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Radical Borylative Cyclization of 1,6-Dienes: Synthesis of Boron-Substituted Six-Membered Heterocycles and Carbocycles

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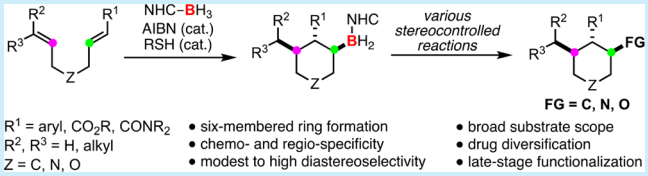
Supporting Information

ABSTRACT: A radical borylative cyclization reaction of 1,6-dienes was developed to assemble boron-handled six-membered heterocycles and carbocycles. This reaction was initiated by the chemo- and regio-controlled addition of an *N*-heterocyclic carbene−boryl radical to one of the alkene tethers, followed by an intramolecular 6-*exo* cyclization to afford a six-membered ring framework. The utility of this method was demonstrated in the synthesis of diverse paroxetine analogues through late-stage derivatization of the boryl functional unit.



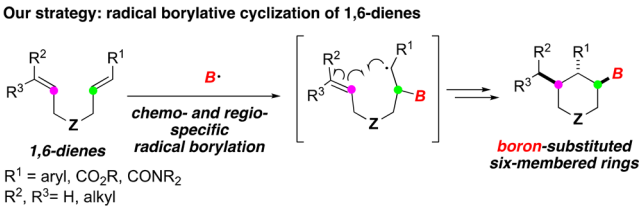
Six-membered heterocyclic and carbocyclic motifs are present as core structures in a variety of bioactive natural products and pharmaceutical drugs.[1] Therefore, developing new, efficient methods to assemble these systems is a preeminent goal in synthetic chemistry.[2] In particular, approaches that can construct boron-handled six-membered rings[3] are more desirable, because of the versatile chemistry of the boryl functional unit for further synthetic and medicinal applications.[4]

Borylative cyclization reactions represent a step-economical strategy to make boron-substituted cyclic molecules, wherein the ring systems and C−B bond are created in a single operation.[5] In this context, many transition-metal-catalyzed reactions,[6] as well as metal-free borylative cyclization reactions,[7] have been reported for specific classes of alkene-containing unsaturated substrates. However, most of them are relatively limited to the formation of five-membered rings, and examples to construct six-membered ones are very rare.[6c,k,7] Thus, there remains both a great demand and a great challenge to explore conceptually distinct borylative cyclization methods that can selectively construct six-membered rings with predictable regiocontrol and stereocontrol. Herein, we describe a chemoselective, regioselective, and diastereoselective radical borylative cyclization reaction of 1,6-dienes for the synthesis of boron-handled six-membered heterocycles and carbocycles (see Scheme 1). Notably, the present method could enable the synthesis of diverse analogues of antidepressant paroxetine through late-stage derivatization of the boryl group in the products.

Lewis base−boryl radicals that can be generated by hydrogen abstraction of Lewis base−BH_3 complexes[8] have been emerging as powerful species to enable a range of radical reactions,[9] including the radical reduction of xanthates,[10] organic halides,[11] nitriles,[12] and thioamides,[13] polymerization of alkenes,[14] homolytic substitution of disulfides,[15] and inverse hydroboration of imines.[16] However, the radical borylation of alkenes and alkynes to access alkyl and alkenyl boron compounds remains elusive.[8d,17] Recently, Curran and Taniguchi,[18] and our group[19] have independently disclosed *N*-heterocyclic carbene (NHC)−boryl radical-promoted borylative cyclization reactions of benzo[3,4]cyclo-dec-3-ene-1,5-diynes and 1,6-enynes, resulting in facile construction of boron-tethered, unsaturated cyclic ring systems. Stimulated by these results, we became interested in the development of a radical borylative cyclization of 1,6-dienes, from which boron-substituted saturated six-membered heterocycles and carbocycles would be assembled. However, this method should be challenging because of the difficulties associated with control of the chemoselectivity, regioselectivity, and diastereoselectivity for densely substituted 1,6-diene substrates.

