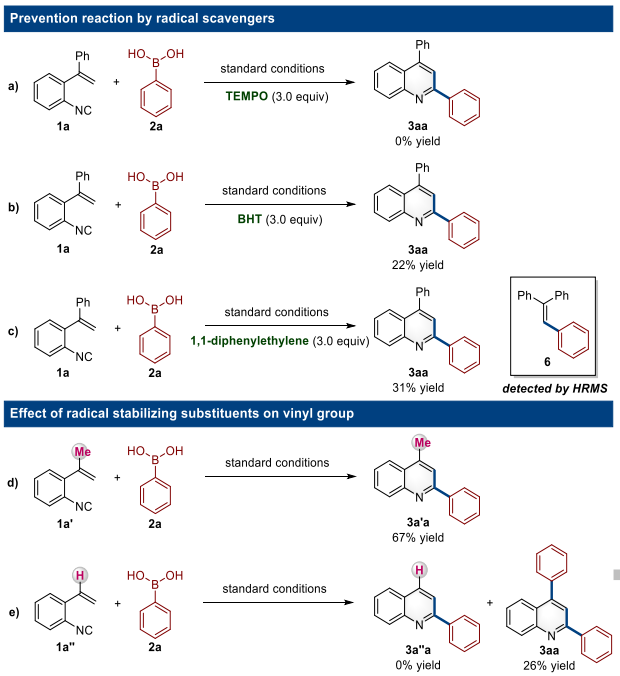
the corresponding *o*-vinyl arylisocyanides and boronic acids in ideal yields (66-84%).



Scheme 5. Synthetic Utility and Applicability.

To gain a deeper mechanistic insight into the reaction process, a series of control experiments were carried out (Scheme 6). When radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)-oxidanyl, BHT (2,6-di-*tert*-butyl-4-methylphenol), and 1,1-diphenylethylene, were added to the model reaction under standard conditions, a significant loss in yield of **3aa** was observed in each case (Scheme 6a-c), suggesting that this transformation might involve a radical process. Notably, an adduct **6** was detected in the control experiment with 1,1-diphenylethylene, indicating that phenyl radical was generated under the standard conditions (Scheme 6c). In addition, when the radical stabilizing substituent on *o*-vinyl group was changed from phenyl to methyl, the corresponding quinoline product **3a'a** was obtained in lower yield (62%, Scheme 6d); when it was altered to H, the reaction of 1-isocyano-2-vinylbenzene (**1a''**) with phenylboronic acid **2a** unexpectedly gave **3aa** rather than desired product **3a"a** (Scheme 6e). In this case, **3aa** might be generated *via* homolytic aromatic substitution (HAS) of **3a"a** by phenyl radical.[31] These results reflected that the radical stabilizing substituents on *o*-vinyl group played a vital role in this reaction.



Scheme 6. Control Experiments.

The plausible mechanism for this reaction was further investigated by DFT calculations. As shown in Figure 2, two pathways (*i.e.* 5-*exo*-trig and 6-*endo*-trig) are possible for the radical addition step. Firstly, the phenyl radical attacks the terminal carbon of isocyano group in **1a** affording the imidoyl radical intermediate **A** *via* the transition state **TS1**. Then, imidoyl radical **A** could add to C1 or C2 of *o*-vinyl group rendering corresponding cyclic radical intermediate **B'** or **B**. For the 5-*exo*-trig pathway, the carbon could attack the C1 to form the five-membered ring radical intermediate **B'** *via* **TS2'**. As for the 6-*endo*-trig pathway, the radical attacked the C2 to generate six-membered ring radical intermediate **B** *via* **TS2**. After calculation, it is obvious that the relative Gibbs free energy of **B** (-66.1 kJ/mol) is much lower than that of **B'** (-45.3 kJ/mol). Hence, the radical 6-*endo*-trig pathway would be more energetically favorable in thermodynamics, which is consistent with our experimental results. However, based on the computational results, the 5-*exo*-trig pathway could not be completely excluded and might contribute to the observed selectivity as well as a minor "invisible" pathway.

In order to verify the significant role of phenyl substituent in the 6-*endo*-trig cyclization process, the calculations of the analogue with H substituent have been performed as a contrast. The results show the barriers for the generation of 6-*endo*-trig

cyclization becomes higher than that of 5-*exo*-trig cyclization respectively (see the Supporting Information for more details), indicating the phenyl substituent favors formation of radical center for the 6-*endo*-trig cyclization product.[12c, 32]

