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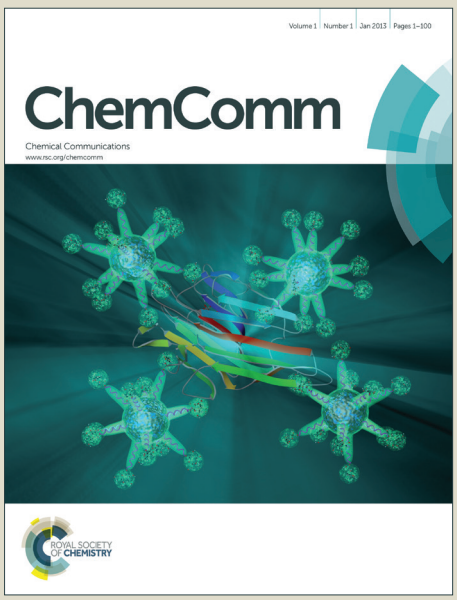

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Coupling cyclizations with fragmentations for the preparation of heteroaromatics: quinolines from *o*-alkenyl arylisocyanides and boronic acids

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Stereoelectronic restrictions on homoallylic ring expansion in alkyne cascades can be overcome by using alkenes as synthetic equivalents of alkynes in reaction cascades that are terminated by C-C bond fragmentation. Implementation of this approach using Mn(III)-mediated reaction of *o*-alkenyl isocyanides and boronic acids lead to efficient synthesis of substituted quinolines.

Due to the ubiquity of alkenes and alkynes, control of their cyclization reactions has fundamental importance for organic chemistry. In particular, alkynes serve as a high energy, carbon-rich starting point for the atom-economical access to conjugated molecules and materials.[1] In this context, the 6-endo-dig cyclization of alkynes provides an attractive direct route to aromatics (Fig. 1). Unfortunately, the effective implementation of the radical version of this process still poses an unresolved challenge due to the competition with the stereoelectronically favorable 5-exo-dig ring closures.[2] The selectivity problem is exacerbated for alkynes where the products of exo-cyclizations cannot be "recycled" in the 6-endo-products via homoallylic ring expansion, a process which is well-documented in alkene chemistry (Fig. 1, right).[3] Such expansion is impossible in alkyne chemistry because the vinyl radicals produced in exo-dig cyclizations are constrained to orthogonality relative to the target π-system (Fig. 1, left).[4]

An innovative solution to the design of formal endo-dig radical cyclizations of alkynes involves combination of endo-trig cyclizations of alkenes with fragmentations. Alkenes undergo homoallylic expansion readily and, even though the products of alkene cyclizations are not fully conjugated, a C-Z bond scission in the initial product can lead to aromatization (Fig. 1, top) that provides the formal 6-endo-dig product.[3] This cascade illustrates how alkenes can be used as stereoelectronically flexible synthetic analogues of alkynes.

In this work, we describe the first application of such concept to the synthesis of heterocycles based on radical 6-endo-trig cyclization of *o*-alkenyl arylisonitriles. We will show that it overcomes limitations faced by the analogous radical alkyne cyclizations[5] where mostly the 5-exo-dig closure was observed (with a single exception[6]).

Undeterred by the earlier literature reports of 5-exo preference in radical cyclizations of *o*-alkenyl arylisocyanides,[7] we took advantage of our recent finding that 5-exo/6-endo trig completion in similar all-carbon systems can be controlled by alkene substitution (Scheme 1) and, for R=alkyl, the formal 6-endo products are formed efficiently and can aromatize to α-Sn naphthalenes via C-C bond scission in situ.[4,3]

The results below indicate that conjugating substituents at the alkene terminus should be avoided and that presence of an appropriate fragmenting group is needed for aromatization into the quinoline product.

