Asymmetric Synthesis

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Efficient Access to Bicyclo[4.3.0]nonanes: Copper-Catalyzed Asymmetric Silylative Cyclization of Cyclohexadienone-Tethered Allenes

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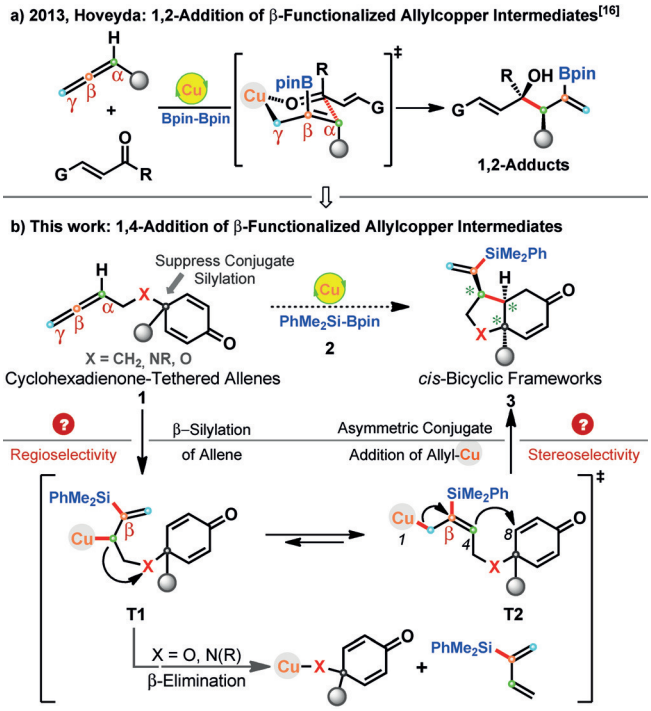
Abstract: *The creation of three consecutive chiral carbon centers in one step is achieved using Cu-catalyzed asymmetric silylative cyclization of cyclohexadienone-tethered allenes. Through regioselective β-silylation of the allene and subsequent enantioselective 1,4-addition to cyclohexadienone, this tandem reaction could afford cis-hydrobenzofuran, cis-hydroindole, and cis-hydroindene frameworks with excellent yields (80–98 %) and enantioselectivities (94–98 % ee) bearing vinylsilane and enone substructures. Meanwhile, this mild transformation is generally compatible with a wide range of functional groups, which allows further conversion of the bicyclic products to bridged and tricyclic ring structures.*

Organosilanes have broad and varied uses ranging from the most frequently employed protecting groups, reducing agents to valuable synthetic intermediates in organic chemistry.[1] The efficient accesses to functionalized organosilanes are continuously expanding to meet emerging needs. Recently, silylboronate reagents introduced by Suginome and Ito[2] have gained significant interest,[3–5] particularly in copper-catalyzed C–Si bond formation.[6] Several research groups have contributed greatly in the field of Cu-catalyzed silylative addition to C=O,[7] C=N,[7c,8] C=C,[9–10] and C≡C[11] bonds, and shaped this arena as it stands today. However, the powerful cascade approach forming multiple chemical bonds and stereocenters was scarce to our knowledge.[12] Herein, we report the first Cu-catalyzed asymmetric silylative cyclization of cyclohexadienone-tethered allenes (1,6-enallenes).

Allenes are like a chameleon in modern organic chemistry and always fascinate chemists owing to their unique structural and electronic properties.[13] It was reported that Cu–Si species could react with allenes to form β-silylated allylcopper intermediates.[14,15] Their three subsequent transformations were reported using different electrophiles: MeOH for hydrosilylation,[14a,b] aldehydes and ketones for 1,2-addition,[14a,c] and CO_2 for silacarboxylation.[15] Despite these advances, the challenging 1,4-addition of β-silylated allylcopper has never been uncovered, because efficient 1,2-addtion remains favored versus 1,4-addition in the addition of β-functionalized allylcopper to α,β-unsaturated carbonyls (Scheme 1 a).[16] To address this issue, allene and α,β-unsaturated carbonyl are integrated into a molecule, cyclohexadienone-tethered allene **1** (Scheme 1 b). In this case, the 1,2- addition of β-silylated allylcopper to ketone becomes rather difficult owing to its inherent site restrictions. However, because the directing group is not required during the selective β-silylation of allene,[14,15] bicyclo[4.3.0]nonane frameworks **3**, including *cis*-hydrobenzofuran, *cis*-hydroindole, and *cis*-hydroindene could be prepared, which overcomes the previous drawback that an O-directing group is necessary.[18d]



Scheme 1. Strategic design for Cu-catalyzed asymmetric silylative cyclization of cyclohexadienone-tethered allenes.