We initiated our studies by evaluating the radical borylation/cyclization of 1,6-diene (**1a**) with NHC−BH_3 (**2**) as the boryl radical precursor. Although there are two alkene moieties in the

Scheme 1. Radical Borylative Cyclization of 1,6-Dienes



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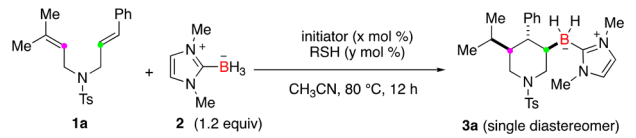
substrate, based on our previous findings,[19] we envisioned that the initial addition of the NHC−boryl radical could occur preferentially at the phenyl-substituted one. As expected, the reaction proceeded in the presence of 2,2-azobis(isobutyronitrile) (AIBN) as the radical initiator, furnishing 3,4,5-trisubstituted piperidine (**3a**) in 32% yield (Table 1, entry 1). Remarkably, a single diastereomer was formed in the cascade sequence to construct three consecutive stereogenic centers. Interestingly, a mixture of *E*/*Z* (5:1) isomers of **1a** was recovered, even though the pure *E* isomer was utilized as the starting material. This result indicated that the initial boryl radical addition to the phenyl-substituted alkene tether should be a reversible process. The addition of *tert*-dodecanethiol as the polarity reversal catalyst[11a,20] increased the yield to 82% (Table 1, entry 2). Reducing the catalyst loading to 20 mol % maintained a good isolated yield of **3a** (Table 1, entry 3), while further reduction to 10 mol % resulted in a diminished yield (Table 1, entry 4). Moreover, the employment of di-*tert*-butyl hyponitrite (TBHN) as the radical initiator gave a comparable result (Table 1, entry 5). No reaction occurred in the absence of a radical initiator, and **1a** was recovered in a quantitative yield (Table 1, entry 6), which suggested that a radical reaction mechanism is involved in this transformation. On the other hand, a series of transition-metal-catalyzed borylative cyclization reactions[6] using **1a** as the substrate were examined. However, no cyclized product **3a** was formed in all cases.[21]

Table 1. Optimization of Reaction Conditions[a]



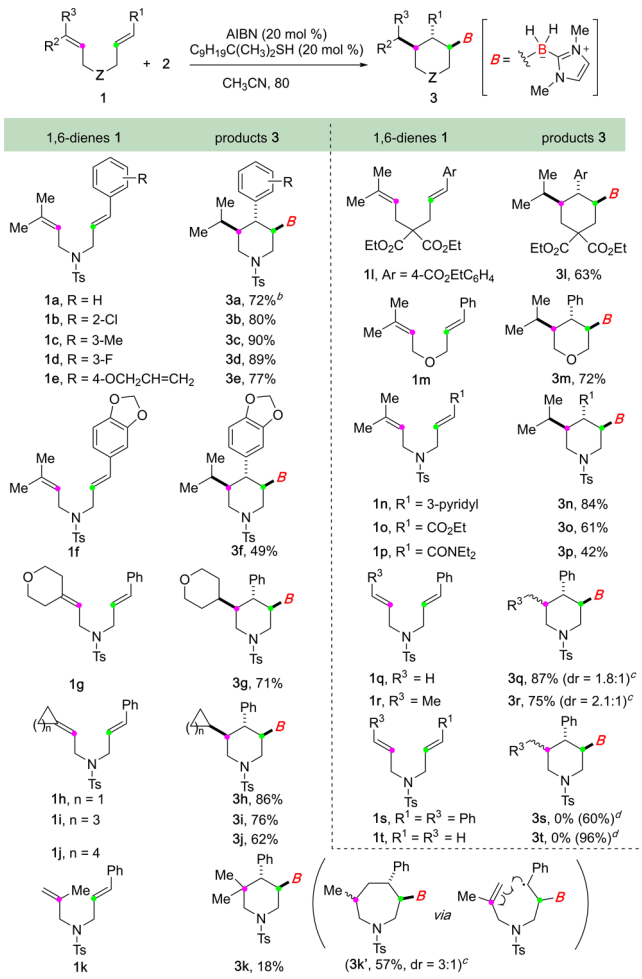
1a + **2** (1.2 equiv) → **3a** (single diastereomer)