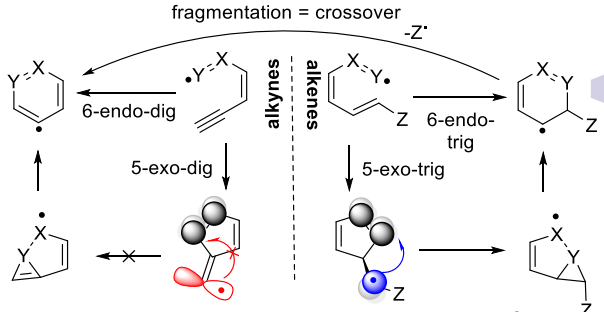
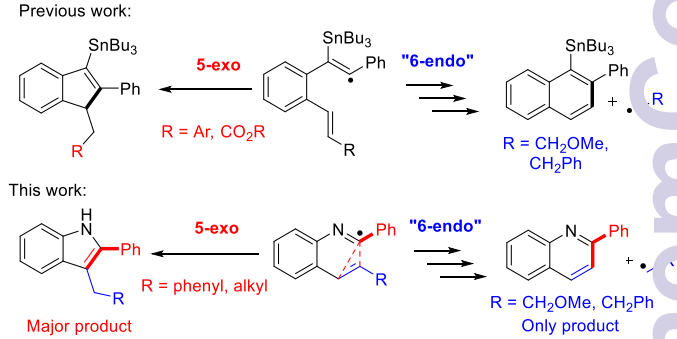


Fig. 1 Left: Stereoelectronic restriction on the 5-exo-dig → 6-endo-dig homoallylic ring expansion. Right: "Recycling" of 5-exo-trig products into 6-endo-trig products via homoallylic ring expansion.



Scheme 1. Alkene substitution controls regioselectivity in enyne cyclizations[7] and enables endo-trig/fragmentation cascades

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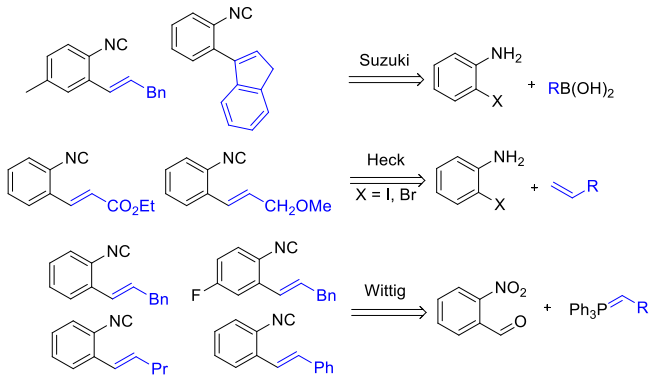
When choosing the suitable leaving group, we took advantage of our earlier findings that both alkoxy and phenyl groups can provide adequate stabilization to the fragmenting radical in the carbon systems in Scheme 1.[3,5]

The isocyanide substrates with a pendant alkene can be prepared via several synthetic pathways (Scheme 2). We have demonstrated that the routes based on Suzuki, Heck and Wittig couplings provide the target isocyanides in good yields. For the Suzuki/Heck routes to the corresponding isocyanide, the overall scheme consists of three steps – a) formylation of the starting aniline, b) Pd catalyzed coupling with an alkene, and c) amide → isocyanide conversion. The Wittig route consisted of four steps that included the installation of pendant alkene via the Wittig reaction followed by functional group manipulations that transform the nitro group into isocyanide (Scheme 2, see SI section for full experimental details). The largest difference between the Suzuki/Heck and the Wittig routes is that the latter provides the target alkenes as a mixture of *Z* and *E* isomers whereas only the *E* isomer is formed with the Suzuki/Heck routes. In our case, no significant difference in yield was observed when an *E*/*Z* mixture was used instead of the pure *E*-isomer.

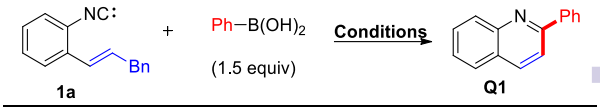
With substrates in hand, and the knowledge that -CH_2Ph, -CH_2OMe groups can facilitate the desired radical fragmentation pathway, we focused our efforts on expanding the utility of these substrates. In the initial attempts, the $PhCH_2$-substituted alkene did not form the target quinolines in the presence of radical species. Interestingly, use of Bu_3SnH/AIBN conditions leads to a mixture with predominately 5-exo product formation. This suggests that the steric bulk of $SnBu_3$ and/or fast H-abstraction can terminate the cascade prematurely. In search of an alternative, we turned to organoboron reagents that provide an increasingly popular choice as radical precursors.[8] The synthetic value of this approach is amplified by the large number of commercially available boronic acids. An additional advantage of such compounds (e.g., $RB(OH)_2$) is that the oxidative approach to their activation via the assistance of mild oxidants such as Mn(III) allows potential fine-tuning of the oxidation state of the cyclizing species.