Returning to the start of this cascade reaction, because the direct conjugate silylation to cyclohexadienone is expected to be suppressed by the neighboring steric hindrance, regioselective β-silylation of the allene should preferentially occur (Scheme 1 b). In addition, Cu–Si addition places the Cu at the less-hindered site of the allene, leading to the formation of β-silylated allylcopper intermediate **T2**, rather than **T1**. Such selective Cu–Si addition, together with the highly reactive nature of cyclohexadienone, could potentially avoid the competitive β-elimination pathway for the heteroatom-linked 1,6-enallenes (X = O, N).[17] The subsequent intra-

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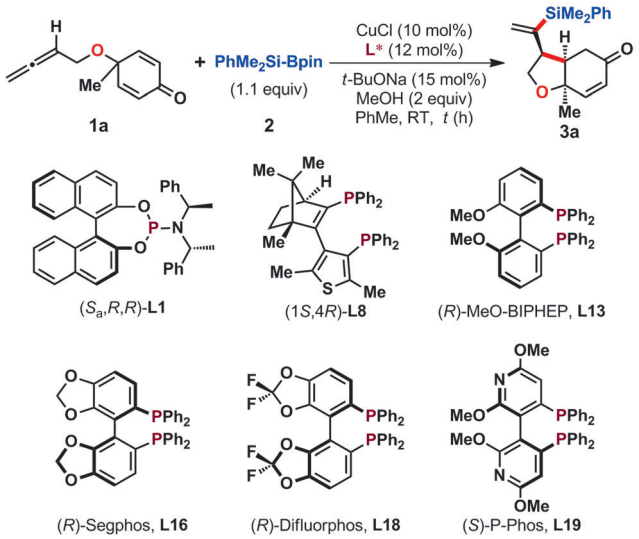
molecular 1,4-addition of **T2** furnishes chiral *cis*-bicyclic framework bearing three consecutive chiral carbon centers.[18] Nevertheless, the remote control of reaction diastereo- and enantioselectivity (1,8-asymmetric induction) remains quite challenging during this addition process.

With these concerns in mind, a set of representative chiral ligands were evaluated for the Cu-catalyzed asymmetric silylative cyclization of 1,6-enallene **1a**, and selected results are summarized in Table 1.[19] When the previous superior PhMe$_2$Si-Bpin (**2**) loading gave no better results (Table 1, entries 7,8). When the reaction was conducted in THF at room temperature, excellent yield (93%), diastereo- and enantioselectivity (14:1 d.r. and 97% *ee*) were all successfully obtained (Table 1, entry 9). Lower temperature proved to be inferior in terms of yield and *ee* value (Table 1, entry 10).

With the optimal reaction conditions identified, we evaluated the scope of O-linked 1,6-enallenes **1** and the results were summarized in Table 2. With the R substituent as alkyl, vinyl, allyl, benzyl, and phenyl group, the reactions proceeded smoothly with excellent yields (92–98%) and enantioselectivities (95–97% *ee*, Table 2, entries 1–9). With a heteroatom (N, O, S, Br, or I) as part of R in substrates **1**, the reaction yields and *ee* values still remained excellent, respectively (Table 2, entries 10–18). Note that the bromo- and iodoalkyl groups in substrates **1q** and **1r** were comfortably tolerated in this transformation (Table 2, entries 17 and 18). In other words, the β-silylated allylcopper selectively underwent 1,4-addition rather than nucleophilic substitution in both cases,[20] which corroborated the high reactivity of cyclohexadienone.

In line with our expectation, as for the N-linked 1,6-enallenes, the corresponding *cis*-hydroindole products, **3s**, **3t**,

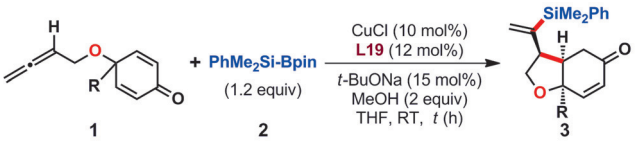
Table 1: Selected optimization studies.[a]



Entry	L	Solvent	*t* [h]	Conv. [%][b]	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**L1**	PhMe	15	60	2.6:1	40	−29
2	**L8**	PhMe	13	20	4.3:1	16	69
3	**L13**	PhMe	11	99	1.9:1	64	−72
4	**L16**	PhMe	12	70	3.5:1	55	−80
5	**L18**	PhMe	11	75	11:1	67	−91
6	**L19**	PhMe	11	70	10:1	60	93
7[e]	**L19**	PhMe	11	90	12:1	79	92
8[f]	**L19**	PhMe	11	90	9:1	55	90
9[e]	**L19**	THF	11	100	14:1	93	97
10[e,g]	**L19**	THF	11	70	16:1	64	96

[a] Reactions were performed under a N_2 atmosphere. [b] Determined by ^{1}H NMR (400 MHz) analysis of unpurified product mixtures. [c] Yield of isolated product **3a**. [d] Determined by HPLC analysis. [e] **2** (1.2 equiv) was used. [f] **2** (1.3 equiv) was used. [g] At 0°C.