entry	initiator (*x*, mol %)	RSH (*y*, mol %)	Yield (%) **3a**[b]	Yield (%) **1a**[c]
1	AIBN (20)		32	65 (5:1)[d]
2	AIBN (20)	$C_9H_{19}C(CH_3)_2SH$ (50)	82	trace
3	AIBN (20)	$C_9H_{19}C(CH_3)_2SH$ (20)	84[e]	trace
4	AIBN (20)	$C_9H_{19}C(CH_3)_2SH$ (10)	63	26 (11:1)[d]
5	TBHN (20)	$C_9H_{19}C(CH_3)_2SH$ (20)	75	trace
6		$C_9H_{19}C(CH_3)_2SH$ (20)	ND	98 (1:0)[d]

[a]Unless otherwise noted, the reactions were performed on a 0.2−0.5 mmol scale of **1a** with 1.2 equiv of NHC−BH_3 (**2**) in the presence of an initiator (x mol %) and RSH (y mol %) in CH_3CN (3 mL) at 80 °C, under a nitrogen atmosphere. [b]NMR yield using tetrachloroethane as an internal standard. [c]Recovery yield of *E*/*Z* isomers of **1a**. [d]The ratio of *E*/*Z* isomers of recovered **1a** is shown in parentheses. [e]Isolated yield.

Having developed the optimized reaction conditions, we examined the generality of this radical borylative cyclization of 1,6-dienes **1** for the synthesis of borylated cyclic products **3** (Table 2). First, a gram-scale reaction of **1a** was tested, and **3a** was isolated in 72% yield. 1,6-Dienes **1** bearing an aryl group as R^1 afforded borylated six-membered ring products **3** in good yields. When R^2 and R^3 both are alkyl groups, only a single diastereomer was formed. Benzene rings possessing various functional groups were compatible, regardless of their electronic nature and substitution pattern (for **3b**−**3f**). A range of cycloalkyl groups could be introduced onto the piperidine ring with exclusive diastereoselectivity (for **3g**−**3j**). Interestingly, when a methyl group was installed at the internal carbon of an alkene moiety, the desired six-membered ring product **3k** with a quaternary carbon was only isolated in 18% yield, whereas a seven-membered ring **3k′**, which could be derived from a 7-*endo* cyclization step, was obtained in 57% yield. The present method allowed the construction of cyclohexane (for **3l**) and pyran (for **3m**) scaffolds. A pyridine motif could be also installed (for **3n**). In replacing an aryl group, an ester (for **1o**) and an amide moiety (for **1p**) could be utilized as the substituent R^1, affording the desired products in good selectivity and efficiency. The reaction of 1,6-dienes with a hydrogen atom as the R^2 substituent gave the cyclized products in good yields, but with lower diastereoselectivity (for **1q** and **1r**), probably due to the diminished steric repulsion effect during the ring closure step. As for the limitation, the present method has thus far not proven successful with bis-styryl-tethered **1s** and terminal alkene **1t**. In the case of **1s**, the reaction became messy, and no identifiable product was isolated. This is probably due to the slow hydrogen transfer rate from the thiol catalyst to the resulted benzyl radical intermediates,[20] thus leading to polymerization.

Table 2. Scope of Radical Borylative Cyclization of 1,6-Dienes[a]



[a]Unless otherwise noted, the reactions were performed on a 0.2−0.5 mmol scale of **1** (1.2 equiv) with NHC−BH_3 (**2**) in the presence of AIBN (20 mol %) and $C_9H_{19}C(CH_3)_2SH$ (20 mol %) in CH_3CN (3 mL) at 80 °C under a nitrogen atmosphere. [b]Isolated yield of a gram scale reaction. [c]The stereochemistry of the major isomer was not determined. [d]Recovery yield of **1**.