To our delight, both the -CH_2Ph, and -CH_2OMe substrates selectively underwent the desired 6-endo cyclization/fragmentation sequence.[9]



Scheme 2. Synthesis of *o*-alkenyl isocyanide substrates

Table 1. Optimization of reaction conditions



Entry	Oxidant	Equiv	Solvent	Temp °C	Yield %[b]
1	$Mn(acac)_3$	1	C_7H_8	90	17
2	$Mn(acac)_3$	2	C_7H_8	90	64
3	$Mn(acac)_3$	3	C_7H_8	90	86
5	$Mn(acac)_3$	3	C_7H_8	Reflux	82
6	$Mn(acac)_3$	3	C_7H_8	rt	0
7	$Mn(acac)_3$	3	C_7H_8	50	59
8	$Mn(OAc)_3 \cdot 2H_2O$	3	C_7H_8	90	67
9	$Mn(OAc)_2$	3	C_7H_8	90	0
10	$Cu(OAc)_2$	3	C_7H_8	90	0
11	$AgNO_3$/ $Na_2S_2O_8$	0.2/3	DCM/ H_2O	90	0
12	$Mn(acac)_3$	3	MeCN	Reflux	79
13	$Mn(acac)_3$	3	C_6H_6	Reflux	84
14	$Mn(acac)_3$	3	DMF	90	trace

Reaction conditions: Isocyanide (0.1 mmol), boronic acid (1.5 equiv), specified amount of oxidant in 3 mL of solvent. Reactions were allowed to stir for 4 hours, with exception of r.t. reaction that was allowed to react for 24 hours. [a]NMR yield based on **1a**.

The Bn substituted alkene **1a** provided higher conversions than its -CH_2OMe analogue **1b** (Table 2) and was chosen for the further optimization.

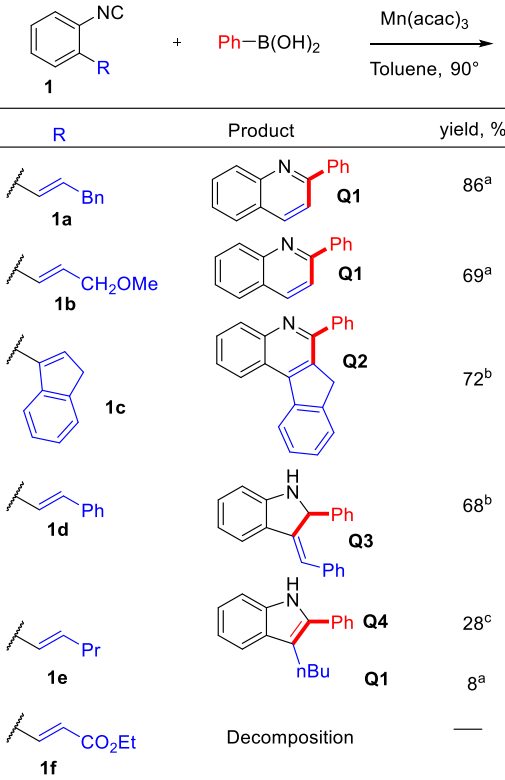
The screening process is depicted in Table 1. The use of 1.5 boronic acid equivalents with 3 equivalents of Mn(III) in toluene at 90°C provided the best results, in agreement with the literature data on the cyclizations of biphenyl isocyanides.[15] Slight excess of organoboron species was used to compensate for partial radical dimerization. Moderately elevated temperatures were required to reach the full conversion (entries 3, 6, 7). Along with Mn(III), several other oxidants were screened. With the optimized conditions, we set forth to better understand the scope and limitation of the new reaction.

