Heterocycle Synthesis

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Modular Synthesis of Phenanthridine Derivatives by Oxidative Cyclization of 2-Isocyanobiphenyls with Organoboron Reagents**

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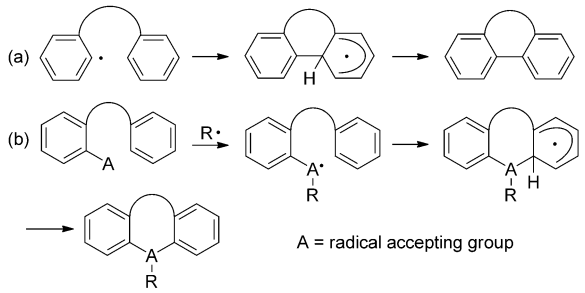
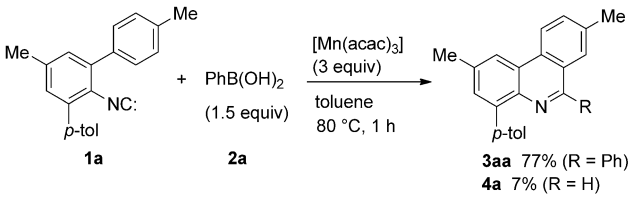
Homolytic aromatic substitution (HAS) by an aryl radical and related processes[1,2] have recently attracted considerable attention as alternatives to transition-metal-catalyzed C–H bond arylation[3] for the construction of biaryl motifs. These HAS reactions have several advantages over the conventional methodology, including unique chemo- and regioselectivity as well as avoiding the requirement for precious-metal catalysts and ligands. Mechanistically, it has been proposed that the HAS reaction proceeds by the addition of an aryl radical to an arene, followed by the oxidative re-aromatization of the resulting cyclohexadienyl-type radical.[1,2] Although there has been only limited application of the intermolecular HAS to the synthesis of biaryl systems because of issues associated with low levels of efficiency and selectivity, the application in intramolecular settings largely alleviates these issues and allows for straightforward access to biaryl moieties embedded in polycyclic system (Scheme 1a). It was envisioned that the utility of this intramolecular HAS could be considerably expanded if a radical generated by the intermolecular addition of an external radical could undergo a HAS type cyclization (Scheme 1b). Herein, we report the development of a reaction guided by this hypothesis for the synthesis of phenanthridine framework.[4]



Scheme 1. C–H bond functionalization by intramolecular homolytic aromatic substitution, see text for details.

To realize the intramolecular HAS reaction depicted in Scheme 1b, an isocyano group was selected as a radical acceptor (A in Scheme 1b) because intermolecular radical addition to isocyanide, forming an imidoyl radical, occurs at a sufficiently fast rate to maintain the efficiency of the overall process.[5] Furthermore, the potential for an imidoyl radical intermediate to participate in a HAS reaction is partly supported by the report that a fragment radical derived from an initiator (such as, AIBN) can induce the radical cyclization of isocyanide by a HAS process.[6]

After examining several radical precursors (see Supporting Information for details), the phenyl radical generated from phenylboronic acid and a manganese salt[7] was identified as promoting the desired cyclization (Scheme 2). Thus, the reaction of isocyanide **1a** with phenylboronic acid (**2a**) in the presence of $[Mn(acac)_3]$ (3 equiv) gave phenanthridine **3aa** in 77% yield under relatively mild conditions (80 °C, 1 h).[8] The only byproduct detected in the reaction mixture was phenanthridine **4a** (7%).[9] The use of more than two equivalents of the manganese salt was required for the complete conversion of **1a**.[10] This result is particularly relevant to the reaction mechanism.



Scheme 2. Manganese(III) mediated annulation of **1a** with **2a**.

