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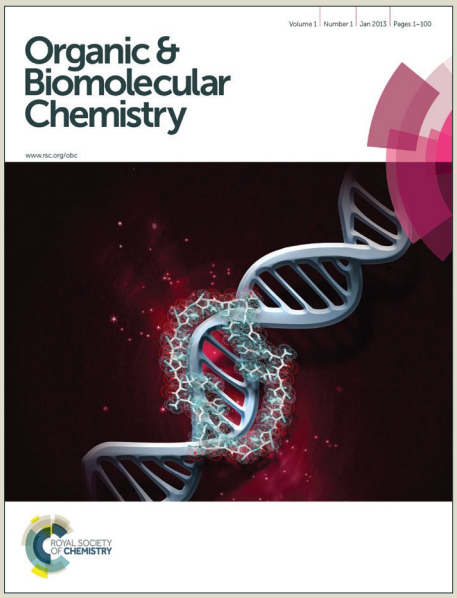

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Efficient access to *cis*-decalinol frameworks: Copper(I)-catalyzed borylative cyclization of allene cyclohexanediones

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Cu-catalyzed borylative cyclization of allene cyclohexanediones has been described through a tandem β-borylation and intramolecular allylic addition process, affording borylated *cis*-decalinols with excellent yields and diastereoselectivities. A good enantioselectivity is also achieved in the asymmetric version. The hemiboronate group in the cyclization products could be subjected to several useful transformations.

Cis-Decalinols represent a ubiquitous bicyclo[4.4.0]decane motif existing in numerous natural products and drugs, for instance, 5β-Hydroxycostic acid,[1] (–)-Patchoulol,[2] (–)-Naloxone,[3] Pterokaurane L_3,[4] and Strophanthidin[5] (Fig. 1). Due to their diverse biological activities, much attention has been paid to their efficient syntheses. One of the most straightforward ways to build such a framework is the catalytic asymmetric desymmetrization of cyclohexanediones (Scheme 1). Over the last decade, transition-metal-catalyzed tandem conjugate addition-aldol cyclization has proved to be effective for the preparation of *cis*-decalinol frameworks (Scheme 1a). The research groups of Krische,[6] Riant,[7] Renaud,[8] Lam[9] and Chiu[10] *et al.* have contributed greatly in this field. Ema and Sakai provided an alternative organocatalytic approach by using N-heterocyclic carbene (NHC) catalyzed intramolecular crossed benzoin reactions.[11] Although these elegant protocols have emerged, their efforts were mainly focused on the enolate-trapping and umpolung strategies.[6-11] Herein, we reported another efficient access to *cis*-decalinol frameworks by using Cu-catalyzed borylative cyclization of allene cyclohexanediones through catalytic tandem β-borylation and allylic addition process (Scheme 1b).

Allenes, particularly the functionalized allenes, serve as useful synthetic building blocks in organic synthesis due to their characteristic structure and electronic properties.[12] Cop-

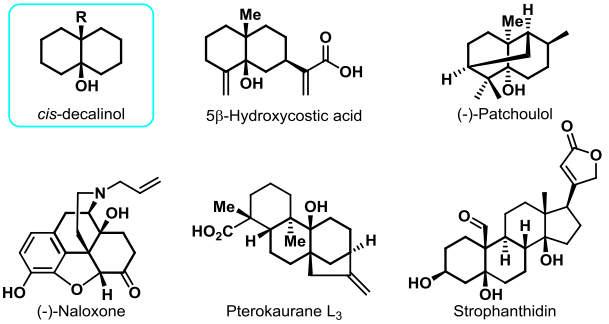
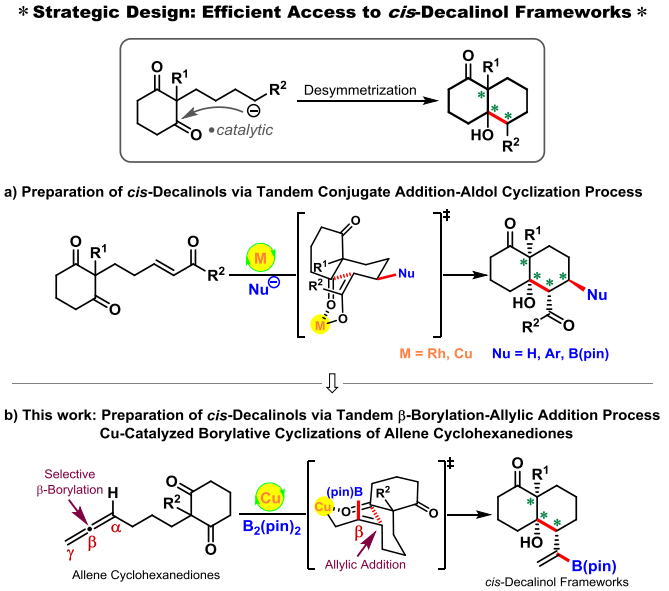