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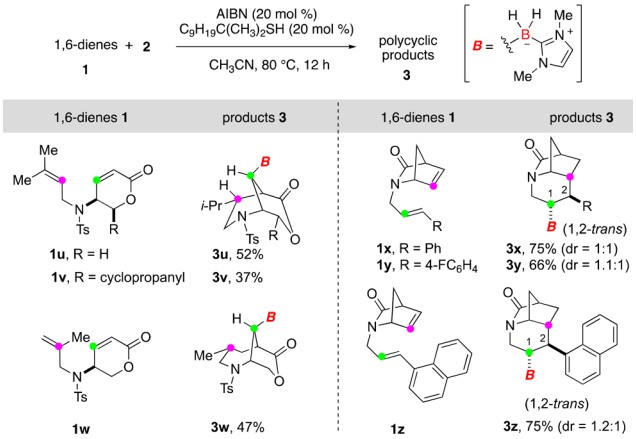
The present method was also determined to be applicable to the facile construction of boron-substituted polycyclic skeletons (Table 3). The radical borylative cyclization of 1,6-dienes bearing a 5,6-dihydro-2*H*-pyran-2-one motif took place nicely to assemble borylated 2-azabicyclo[3.3.1]nonanes as single diastereomers in acceptable yields (for **3u** and **3v**). When **1w** was subjected to the reaction conditions, a 7-*endo* cyclization proceeded to give unique boron-containing 2-azabicyclo[4.3.1]-decane **3w**. Notably, many structurally complex tricyclic architectures, such as **3x**, **3y**, and **3z**, were constructed from 1,6-dienes tethering a vince lactam unit. By replacing the phenyl group (R in **1x**) with a hydrogen atom, a mixture of some inseparable boron-containing products was resulted, most likely from the initial boryl radical addition to the bicyclic alkene moiety,[22] but with low regioselectivity and diastereoselectivity.

To verify the radical reaction mechanism of this borylative cyclization process, a radical clock experiment was conducted. The reaction of **1aa**, in which a cyclopropyl radical clock[23] was installed at one end of the alkene, provided the ring-opening product **3aa** in good yield (Scheme 2a). This result strongly supported the existence of the cyclopropyl carbinyl radical intermediate **A** in the reaction sequence. Based on this result, and previous findings for NHC−boryl radical chemistry,[8,9] a plausible mechanism for the formation of **3a** was outlined in Scheme 2b. The NHC−boryl radical **I** is initially generated by hydrogen abstraction from **2**.[8b,c] The addition of **I** takes place specifically at the phenyl-substituted alkene part to give intermediate **II**. Such an addition process should be reversible, as the *E*/*Z* isomerization of **1a** was observed when the reaction was not completed (Table 1). The following radical 6-*exo*-*trig* ring-closure step may proceed through 6-membered chairlike transition states **II-a** or **II-b**, wherein the boryl moiety and the phenyl group are both located in *pseudo*-equatorial positions. However, the cyclization of **II-a** predominates, because of the lower 1,3-diaxial steric strain, thus leading to exclusive *trans* stereoselectivity. In the reactions of **1q** and **1r**, such a 1,3-diaxial steric effect decreases, and a diastereomeric mixture is obtained. Hydrogen atom transfer from the thiol catalyst to alkyl radical **III** occurs to afford product **3a** with the generation of a sulfur radical (RS•), which, in turn, abstracts a hydrogen atom from **2** to regenerate RSH and **II** with the propagation of the radical chain reaction.