Table 2: *O*-Linked 1,6-enallene scope.[a]



1a: R = Me- **1b**: R = Et- **1c**: R = *i*-Pr-
1d: R = *c*-Hex **1e**: R = CH_2=CH- **1f**: R = CH_2=CH-CH_2-
1g: R = C_6H_5-CH_2- **1h**: R = C_6H_5- **1i**: R = 4-Br-C_6H_4-
1j: R = BocN(H)-$(CH_2)_2$- **1k**: R = CH_3-$(CH_2)_2$-O- **1l**: R = TBSO-$(CH_2)_2$-
1m: R = AcO-$(CH_2)_2$- **1n**: R = MeOC(=O)-CH_2- **1o**: R = EtOC(=O)-$(CH_2)_2$-
1p: R = AcS-$(CH_2)_2$- **1q**: R = Br-$(CH_2)_3$- **1r**: R = I-$(CH_2)_3$-

Entry	Subs. **1**	*t* [h]	d.r.[b]	Prod. **3**	Yield [%][c]	*ee* [%][d]
1	**1a**	11	14:1	**3a**	93	97
2	**1b**	11	16:1	**3b**	94	95
3	**1c**	11	>20:1[e]	**3c**	94	96
4	**1d**	16	>20:1[e]	**3d**	93	96
5	**1e**	15	12:1	**3e**	92	98
6	**1f**	15	>20:1[e]	**3f**	95	95
7	**1g**	16	12:1	**3g**	92	95
8	**1h**	15	>20:1[e]	**3h**	98	97
9	**1i**	12	>20:1[e]	**3i**	97	97
10	**1j**	16	12:1	**3j**	92	94
11	**1k**	15	>20:1[e]	**3k**	90	94
12	**1l**	14	>20:1[e]	**3l**	96	96
13	**1m**	14	17:1	**3m**	90	96
14	**1n**	15	13:1	**3n**	93	96
15	**1o**	15	>20:1[e]	**3o**	96	96
16	**1p**	14	10:1	**3p**	91	95
17	**1q**	15	13:1	**3q**	91	96
18	**1r**	15	12:1	**3r**	92	95

[a] Reactions were performed under a N_2 atmosphere. [b] Determined by the ratio of isolated yield of product **3** and its minor diastereomer. [c] Yield of isolated product **3**. [d] Determined by HPLC analysis. [e] The minor diastereomer was not observed.

phosphoramidite ligand **L1** was tested,[18d] the desired silylative cyclization product **3a** was obtained without the formation of β-elimination product, albeit in poor diastereo- and enantioselectivity (Table 1, entry 1). The bisphosphine ligand **L8** was recently reported to effectively promote the asymmetric 1,2-addition of β-borylated allylcopper complexes.[16] In our case, the *ee* value was dramatically increased to 69% despite with low yield and d.r. value (Table 1, entry 2). Several bisphosphine ligands **L13**, **L16**, **L18**, and **L19** were subjected to this reaction afterwards. To our delight, all the yields, d.r. and *ee* values of **3a** were greatly improved, especially for (*S*)-P-Phos (**L19**) (Table 1, entry 6). Increasing