Fig. 1 *cis*-Decalinol frameworks existing in natural products and drugs.



Scheme 1 Design plan: Cu-catalyzed borylative cyclizations of allene cyclohexanediones for the preparation of *cis*-decalinol motifs. B(pin) = (pinacolato)boron.

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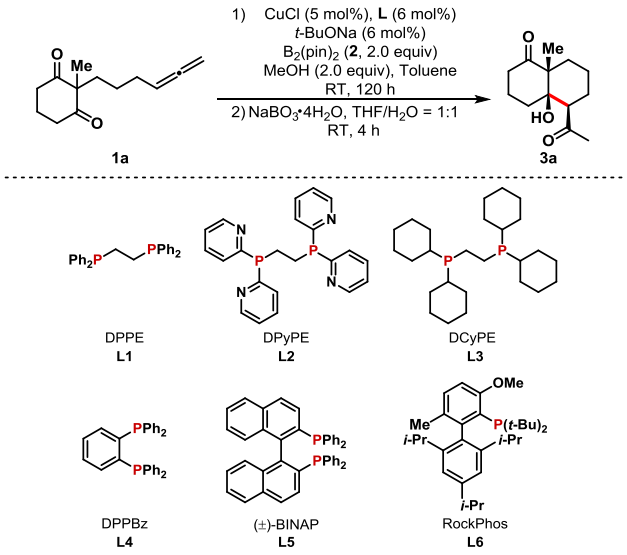
per–boryl (Cu–B) complexes, generated *in situ* from transmetallation of bis(pinacolato)diboron ($B_2(pin)_2$) with CuCl in the presence of base, have been recognized as nucleophilic boryl synthons.[13] The reactions of Cu–B species with allenes result in the formation of β-boryl-functionalized σ-allyl copper intermediates. Very recently, several post-transformations of such intermediates with different electrophiles were successively uncovered.[14,15,16,17,18] Notably, Hoveyda and co-workers have described the intermolecular allylic addition to ketones, furnishing linear 2-(pinacolato)boron-substituted homoallylic alcohols with excellent diastereo- and enantioselectivities.[15] Encouraged by these findings, we envisioned that the intramolecular fashion could afford the cyclic skeleton, and thus allene and cyclohexanedione are integrated into a molecule for the preparation of *cis*-decalinol motifs (Scheme 1b). In this case, the chairlike *pseudo*-Zimmerman–Traxler-type transition-state[19] during the intramolecular allylic addition remains favored and enables the preferential formation of *cis*-decalinols.

With this in mind, a set of representative phosphine ligands were evaluated for Cu-catalyzed borylative cyclization of allene cyclohexanedione **1a**, and the results were summarized in Table 1.[20] Initially, the conventionally used bisphosphine ligand, DPPE (**L1**), was examined. Fortunately, the desired cyclization product **3a** was obtained with moderate yield and excellent diastereoselectivity (Table 1, entry 1). Then several bisphosphine ligands, including DPyPE (**L2**), DCyPE (**L3**), DPPBz (**L4**), and (±)-BINAP (**L5**), were tested. Excellent diastereoselectivities were observed in all cases and only (±)-BINAP (**L5**) gave an acceptable yield (Table 1, entries 2–5).[21] Next, the monophosphine ligand RockPhos (**L6**) and PPh_3 (**L7**) were investigated (Table 1, entries 6–7). To our delight, excellent yield was successfully achieved using PPh_3 as ligand. Increasing $B_2(pin)_2$ (**2**) loading resulted in a further improvement of yield (Table 1, entry 8).