Substrate scope was further evaluated by incorporating a variety of different pendant groups at the alkene moiety (Table 2). It was observed that only the -CH_2OMe, and -CH_2Ph groups selectively afforded the 6-endo/fragmentation product (mechanism shown in Scheme 3).

The slightly higher yields observed for the -CH_2Ph group are consistent with the stabilities of the fragmenting radicals (Bn>CH_2OR>alkyl).[3,9] On the other hand, a structurally constrained substrate (**1c** in Table 2) yielded only the 6-endo product without fragmentation (mechanism shown in Scheme 4). A switch in regioselectivity was observed for a phenyl substituted alkene where exclusive formation of a 5-exo product was observed. Presumably, when the radical formed upon 5-exo cyclization is stabilized by benzylic resonance, this stabilization deactivates this species towards the further rearrangement.[3,10]

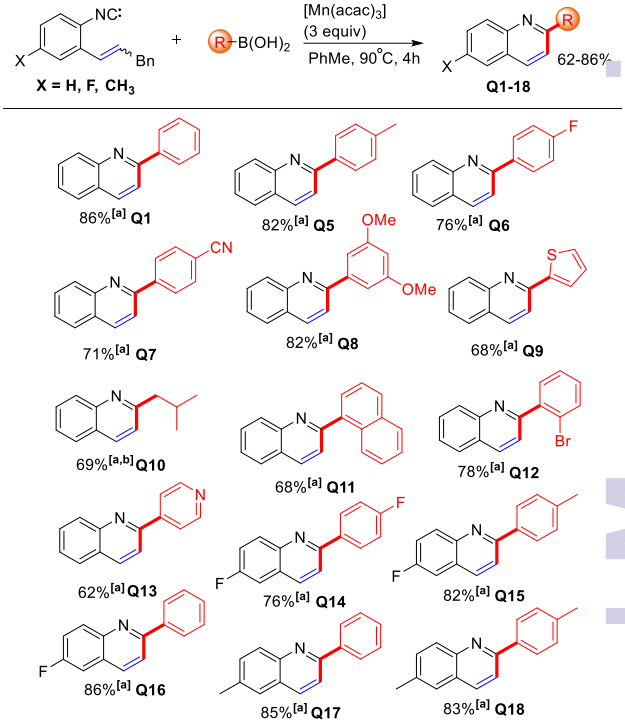
An interesting result was obtained for an alkyl substituent (propyl), which should not prevent the ring expansion of the

Table 2. Optimization of pendant alkene moiety

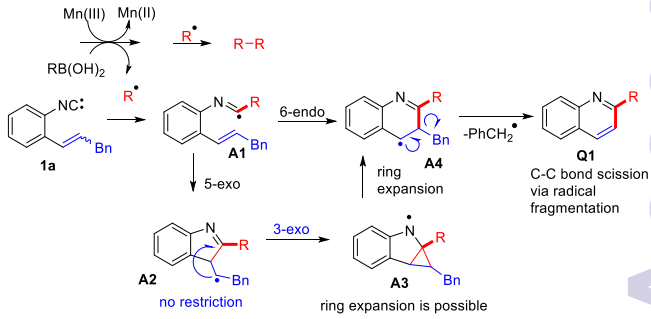


Reaction conditions: Isocyanide (0.1mmol), boronic acid (1.5 equiv), $Mn(acac)_3$ (3 equiv), and toluene (3 mL) were heated at 90°C for 4 hours. Complete conversion was observed in all cases. [a]Isolated yield. [b]NMR yield based on starting material. [c]Product yield of isolated major product with trace components identified as mixture of product Q1 and other six member cycles.

Table 3. Scope of boronic acids



[a] Yield of isolated product from starting materials. [b] 3 equivalents of boronic acid was used.