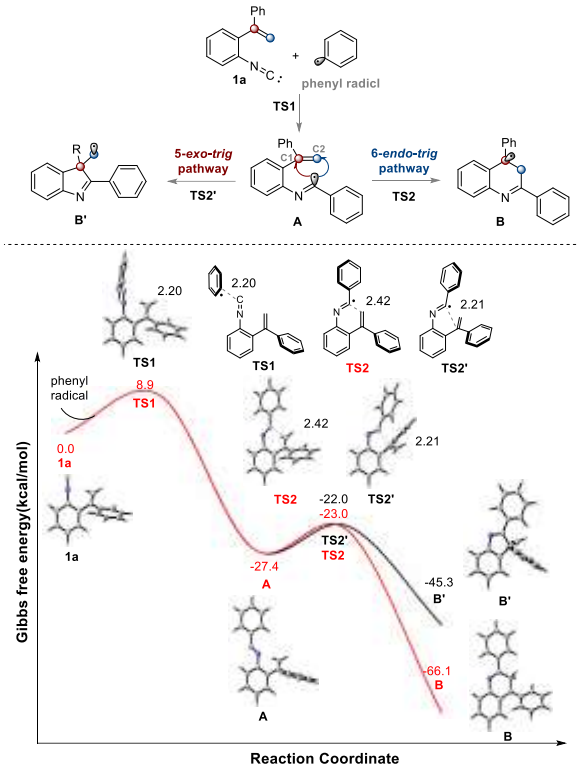
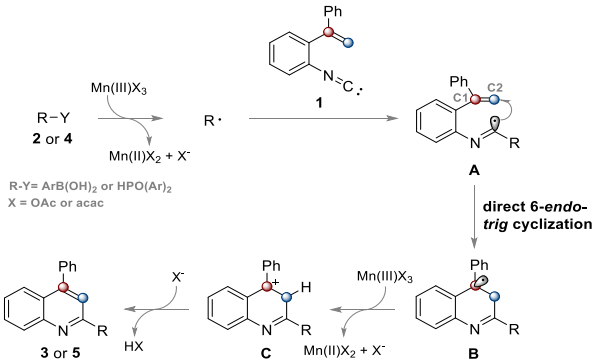


Figure 2. The Free Energy Profiles (Unit: Å).[a) a)] All the calculations in the manuscript were calculated at the M06-2X/6-31G(d,p) level. And the solvent effect has been also considered using self-consistent reaction field (SCRF) polarizable continuum model, in which acetonitrile is employed as solvent.

Based on the experimental results and previous reports,[23-24] a plausible mechanism was proposed (Scheme 7). Initially, the radical R· was *in situ* generated from radical precursors (arylboronic acids or diarylphosphine oxides) in the presence of Mn(III) salts. Then R· underwent a chemoselective addition to isonitrile rather than vinyl group giving the corresponding imidoyl radical intermediate **A**.[33] Subsequently, radical **A** underwent direct 6-*endo*-trig cycloaddition to C2 of *o*-vinyl group to render the cyclic radical intermediate **B**. Single electron oxidation of **B** by Mn(III) salts led to the formation of cationic intermediate **C**. Finally, 2-functionalized quinolines **3** or **5** were obtained after deprotonation, where the anions in manganese salts might act as Lewis bases to abstract protons.



Scheme 7. Proposed Mechanism.

In conclusion, we have developed a Mn(III)-mediated regioselective 6-*endo*-trig radical cyclization reaction of *o*-vinyl arylisocyanides and arylboronic acids or diarylphosphine oxides to synthesize a variety of 2-funtionalized quinolines. This method not only provides a practical and efficient approach to structurally unique and biologically potential 2-functionalized quinoline derivatives, but also discloses an unprecedented insight into the direct 6-*endo*-trig radical cyclization mechanism which is complementary to the radical cascade cyclization of *o*-vinyl arylisocyanides.

Experimental Section

General Procedure: In a 5 mL flask, to the solution of *o*-vinyl 1-isocyano-2-(1-phenylvinyl)benzene **1a** (41 mg, 0.2 mmol) in MeCN (2 mL, 0.1 M) was added phenylboronic acid **2a** (49 mg, 0.4 mmol) and $Mn(acac)_3$ (141 mg 0.4 mmol). The mixture was allowed to stir at 80 °C for 1 h and monitored by TLC. After **1a** was completely consumed, the reaction mixture was cooled to room temperature and then filtered through Celite. The residue was washed with CH_2Cl_2 (5 mL × 2). The filtrates were combined, and the solvents were removed under reduced pressure. The crude product was finally purified by column chromatography with petroleum ether/ethyl acetate as an eluent to afford the desired product **3aa**.

Acknowledgements

We acknowledge the financial support from National Natural Science Foundation of China (21501010, 21971224), China Postdoctoral Science Foundation (2019M652561), Key Research Projects of Universities in Henan Province (20A150006, 20B150021), Henan Province Young Talents Elevation Program (2019HYTP023) and Hunan Provincial Key Laboratory of Materials Protection for Electric Power and Transportation (2019CL03).

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10.1002/adsc.201901300

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