With the optimal conditions identified, we next evaluated the scope of allene cyclohexanediones **1**, and the results were summarized in Table 2. With the R^2 substituent as alkyl group, including methyl, ethyl, *n*-propyl, and *i*-butyl, the reactions proceeded smoothly with excellent yields (92%–96%) and diastereoselectivities (all d.r. > 20:1, Table 2, entries 1–4). With the R^2 substituent as allyl and phenylpropyl group, the reaction yields and diastereoselectivities still remained excellent, respectively (Table 2, entries 5–6). With the R^2 substituent as alkyl, allyl, and phenylpropyl group for 5,5-dimethyl substituted cyclohexanediones, the reactions still proceeded equally well to give *cis*-decalinol products (Table 2, entries 7–10).

In our cases, the alkenyl pinacol boronates are unstable to silica gel.[20] In order to obtain the stable boronate products for further potential transformations, another diboron compound, bis(neopentyl glycolato)diboron ($B_2(nep)_2$, **4**) was subsequently investigated together with model substrate **1a** in this cyclization. Luckily, the stable boracyclic hemiester **5a** was generated with excellent yield (95%) and diastereoselectivity (d.r. > 20:1)

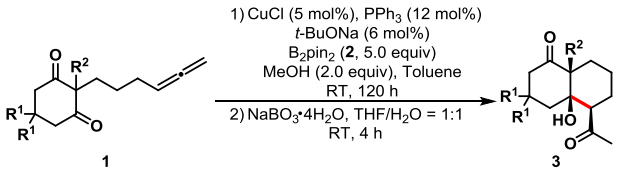
Table 1 Optimization studies using $B_2(pin)_2$ (**2**) as boron source.[a]



Entry	L	d.r.[b]	Yield (%)[c]
1	**L1** (DPPE)	>20:1	59
2	**L2** (DPyPE)	>20:1	62
3	**L3** (DCyPE)	>20:1	53
4	**L4** (DPPBz)	>20:1	71
5	**L5** ((±)-BINAP)	>20:1	81
6[d]	**L6** (RockPhos)	>20:1	41
7[d]	**L7** (PPh_3)	>20:1	92
8[d,e]	**L7** (PPh_3)-	>20:1	96

[a]Reactions were performed under an Ar atmosphere. [b]Determined by ^1H NMR analysis. [c]Yield of isolated product **3a**. [d]**L6**/**L7** (12 mol%) was used. [e]$B_2(pin)_2$ (**2**, 5.0 equiv).

Table 2. Substrate scope using $B_2(pin)_2$ (**2**) as boron source.[a]



For **1a** to **1f**, R^1 = H;
1a: R^2 = CH_3- **1b**: R^2 = CH_3CH_2- **1c**: R^2 = $CH_3CH_2CH_2$-
1d: R^2 = $(CH_3)_2CH$-CH_2- **1e**: R^2 = CH_2=CH-CH_2- **1f**: R^2 = C_6H_5-$(CH_2)_3$-

For **1g**–**1k**, R^1 = Me.
1g: R^2 = CH_3CH_2- **1h**: R^2 = $CH_3CH_2CH_2$- **1i**: R^2 = $(CH_3)_2CH$-CH_2-
1j: R^2 = CH_2=CH-CH_2- **1k**: R^2 = C_6H_5-$(CH_2)_3$-

Entry	Substrate **1**	Product **3**	d.r.[b]	Yield (%)[c]
1	**1a**	**3a**	>20:1	96
2	**1b**	**3b**	>20:1	92
3	**1c**	**3c**	>20:1	93
4	**1d**	**3d**	>20:1	92
5	**1e**	**3e**	>20:1	97
6	**1f**	**3f**	>20:1	94
7	**1g**	**3g**	>20:1	89
8	**1h**	**3h**	>20:1	90
9	**1i**	**3i**	>20:1	83
10	**1j**	**3j**	>20:1	92
11	**1k**	**3k**	>20:1	91

[a]Reactions were performed under an Ar atmosphere. [b]Determined by ^1H NMR analysis. [c]Yield of isolated product **3**.