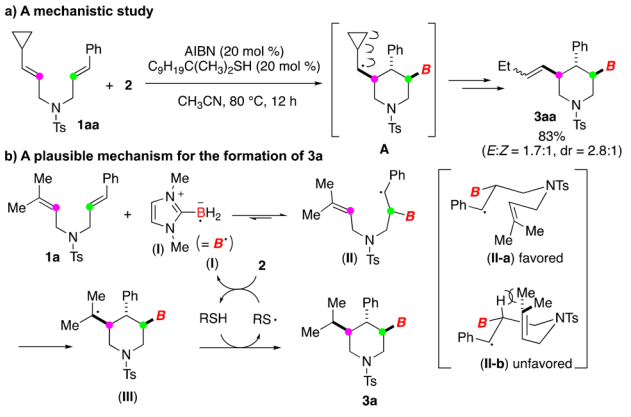
The synthetic practicability and utility of this radical borylative ring construction method was demonstrated in the synthesis of a diverse array of paroxetine analogues.[24] The reaction of **1ab** and **2** afforded boryl-functionalized paroxetine (**3ab**) in good yield, albeit with lower diastereoselectivity (see Scheme 3). The oxidation of **3ab** by H_2O_2 provided hydroxylated paroxetine (**4**) in 86% yield. Treatment of **3ab** with 2 M HCl[25] in the presence of pinacol led to alkyl pinacol boronic ester (**5**) in 82% yield. The subsequent arylation reaction following Aggarwal's protocol[26] gave the furan-substituted paroxetine (**6**). In addition, an aminated paroxetine derivative **7** was obtained in 62% yield via the conversion of boronic ester **5** to potassium alkyltrifluoroborate,[27] followed by amination with benzyl azide in the presence of $SiCl_4$.[28] It is noteworthy that diastereomeric mixtures of compounds **4**, **6**, and **7** could be easily separated by column chromatography,

Table 3. Scope for the Synthesis of Boron-Handled Polycyclic Molecules[a]

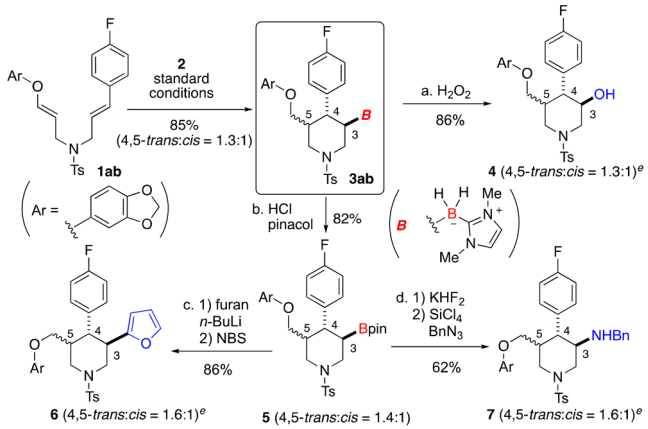


[a]Unless otherwise noted, the reactions were carried out on a 0.2−0.5 mmol scale of **1** (1.2 equiv) with NHC−BH_3 (**2**) in the presence of AIBN (20 mol %) and $C_9H_{19}C(CH_3)_2SH$ (20 mol %) in CH_3CN (3 mL) at 80 °C under a nitrogen atmosphere.

Scheme 2. A Mechanistic Study and a Plausible Mechanism for the Formation of 3a



Scheme 3. Synthesis and Diversification of Boryl-Handled Paroxetine[a]



[a]Reagents and conditions: (a) H_2O_2 (30%, 8 equiv), MeOH/CH_3CN, room temperature (rt), 6 h; (b) aqueous HCl (2 M, 2.5 equiv), pinacol (2 equiv), CH_3CN, rt, 6 h; (c) (1) furan (6 equiv), *n*-BuLi (6 equiv), THF, −20 °C, 1 h, (2) NBS (6 equiv), THF, −20 °C, 5 h; and (d) (1) KHF_2 (2.5 equiv), MeOH, rt, 3 h, (2) $SiCl_4$ (10 equiv), BnN_3 (3 equiv), toluene, rt to 60 °C, 11 h.

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thus offering the potential for rapid testing of diastereomeric analogues for biological activity.

In summary, we have disclosed a strategically new radical borylative ring construction method to assemble boron-handled six-membered rings from 1,6-dienes. A range of boron-substituted cyclohexane, piperidine, pyran, and polycyclic systems were constructed from C-, N-, and O-tethered 1,6-dienes. This approach was successfully applied to the synthesis of boryl-functionalized antidepressant drug paroxetine; the following derivatization reactions afforded a diverse array of analogues that would be potentially useful for drug development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00694.

Detailed experimental procedures and characterization of new compounds (PDF)

Accession Codes

CCDC 1815343 and 1815345−1815347 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(21) See Scheme S-1 in the Supporting Information for details.
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