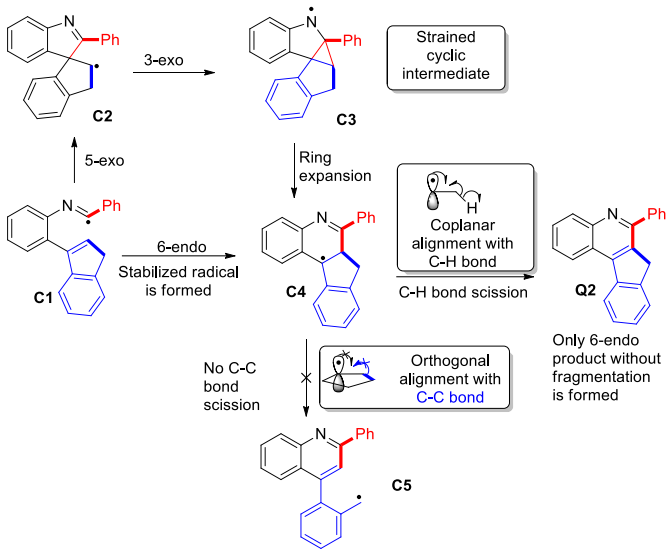


Scheme 3 Proposed radical pathway for 6-endo/5-exo product formation.

5-exo-radical but cannot provide stabilization to the fragmentation step.The major observed product was the 5-exo indole product **Q4,** along with 8% of the desired quinoline **Q1** (Table 2).

The scope of reaction is quite broad, and a variety of functional groups was tolerated (Table 3). High yields were observed for both donor and acceptors. The importance of >2-fold excess of the oxidant for achieving the full conversion suggests the possibility of further one-electron oxidation of the intermediate radical(s). A similar possibility was suggested for the Mn(III)/$RB(OH)_2$-mediated cyclization of biphenyl isocyanides where one-electron oxidation by the second equivalent of Mn(III) generates a cationic intermediate that undergoes a proton loss to rearomatize in the products.[11] We have considered a similar cationic mechanism in our system.[12,13] However, additional experimental studies did not support the cationic pathway. For example, the introduction of nucleophilic species into the reaction mixture did not trap any of the putative intermediate cations or the fragmented benzyl cation. In particular, we did not detect formation of the respective ethers in the presence of alcohols (MeOH, BnOH) and diisopropyl benzyl amine in the presence of *i*-Pr_2NH. Similarly, no N-benzylacetamide was formed in the presence of CH_3CN/H_2O, where nucleophilic trapping of the cation could be provided by acetonitrile. Instead, the full reaction cascade took place without deleterious effects in the presence of added nucleophiles. In fact, when the 4:1 CH_3CN/H_2O solvent mixture was used to trap the cationic species, the yield was slightly improved over the reaction in dry CH_3CN (79% vs. 84%).

The combination of available experimental data suggests the following mechanistic picture (Scheme 3). The reaction is initiated by an aryl radical formed in the reaction of Mn(III) and the boronic acid. The regioselective intermolecular addition generates iminoyl radical **A1** capable of following the reaction routes outlined in Scheme 3. The formal 6-endo-product **Q1** may be produced via homoallylic ring expansion of the initially formed 5-exo-trig radical **A2**.[3] Such expansion would be impossible for alkynyl systems but becomes possible when alkenes are used as synthetic equivalents of alkynes in radical transformations. The 6-endo product formation via the pathway outlined in Scheme 3 was observed exclusively when suitable fragmenting groups were used (e.g. CH_2OMe, and CH_2Ph). To further evaluate the stereoelectronic effect on the



Scheme 4 Radical pathway for C-H bond cleavage in a stereoelectronically restricted cycle

C-C bond scission step, we have prepared 3-(2-isocyanophenyl)-1H-indene **1c**, as shown in Scheme 4. Example **1c** was observed to yield solely the 6-endo product **Q2**, but without the C-C fragmentation. This is due to the fused 5-member system "locking" the cycles into a planar structure. This constraint places the intermediate radical **C4** perpendicular to the C-C bond that would usually fragment, which aligns it with a C-H bond. The stereoelectronic alignment leads to this C-H bond scission and prevents the C-C fragmentation.

In conclusion, we have developed a synthetic equivalent of 6-endo-dig cyclization for the synthesis of quinolines from isonitriles using a combination of an endo-trig cyclization and fragmentation. A variety of functional groups is tolerated. This reaction utilizes inexpensive Mn(III) salts and readily available boronic acids. Successful utilization of cyclization / fragmentation sequences expands the use of alkenes as alkyne equivalency towards heterocycle synthesis.

ACKNOWLEDGMENT

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