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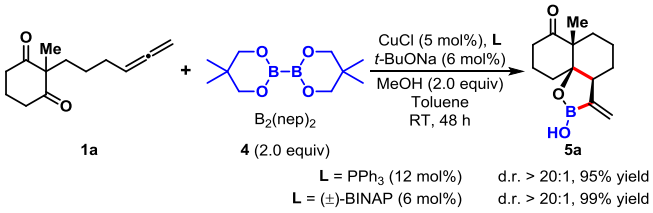
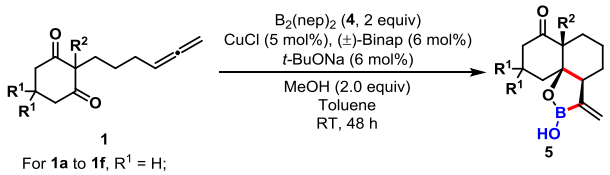


Scheme 2 Cu-catalyzed borylative cyclization of allene cyclohexanedione **1a** using $B_2(nep)_2$ (**4**) as boron source.

Table 3. Substrate scope using $B_2(nep)_2$ (**4**) as boron source.[a]



For **1a** to **1f**, R^1 = H;
1a: R^2 = CH_3- **1b**: R^2 = CH_3CH_2- **1c**: R^2 = $CH_3CH_2CH_2$-
1d: R^2 = $(CH_3)_2CH$-CH_2- **1e**: R^2 = CH_2=CH-CH_2- **1f**: R^2 = C_6H_5-$(CH_2)_3$-

For **1g**–**1k**, R^1 = Me.
1g: R^2 = CH_3CH_2- **1h**: R^2 = $CH_3CH_2CH_2$- **1i**: R^2 = $(CH_3)_2CH$-CH_2-
1j: R^2 = CH_2=CH-CH_2- **1k**: R^2 = C_6H_5-$(CH_2)_3$-

Entry	Substrate **1**	Product **5**	d.r.[b]	Yield (%)[c]
1	**1a**	**5a**	>20:1	99
2	**1b**	**5b**	>20:1	96
3	**1c**	**5c**	>20:1	95
4	**1d**	**5d**	>20:1	91
5	**1e**	**5e**	>20:1	97
6	**1f**	**5f**	>20:1	94
7	**1g**	**5g**	>20:1	96
8	**1h**	**5h**	>20:1	94
9	**1i**	**5i**	>20:1	88
10	**1j**	**5j**	>20:1	92
11	**1k**	**5k**	>20:1	91

[a]Reactions were performed under an Ar atmosphere. [b]Determined by ^{1}H NMR analysis. [c]Yield of isolated product **5**.

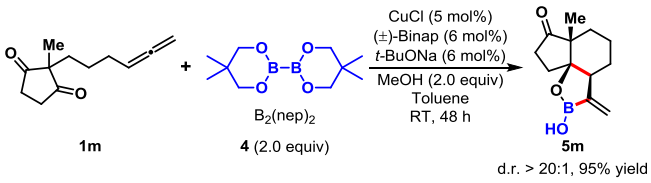
using the aforementioned PPh_3 as ligand (Scheme 2). When the bisphosphine ligand, (±)-BINAP (**L5**), was checked, almost quantitative yield was triumphantly achieved.

Various allene cyclohexanedione substrates **1** were then screened using $B_2(nep)_2$ (**4**) as boron source and the results were summarized in Table 3. As for the all substrates, the corresponding boracyclic hemiester products **5** were constructed with exceptionally excellent yields (88–99%) and diastereoselectivities (all d.r. > 20:1).

The allene cyclopentanedione **1m** was also investigated in this borylative cyclization and the desired octahydroindenyl boracyclic hemiester product **5m** was furnished with excellent yield (95%) and diastereoselectivity (d.r. > 20:1, Scheme 3).

The all *cis*-configurations of cyclization products **3k** and **5e** were unambiguously determined by the X-ray diffraction analysis (Fig. 2),[22] which was exactly conformed with our initial expectation.

Next, we paid our attention to the asymmetric version. A set of representative chiral phosphine-containing ligands were checked for Cu-catalyzed asymmetric cyclization of substrate **1a**. Using $B_2(pin)_2$ (**2**) as boron source, the *ee* values of product (–)-**3a** were generally below 50%, albeit in excellent diastereoselectivities in most cases.[23] Only chiral bisphosphine ligand, (*S*)-DTBM-Segphos, could give 53% *ee* (Scheme 4). When $B_2(nep)_2$ (**4**) was used as boron source, the *ee* value of chiral boracyclic hemiester product (–)-**5a** was significantly increased to 73%.