As revealed in Table 1, a broad range of arylboronic acids were successfully coupled with isocyanide **1b** to give the corresponding phenanthridine bearing substituents adjacent to the ring nitrogen atom.[11] Ethers, esters, fluorides, chlorides, and bromides are readily tolerated (entries 2–6).[12] A sterically hindered 2-tolyl group was also incorporated without significant loss in the yield (entry 7). Fused arene and heteroaromatic systems, including an indole, a pyridine, and a thiophene, were also compatible with the reaction conditions (entries 8–11), which represented a significant outcome

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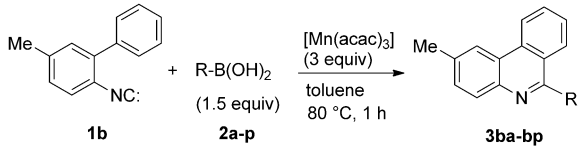
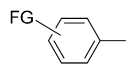
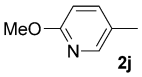
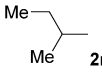
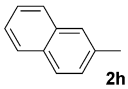
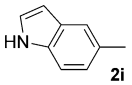
Table 1: Scope of boronic acid.

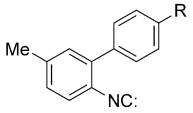
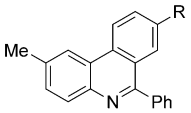
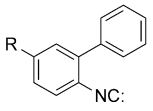
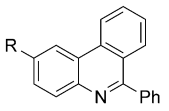
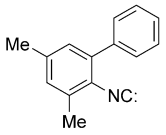
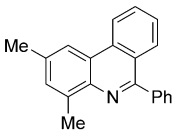
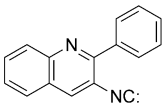
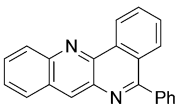
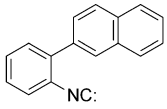
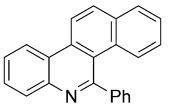
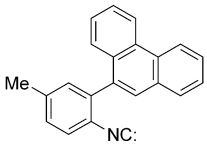
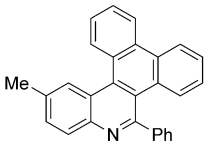


1b 2a-p 3ba-bp

Entry	R	Yield [%][a]	Entry	R	Yield [%][a]
1–7			10	 **2j**	68
1	FG = H (**2a**)	84	11	 **2k**	59
2	4-OMe (**2b**)	84	12[c,d]	$Me(CH_2)_3$— **2l**	59
3	4-CF_3 (**2c**)	74	13[c,d]	$BrCH_2(CH_2)_5$— **2m**	54
4	4-CO_2Me (**2d**)	63	14	 **2n**	72
5	4-Br (**2e**)	84	15[e]	 **2o**	76
6	4-Cl (**2f**)	72	16[c,f]	 **2p**	67
7	2-Me (**2g**)	76			
8	 **2h**	59			
9[b]	 **2i**	49			

[a] Yield of isolated product based on **1b**. [b] Run for 2 h. [c] Boronic acid (3 equiv) was used. [d] Run for 24 h. [e] Run for 15 h. [f] Run for 3 h.

Table 2: Scope of the annulation of isocyanides with **2a**.

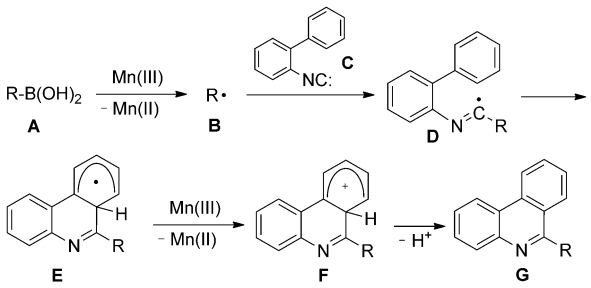
Entry	Isocyanide	Product[a]
1	 R = H **1b**	 **3ba** 84%
2	R = F **1c**	**3ca** 73%
3	R = OMe **1d**	**3da** 68%
4	 R = Cl **1e**	 **3ea** 72%
5	R = F **1f**	**3fa** 76%
6	 **1g**	 **3ga** 72%
7[b]	 **1h**	 **3ha** 65%
8	 **1i**	 **3ia** 63%
9[b]	 **1j**	 **3ja** 51%

[a] Yield of isolated product based on **1**. [b] Run for 2 h.

given the utility of these substructures in medicinal chemistry. Notably, alkyl boronic acids were found to be suitable coupling partners. Pleasingly, primary, branched, and cyclic alkylboronic acids uniformly produced the corresponding phenanthridine derivatives (entries 12–16). It is worthy of note that a bromoalkyl moiety remained intact under these conditions, demonstrating the mild nature of the reaction conditions (entry 13).