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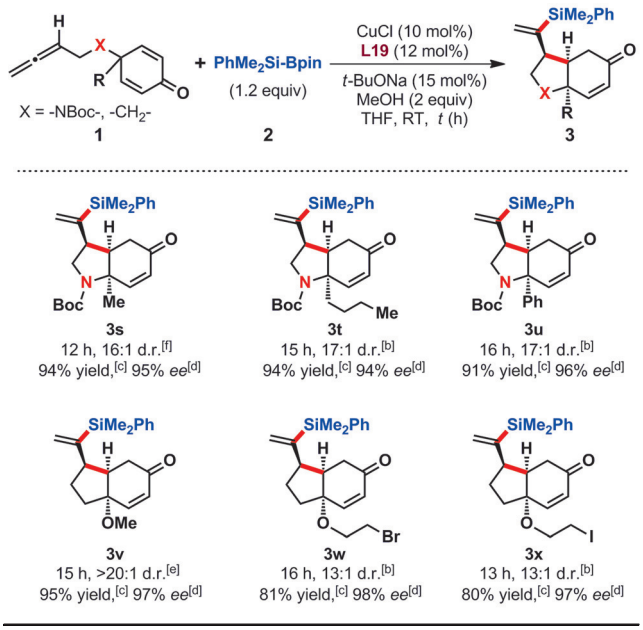
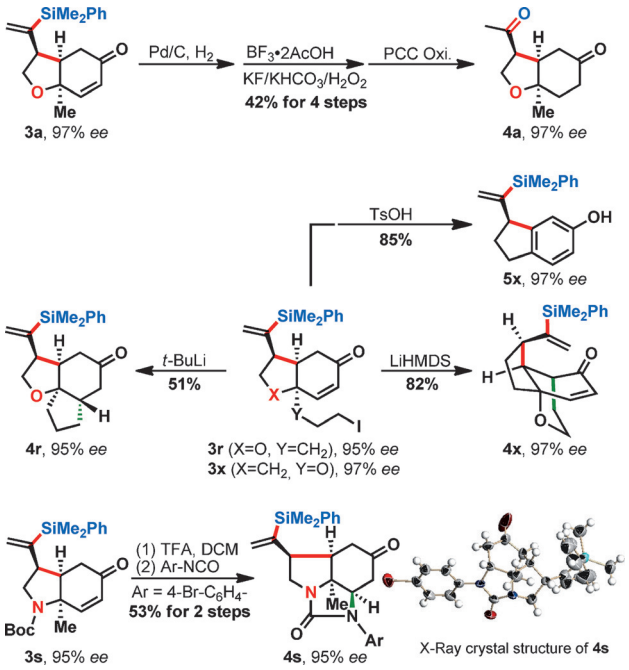
Table 3: N- and C-Linked 1,6-enallene scope.[a]



[a] Reactions were performed under a N_2 atmosphere. [b] Determined by the ratio of isolated yield of product **3** and its minor diastereomer. [c] Yield of isolated product **3**. [d] Determined by HPLC analysis. [e] The minor diastereomer was not observed. [f] Determined by ^{1}H NMR (400 MHz) analysis of unpurified product mixture.



Scheme 2. Selected examples of subsequent transformations, see text for details. Crystal structure: O red, N dark blue, Si light blue.

and **3u**, were constructed with exceptionally excellent yields (91–94%) and enantioselectivities (94–96% *ee*; Table 3). For the C-linked 1,6-enallenes, the reactions still proceeded equally well to give optically pure *cis*-hydroindene products, **3v**, **3w**, and **3x**, (80–95% yield, 97–98% *ee*, Table 3). As revealed in Tables 2 and 3, the mild reaction conditions are compatible with a wide range of functional groups, providing a versatile platform for further synthetic manipulations.

The absolute configuration of the cyclization product **3a** was assigned as (3*S*,3a*R*,7a*R*).[21] The vinylsilane, enone functionalities and diverse substituents in the cyclization products can serve as synthetically valuable handles for further transformations. Through the successive hydrogenation, Fleming–Tamao oxidation and PCC oxidation of **3a**, the diketone product **4a** could be readily prepared (Scheme 2). Upon treatment of **3r** with *t*BuLi, the resulting alkyllithium underwent an intramolecular Michael addition to give the tricyclic product **4r**. When the C-linked product **3x** was treated with LiHMDS, an intramolecular alkylation proceeded uneventfully to deliver the bridged ring product **4x** (Scheme 2). Dealcoholization of **3x** took place under acidic conditions and the simultaneous aromatization afforded the phenol product **5x** (Scheme 2). As for N-linked product **3s**, the Boc group was easily removed and the resulting amine could react with 4-bromophenyl isocyanate, to give a tricyclic product **4s**, whose absolute configuration was established by X-ray crystallography (Scheme 2) and vibrational circular dichroism (VCD) analysis.[21,22] No loss of enantiomeric ratios was observed in all above transformations.

In summary, the Cu-catalyzed asymmetric silylative cyclization reaction has been accomplished through a tandem process: selective β-silylation of the allene and subsequent enantioselective 1,4-addition to cyclohexadienone. This reaction proceeded smoothly to afford *cis*-hydrobenzofuran, *cis*-hydroindole, and *cis*-hydroindene frameworks bearing three consecutive chiral carbon centers with excellent yields and enantioselectivities. The cyclization products could be subjected to several transformations for elaborating synthetic utility. Further studies on the applications of cyclohexadienone-tethered allenes are underway.

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