Scheme 3 Cu-catalyzed borylative cyclization of allene cyclopentanedione **1m**.

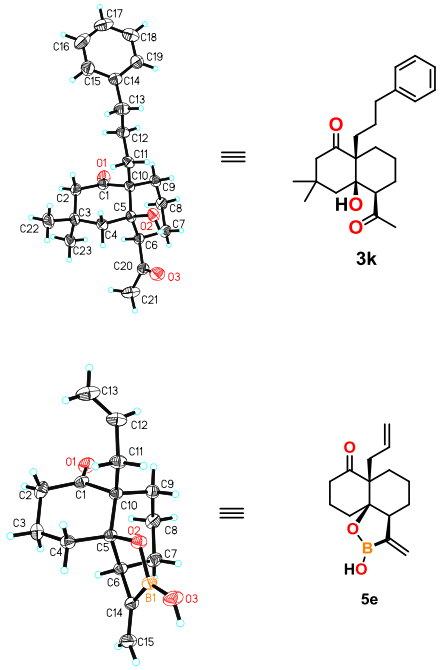
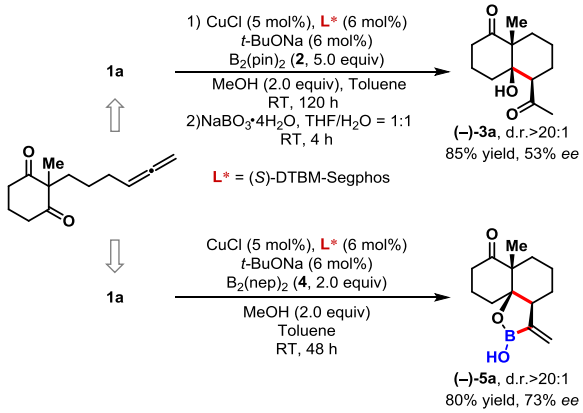


Fig. 2 X-Ray single crystal structures of cyclization products **3k** and **5e**.



Scheme 4 Cu-catalyzed asymmetric borylative cyclization of allene cyclohexanedione **1a**.

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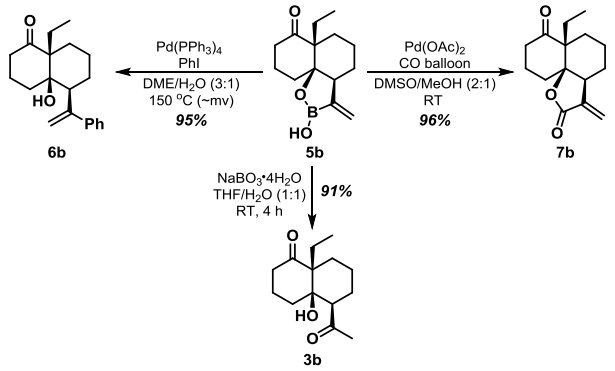

Scheme 5 Several transformations of cyclization product **5b**.

The stable hemiboronate group enables its further conversion and Scheme 5 displays three chemical transformations. A facile oxidation of vinyl hemiboronate **5b** produced the methylketone **3b** in 91% yield. Suzuki–Miyaura coupling with phenyl iodide gave styrene derivative **6b** in 95% yield. Pd-catalyzed deborylative CO insertion of **5b** provided tricyclic α,β-unsaturated lactone **7b** in 96% yield.

In summary, the first Cu-catalyzed borylative cyclization of allene cyclohexanediones has been established through a tandem process: selective β-borylation of the allene and subsequent intramolecular allylic addition to cyclohexanedione, affording borylated *cis*-decalinol frameworks with excellent yields and diastereoselectivities. The asymmetric version is also screened to achieve an acceptable enantioselectivity. The hemiboronate group in the cyclization products could be subjected to several transformations for elaborating its synthetic utility. Further studies on the applications of allene cyclohexanediones are in progress in our laboratories will be reported in due course.

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20 The alkenyl pinacol boronates are unstable to silica gel, thus the oxidation of boronates was conducted to afford methyl ketones for analysis.

21 Without MeOH additives, the conversion was below 5% using (±)-BINAP ligand. It showed that MeOH accelerated the cyclization reaction.

22 CCDC 1472930 (**3k**) and 1472931 (**5e**) contain the supplementary crystallographic data for this paper.

23 For more details, see section 5 in the Supporting Information.