The cyclocoupling method was also successfully applied to a variety of different 2-isocyanobiaryl compounds, which can themselves be readily prepared from the parent anilines (Table 2). Electronically and sterically different isocyanides underwent annulation with **2a** successfully (Table 2, entries 2–6). The method was readily applied to the synthesis of 1,5-naphthyridine ring system by using heteroaryl isocyanide **1h** (Table 2, entry 7). When an isocyanide bearing a 2-naphthyl group was used, the cyclization occurred exclusively at the 1-position to furnish **3ia**, with none of the 3-position regioisomer being detected (Table 2, entry 8). The regioselectivity observed in this particular case is a characteristic outcome of HAS.[13] In contrast, it is worthy of note that the corresponding transition-metal-mediated reactions invariably provide a mixture of regioisomers.[14] Further extension of π-system was readily accomplished by modifying the 2-aryl group in the starting isocyanide, as in **1j**, enabling the assembly of the otherwise difficult to access pentacyclic azaarene **3ja** (Table 2, entry 9).

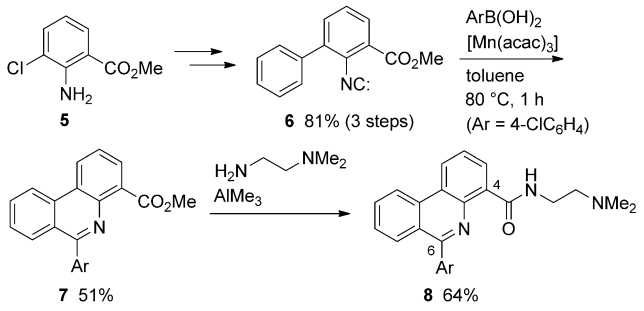
A mechanistic pathway for the current manganese(III)-mediated annulation of 2-isocyanobiphenyl with boronic acid is depicted in Scheme 3. The reaction of boronic acid **A** with Mn^{III} salt generates aryl or alkyl radical **B**,[7] which undergoes intermolecular addition to isocyanide **C** to form the imidoyl radical **D**.[5] Intramolecular attack of the imidoyl radical on the pendant aromatic ring subsequently provides a cyclohexadienyl-type radical **E**, which ultimately aromatizes to afford phenanthridine **G**. Although there are several possi-



Scheme 3. Proposed reaction mechanism.

bilities,[1] it was envisaged that the re-aromatization proceeded via cationic intermediate **F** through single-electron oxidation by Mn^{III} followed by deprotonation, on the basis of the observation that more than two equivalents of Mn^{III} were required to drive the reaction to completion. Several experiments were performed to provide support for the proposed mechanism. One such experiment involved the addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) to effectively quench the reaction, and the putative alkyl radical intermediate was intercepted by TEMPO (See Supporting Information). In a separate experiment, the use of 5-hexenylboronic acid (**2q**) exclusively afforded phenanthridine bearing a cyclopentylmethyl group, indicating that a rapid 5-exo process preceded the intermolecular addition to isocyanide (See Supporting Information).[15]

To further demonstrate the value of the current two-component cyclization, we implemented this method in the synthesis of phenanthridine derivative **8**, which displays in vivo antitumor activity (Scheme 4).[16] Our synthetic scheme features a late-stage introduction of a C6 substituent



Scheme 4. Application in the synthesis of **8**.

as well as amide at C4, allowing for rapid access to the product diversity required for structure–activity relationship studies.

In conclusion, we have developed a novel bimolecular coupling of 2-isocyanobiaryls with organoboronic acids by a formal HAS. The method enables the rapid divergent synthesis of phenanthridine and its π-extended analogues bearing aryl, heteroaryl and alkyl groups at the C6 position from readily accessible starting materials and a promoter. Further efforts are currently underway to develop synthetic methods capable of exploiting HAS and related processes in the transformation of C–H bonds.

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